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Matrix metalloproteinases participation in the metastatic process and their diagnostic and therapeutic applications in cancer

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ABSTRACT

Matrix metalloproteinases (MMPs) participate from the initial phases of cancer onset to the settlement of a metastatic niche in a second organ. Their role in cancer progression is related to their involvement in the extracellular matrix (ECM) degradation and in the regulation and processing of adhesion and cytoskeletal proteins, growth factors, chemokines and cytokines. MMPs participation in cancer progression makes them an attractive target for cancer therapy. MMPs have also been used for theranostic purposes in the detection of primary tumor and metastatic tissue in which a particular MMP is overexpressed, to follow up on therapy responses, and in the activation of cancer cytotoxic pro-drugs as part of nano-delivery-systems that increase drug concentration in a specific tumor target.

Herein, we review MMPs molecular characteristics, their synthesis regulation and enzymatic activity, their participation in the metastatic process, and how their functions have been used to improve cancer treatment.

1. Introduction

Cancer is the most important death cause worldwide ascending to 18.1 million new cases in 2018 (International Agency for Research on Cancer, 2018). In spite of all efforts to develop new target therapy, about 90% of cancer patients' morbidity and mortality is still due to metastasis because of the systemic nature of the disease and the resistance of metastatic cells to existing therapeutic agents (Valastyan and Weinberg, 2011).

To develop a metastasis, neoplastic cells must acquire certain characteristics to be able to undergo several sequential steps that constitute the metastatic process. In this context the participation of the matrix metalloproteinases (MMPs) during cancer progression has been identified and a correlation among an over-expression and/or high enzymatic activity of a particular MMP with an increase of the disease aggressiveness has been established; that fact appointed MMPs as probable prognostic markers and therapeutic targets in this ailment.

Therefore, the present review describes how a metastatic colony is established and what roles MMPs play in the metastatic cascade. This manuscript also examines MMPs diagnostic uses and their potential as tools to follow up cancer progression. It also considers some strategies to inhibit MMPs activity in an attempt to improve patients' overall survival.

2. Matrix metalloproteinases

MMPs or matrixins are a group of endopeptidases that require calcium-zinc ions for their enzymatic activity; they are able to disrupt all basement membrane (BM) and extracellular matrix (ECM) molecules (Murphy and Nagase, 2008). MMPs are also involved in activation and release of different chemokines, cytokines, growth factors, adhesion molecules, and cytoskeletal proteins that allow them to participate in physiological events, as for instance inflammation, embryogenesis, wound healing, angiogenesis and bone remodeling (Loffek et al., 2011). MMPs belong to the metzincin superfamily as well as the reprolysins, astacins, semalysins, meprins and the adamalysins or ADAMs (a desintegrin and metalloproteinases). Until now, 28 MMPs have been identified in vertebrates and 24 in humans including two equivalent

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Table 1
Human matrix metalloproteinases (MMPs) classification according to substrate, domain structure and chromosome location.

Group	MMP	Common name	human CHROMOSOME	MW kDa Pro/Active	Substrate
Collagenases	MMP-1	Interstitial collagenase-1	11q21-q22	55/45	Collagen I, II, III, VII, VIII, X, gelatin, aggrecan, α1-antitrypsin inhibitor, α1-antichymotrypsin, casein, entactin, IGF-BP-3, IGF-BP-5, IL-Iβ, 2-macroglobulin, nidogen, ovostatin, perlecan, proteoglycan link protein, L-selectin, pro-TNFα, SDF-1, serpins, tenascin-C, versican
	MMP-8	Collagenase-2 or neutrophil collagenase	11q21-22	75/55	Collagen I, II, III, V, VII, VIII, X, gelatin, aggrecan, α2-antiplasmin, elastin, fibronectin, laminin, 2-macroglobulin, nidogen, pro-MMP-8, serpins
	MMP-13	Collagenase-3	11q22.3	60/48	Collagen I, II, III, IV, V, IX, X, XI, XIV, gelatin, aggrecan, casein, fibronectin, laminin, perlecan, plasminogen activator 2, pro-MMP-9, pro-MMP-13, SDF-1, tenascin
	MMP-18	Collgenase-4	12q14	70/53	Collagen I, II, III, gelatin, α1-antitrypsin
Gelatinases	MMP-2	Gelatinase-A	16q13-q21	72/63	Collagen I, II, III, IV, V, VII, X, XI, XIV, gelatin, active MMP- 9 and MMP-13, aggrecan, elastin, fibronectin, FGF-RI, IGF-BP-3, IGF-BP-5, IL-1β, laminin, nidogen, proteoglycan link protein, pro-TNF-α, TGF-β, versican
	MMP-9	Gelatinase-B	20q12-q13	92/86	Collagen IV, V, VII, X, XIV, gelatin, aggrecan, CXCL5, fibrillin, fibronectin, IL-1β, IL2-R, laminin, nidogen, osteonectin 2, plasminogen, proteoglycan link protein, pro-TNFα, SDF-1, TGF-β, versican
Stromelysins	MMP-3	Stromelysin-1	11q22.3	57/45	Collagen II, III, IV, V, IX, X, XI, gelatin, aggrecan, α1-antichymotrypsin, antithrombin III, E-cadherin, casein, decorin, elastin, fibronectin, fibrinogen, IGF-BP-3, laminin, nidogen, ovostatin, perlecan, proteoglycan, proteoglycan link protein, α1-proteinase inhibitor, pro-HB-EGF, pro-IL-β, pro-MMP-1, pro-MMP-8, pro-MMP-9, pro-MMP-13, L-selectin, SDF-1, pro-TNFα, versican
	MMP-10	Stromelysin-2	11q22.3	57/44	Collagen III, IV, V, aggrecan, casein, gelatin, elastin, fibronectin, laminin, nidogen, pro-MMP-1, pro-MMP-7, pro-MMP-8, pro-MMP-9, pro-MMP-10, pro-MMP-13
	MMP-11	Stromelysin-3	22q11.23	51/44	Aggrecan, α1-antitrypsin, fibronectin, IGF-BP-1, laminin, α1-proteinase inhibitor
Matrilysins	MMP-7	Matrilysin-1	11q21-q22	29/20	Collagen I, II, III, IV, V, X, aggrecan, casein, decorin, E-cadherin, elastin, enactin, Fas-ligand, β4 integrin, laminin, nidogen, plasminogen, proteoglycan link protein, pro-MMP-2, pro-MMP-7, pro-MMP-8, pro-TNFα, transferrin, tenascin, syndecan, versican
	MMP-26	Matrilysin-2	11p15	28/19	Collagen IV, gelatin, casein, fibrin, fibrinogen, fibronectin, β1-proteinase inhibitor, TNF-α converting enzyme (TACE), vitronectin, pro-MMP-2
Transmembrane Type 1	MMP-14	MT1-MMP	14q11q-12	66/56	Collagen I, II, III, gelatin, aggrecan, CD44, dermatan sulfate proteoglycan, gCIqR, elastin, fibrin, fibrillin, fibronectin, αvβ3 Integrin, laminin, 2-macroglobulin, nidogen, perlecan, tenascin, pro-MMP-2, pro-MMP-13, pro-TNFα, SDF-1, tissue transglutaminase, vitronectin
	MMP-15	MT2-MMP	16q13	72/50	Collagen I, II, III, gelatin, aggrecan, fibronectin, laminin, nidogen, perlecan, pro-MMP-2, pro-MMP-13, tissue transglutaminase, tenascin, vitronectin
	MMP-16	MT3-MMP	8q21	64/52	Collagen I, III, gelatin, aggrecan, casein, fibronectin, laminin, 2-macroglobulin, perlecan, proteoglycans, pro-MMP-2, proMMP-13, vitronectin
	MMP-24	MT5-MMP	20q11.2	57/53	Gelatin, N-cadherin, chondroitin sulfate, dermatan sulfate, fibrin, fibronectin, pro-MMP-2, pro-MMP-13
Transmembrane Type 2	MMP-23	CA-MMP	1p36.3	28/19	Gelatin
GPI-anchored	MMP-17	MT4-MMP	12q24.3	57/53	Gelatin, fibrin, fibrinogen, fibronectin, TNFα precursor
	MMP-25	MT6-MMP	16p13.3	34/28	Collagen IV, gelatin, fibrin, fibronectin, pro-MMP-2, α-proteinase inhibitor
Other MMPs	MMP-12	Macrophage elastase	11q22.3	54/45–22	Collagen IV, gelatin, casein, elastin, fibrillin, fibronectin, laminin, plasminogen, vitronectin
	MMP-19	RASI-1	12q14	54/45	Collagen I, IV, gelatin, aggrecan, casein, fibronectin, laminin, nidogen, tenascin
	MMP-20	Enamelysin	11q22.3	54/22	Collagen V, aggrecan, amelogenin, cartilage oligomeric protein
	MMP-21		10q26.3	62/49	Gelatin, α1-antitrypsin
	MMP-27		11q24	~59	Gelatin, casein
	MMP-28	Epilysin	17q21.1	56/45	Casein

GPI, Glycosyl-phosphatidyl-inositol; MT-MMP, membrane type MMP.

forms of MMP-23 (MMP-23A and MMP-23B) encoded by 2 distinct genes in chromosome 1 (Jackson et al., 2010; Cui et al., 2017; Mittal et al., 2016). Ten of the MMPs genes are located on chromosome 11 while the other MMPs are encoded by different chromosomes (Table 1). They have been denominated in a sequential order from MMP-1 to MMP-28. At this point, it is important to clarify that the terms MMP-4, MMP-5 and MMP-6 are not used because they correspond to MMT4-MMP (MMP-17), MT5-MMP (MMP-24) and MT6-MMP (MMP-25) respectively. Likewise, MMP-22 is expressed in chicken fibroblasts and its human homolog is MMP-27 (Jackson et al., 2010; Cui et al., 2017; Mittal et al., 2016).

According to domain organization, sequence similarity and substrate specificity, MMPs might be classified in collagenases, gelatinases, stromelysins, matrilysins, transmembrane type I, transmembrane type II, glycosylphosphatidylinositol-anchored (GPI-anchored) MMPs and other MMPs (Table 1) (Murphy and Nagase, 2008).

2.1. MMPs structure

MMPs are proteins with many different domains but their basic molecular structure consists of a signal peptide that directs MMPs to the secretory pathways except for the membrane type MMPs (MT-MMPs), an N-terminal pro-peptide, a catalytic site that includes a zinc atom, a hinge or linker domain rich in proline residues and a C-terminal hemopexin-like region that confers substrate or ligand specificity, localization and MMPs enzymatic activity regulation (Fig. 1) (Somerville et al., 2003). This basic structure exists in almost all MMPs except for MMP-7 and MMP-26 that do not contain the hemopexin domain. Other MMPs have other domains such as the furin recognition site present in MMP-11, MMP-21 and MMP-28, in the transmembrane type I MMPs (MMP-14, MMP-15, MMP-16 and MMP-24), in the transmembrane type II MMP, MMP-23, and in MMP-17 and MMP-25. MMP-17 and MMP-25 contain also a glycosyl-phosphatidylinositol (GPI)-anchored domain (Fig. 1).

2.2. MMPs regulation

Since MMPs are able to degrade the ECM, their proteolytic activity must be tightly regulated to avoid tissue damage. Uncontrolled enzymatic activity drives tissue homeostasis havoc as it occurs in rheumatoid arthritis, gastrointestinal ulcer, neuroinflammatory diseases, pulmonary emphysema and cancer (Amălinei et al., 2010).

MMPs enzymatic activity is controlled in different ways: gene expression, compartmentalization, pro-enzyme activation and enzymatic inhibition.

2.2.1. Gene expression regulation

Most MMPs synthesis is influenced by chemical agents, physical stress, oncogene products, growth factors, cytokines and cell–cell or cell–ECM interactions. Likewise, glucocorticoid hormones, retinoic acids and the transforming growth factor-β1 (TGFβ1) also interfere with the expression of some MMPs (Kim and Joh, 2012). These effectors trigger intracellular signaling pathways as for instance nuclear factor-κB (NFκB), Janus kinase/signal transducer and activator of transcription (JAK/STAT) and mitogen-activated protein kinases (MAPKs) that induce MMPs synthesis. According to their conformation, MMPs promoters are divided in three groups (Yan and Boyd, 2007). The first group is comprised by MMPs promoters that have an activator protein-1 (AP-1) site around −70 bp and a TATA box at nearly −30 bp. This group includes MMP-1, MMP-3, MMP-7, MMP-9, MMP-10, MMP-12, MMP-13, MMP-19, and MMP-26. An upstream polyoma enhancer activator protein-3 (PEA-3) binding site is very often associated with this kind of promoters. Cytokines or growth factors including platelet-derived growth factor (PDGF), tumor necrosis factor-α (TNF-α), interleukins (ILs), keratinocyte growth factor (KGF), epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF) and the TGFβ participate in the expression control of this MMPs' group. The second group of MMPs promoters includes a TATA box but not a promoter-proximal AP-1 site. To this group belong: MMP-8, MMP-11, and MMP-21. The regulation of these MMPs is relatively less restrictive than in the first group. Interestingly, MMP-11 has a retinoic acid response element (DR1-RARE) in its proximal promoter that allows gene expression stimulated by retinoic acid, and two upstream DR2-RAREs that participate in its basal expression (Clark et al., 2008). The third group is constituted by MMPs promoters with no TATA box (MMP-2, MMP-14 and MMP-28). Multiple GC boxes that bind to specificity protein-1 (Sp1) and Sp3 transcription factors have been identified in their proximal promoters. The MMPs from this group are synthesized in a constitutive manner and have little inducibility by some cytokines and growth factors.

MMPs transcription is also regulated by epigenetic mechanisms. Cytosine methylation within CpG in the promoter region inhibits gene expression while histone H3 and H4 acetylation produces a more relaxed chromatin with gene activation (Yan and Boyd, 2007).

Gene expression is also controlled at the post-transcriptional level and depends of cytosolic mRNA stability. TGFβ for instance increases MMP-2 and MMP-9 levels extending their mRNA half-life and also increases MMP-13 synthesis inducing transcription and stabilizing the transcript (Overall et al., 1991; Delany and Canalis, 2001). Post-transcriptional regulation requires the participation of trans-acting RNA-binding proteins which recognize diverse cis-elements sites of the mRNA. This interaction produces either stabilization or destabilization of the transcript. For example, MMP-9 protein expression in renal mesangial cells depends on the binding of the human antigen-R (HuR) protein to the AU rich elements (AREs) localized in the 3′untranslated regions (UTRs) from the MMP-9 mRNA (Huwiler et al., 2003). The use of the ATP analog ATPγS increases the HuR complexes with MMP-9 mRNA enhancing transcript stability while the incubation of mesangial cells with nitric oxide decreases HuR expression with an increase of MMP-9 mRNA degradation (Akool et al., 2003). Likewise, microRNAs (miRNA) are also involved in regulating mRNA stability by binding to the 3′UTR of MMPs transcripts, for example, miR-29 interacts with MMP-2, and miR-24, miR26, and miR-181 with MMP-14 (Clark et al., 2008). Aberrant miRNA expression has been identified in several cancers as for instance the increased levels of miR-20a found in colorectal cancer (Xu et al., 2015a). This miRNA favors MMP-2 and MMP-9 protein synthesis and inhibits TIMP-2 protein expression. Likewise, a low expression of miR-29b with an increase of MMP-2 levels was observed in tissue from non-small cell lung cancer (NSCLC) patients in comparison with normal tissue, and in high-metastatic A549 cells (Wang et al., 2015). In this regard, the transcription factor called serum response factor (SRF) was also increased in these cells and in NSCLC tissue (Wang et al., 2015). SRF is involved in angiogenesis, cell proliferation, apoptosis and migration (Lee et al., 2007). It was found, in the in vitro A549 cell model, that SRF binds precisely to the promoter site of miR-29b inhibiting its transcription and indirectly inducing MMP-2 protein expression (Wang et al., 2015). Another member of the miR-29 family, the miR-29c, inhibits cell adhesion, proliferation and invasion by binding to MMP-2 and β_1 integrin mRNA 3′UTR regions in sub-clones of the PLA-801 cell line, a large cell lung carcinoma (Wang et al., 2013). This miRNA was upregulated in the 95C sub-clone which had a low metastatic potential; contrastingly, it was downregulated in the highly metastatic 95D sub-clone. The miR-133a has also been studied in lung cancer. This miRNA decreases A549 and NCI-H1299 (both NSCLC cell lines) cell proliferation, migration and invasion through the direct inhibition of MMP-14 expression (Xu and Wang, 2013). Likewise, MMP-13 protein expression is regulated by the miR-125b in lung tissue (Yu et al., 2015). This miRNA was downregulated and MMP-13 was increased in tissue from NSCLC patients which had lymph node (LN) metastasis. Furthermore, patients with a progression-free survival had

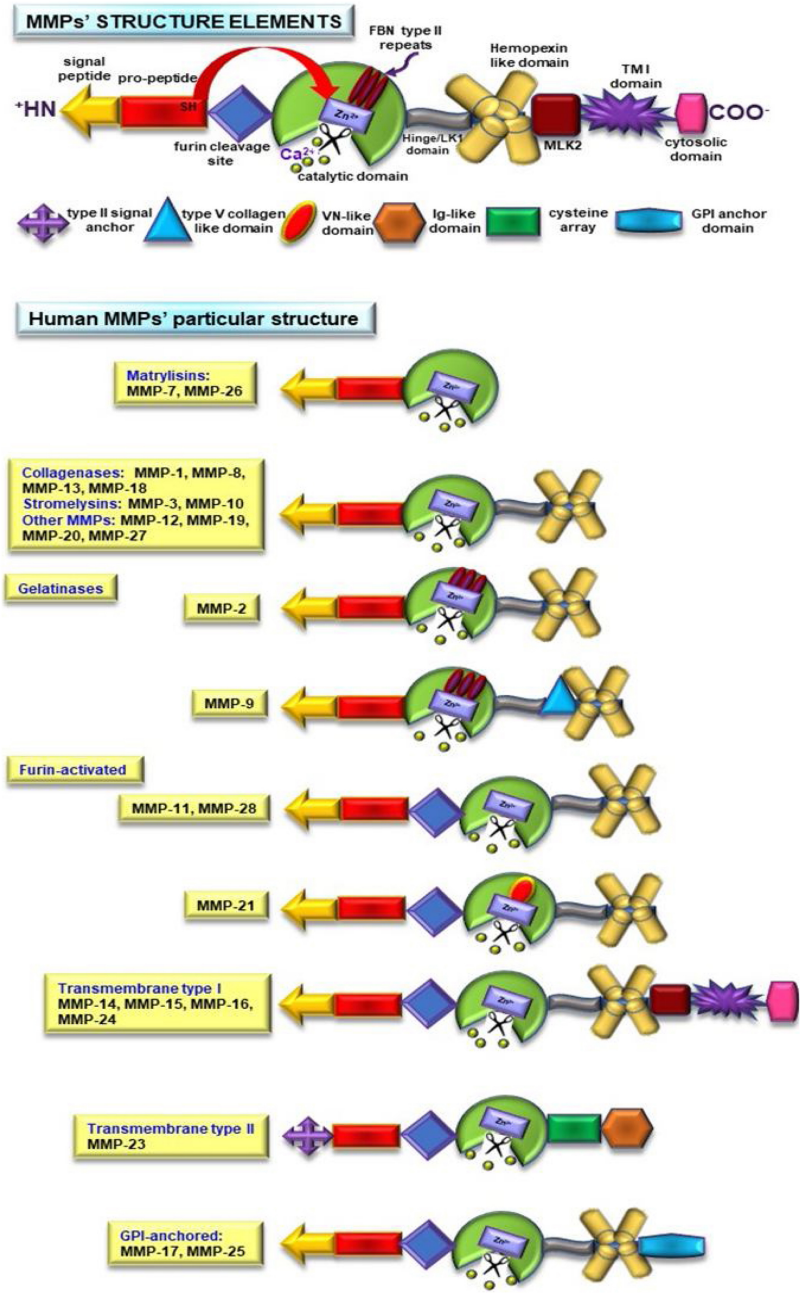

Fig. 1. MMPs' structural characteristics. Most MMPs share a similar structure: a signal peptide, a pro-peptide with the amino sequence PRCGXPD including a cysteine thiol group (-SH) linked to the Zn^{2+} in the catalytic cleft. Likewise, the catalytic region has a Zn^{2+} binding sequence HEXXHXXGXXH and two Zn^{2+} ions, one that participates in the enzymatic regulation, and another included in the active site structure; a linker 1 (LK1) or hinge domain and an hemopexin-like region. Collagenases, stromelysins and other MMPs have this basic structure. Contrastingly, matrilysins lack the LK1 and the hemopexin domains. Gelatinases express other elements in their structure. Both MMP-2 and MMP-9 have fibronectin (FBN) motifs in their catalytic region. In addition, MMP-9 has a type V collagen like domain. Some MMPs include a furin-convertase recognition site (RXKR or RRKR) in the middle of the pro-peptide and the active region. MMP-21 includes a vitronectin (VN)-like structure in its catalytic site. The transmembrane type I MMPs contain a membrane linker2 domain (MLK2), a transmembrane domain type 1 (TMI) and a cytosolic domain, while the transmembrane MMPs MMP-17 and MMP-25, in contrast, possess a glycosylphosphatidylinositol (GPI) anchoring region. MMP-23 structure is very peculiar, since it contains a transmembrane type II signal anchor in the N-terminal of the pro-peptide, a cysteine array and an immunoglobulin (Ig)-like proline rich domain in its C-terminus extreme.

high miR-125b levels. Dual-luciferase reported assay demonstrated that MMP-13 is a direct target of this miRNA in A549 and H520 (a squamous cell lung carcinoma cell line) cells (Yu et al., 2015).

Some miRNA regulate MMPs' translation in an indirect manner as for example the miR-129 that, when overexpressed, inhibits the phosphatidylinositol-3-kinase/protein kinase-B (PI3K/Akt) signaling pathway, hindering in turn the induction of MMP-9 translation by the epidermal growth factor receptor (EGFR) in A549 and H460 (a large cell lung cancer line) cells (Li et al., 2015a). The important role of miR-129 is clearly observed in tissue from NSCLC patients, where a decrease in miR-129 with an increase in EGFR phosphorylation and MMP-9 expression was associated with a more aggressive form of the disease (Li et al., 2015a).

2.2.2. Compartmentalization

Cell compartmentalization is another form of MMPs' enzymatic activity regulation. MMPs can be found anywhere in the cell because they participate in the metabolism of a large variety of intracellular components (Cauwe and Opdenakker, 2010). MMPs different localization in the cell can be explained by variations in their signal peptide sequences that for instance, prevent proteins translocation through the endoplasmic reticulum (ER) allowing them to remain in the cytosol (Hegde and Bernstein, 2006). In this context, the occurrence of a Pro residue in the N-terminal signal sequence of MMP-1, MMP-3, MMP-8, MMP-9, MMP-13 and MMP-14 renders their signal peptides inefficient and, consequently these MMPs are driven either to the ER-Golgi secretory pathway or to the cytosol (Cauwe and Opdenakker, 2010). Meanwhile, MMPs sorted out into the secretory pathway are transported in vesicles in active and/or latent forms depending on the cell type, and are secreted to the extracellular space. MMP-2 and MMP-9 for instance, are contained in secretory vesicles associated with Sec8 (a subunit of the exocyst complex) that participates in invadopodia formation in oral squamous cell carcinoma (SCC) (Yamamoto et al., 2013a). In contrast, in breast cancer cells, MMP-2 and MMP-9 are

localized in vesicles associated to membrane protein-4 (VAMP4) and Ras related protein Rab-40b; these secretory vesicles prevent mistargeting to lysosome and drive MMPs to the invadopodia (Jacob et al., 2013). In astrocytes, MMP-2 and MMP-9 are also present in distinct types of vesicles (Sbai et al., 2010). MMP-2 is co-localized with the motor proteins myosin V (5%) and kinesin (21%) while MMP-9 is co-localized with myosin V (39%) and kinesin (91%) in this type of cells. Lysosome-associated membrane protein-2 (LAMP-2), a specific molecule of the endocytic compartment, is also contained in MMP-9-vesicles (Sbai et al., 2010). Similarly, MMPs are also collected in specific granules until the cell is stimulated to release them. Polymorphonuclear cells (PMN) for example, hold MMP-8 and MMP-25 that are released to the extracellular medium upon cytokine or chemokine stimulation during the immunological response (Kang et al., 2001). MMP-9 has been also identified in PMN tertiary granules and is released when cells migrate through the endothelium in their way to the inflammatory site (Soehnlein et al., 2009). MMP-1, MMP-2 and MMP-3 have been observed in platelet α-granules participating with MMP-9 and MMP-14 in thrombus formation (Villeneuve et al., 2009; Mastenbroek et al., 2015). Likewise, MMP-3 is stored into neurosecretory granules from the magnocellular neurons dendrites localized in the arginine vasopressin (AVP)-positive cells of the supraoptic nucleus and in the magnocellular neurons terminals in the AVP-positive cells from the neurohypophysis (Miyata et al., 2005). Although MMP-3 function is not well understood, this MMP probably participates in the structural plasticity of the hypothalamo-neurohypophysial system in response to physiological changes.

Furthermore, MMPs may enter the cell by clathrin-dependent (MMP-2, MMP-3, MMP-7, MMP-13 and MMP-14) or clathrin-independent (MMP-14) endocytosis (Cauwe and Opdenakker, 2010).

Once MMPs are in the early endosome, they are released from the cargo receptors probably because of the lightly acidic environment of the lumen. Although the manner in which MMPs escape the endosome is not well known, a conformation change due to a pH-dependent or pH-independent mechanism as is the case for MMP-7, could be implicated (Cauwe and Opdenakker, 2010). When MMPs are internalized they are driven to different cell sites including the cell surface as for instance MMP-14 active form (Cauwe and Opdenakker, 2010). This explains why MMP-7 and MMP-9 have been identified at the cytosol of cells from temporomandibular joint disk with internal derangement (Loreto et al., 2013). Likewise, a rise in cytosolic MMP-9 activity was detected in satellite cells/myoblasts during muscle fiber adaptation to exercise while cytosolic MMP-3 participation in apoptosis was demonstrated in dopaminergic cells (Yeghiazaryan et al., 2012; Choi et al., 2008).

On the other hand, there is evidence of the nuclear localization of several MMPs although their function is not well understood (Mannello and Medda, 2012). For example, MMP-2 has been observed in cardiac myocytes' nucleus associated with Poly ADP-ribose polymerase (PARP) degradation (Kwan et al., 2004). MMP-2 was also identified in apoptotic pulmonary artery endothelial cells' nucleus after cigarette smoke exposure (Aldonyte et al., 2009). Similarly, MMP-3 with a transcription factor-like function was found in the chondrocyte nucleus (Eguchi et al., 2008). The presence of MMP-13 was also corroborated in glucose and oxygen deprived neuronal nuclei (Cuadrado et al., 2009). Moreover, MMP-2 and MMP-14 have been observed in hepatocellular carcinoma cell nuclei, and an association among carcinoma aggressiveness and poor prognosis has been established with the nuclear presence of MMP-14 (Ip et al., 2007).

MMPs have also been localized in the mitochondria. MMP-1 has been identified in mitochondria clusters around the nucleus and nuclear fragments during apoptosis, implying a probable function in the regulation of laminin A/C degradation, caspases activation and DNA fragmentation in human Muller glia cells (Limb et al., 2005). MMP-1 has been co-localized in mitochondria from Tenon's fibroblasts, retinal pigment epithelial cells and corneal fibroblasts (Limb et al., 2005). MMP-2 is present in cardiomyocyte mitochondria during acute myocardial dysfunction after ischemia reperfusion injury. It is associated with mitochondria damage characterized by disturbed mitochondria respiration and excessive lipid peroxidation (Wang et al., 2002; Zhou et al., 2007). MMP-2 was identified in mitochondria from retinal endothelial cells; high levels of glucose concentrations provoked MMP-2 activation with a decrease of mitochondria heat shock protein-60 (Hsp60) and connexin-43, damage of mitochondrial transport pores and Bcl-2 associated X (Bax) increased levels, conditions that favored apoptosis (Mohammad and Kowluru, 2011). MMP-9 was observed in cardiac myocyte mitochondria (Moshal et al., 2008). High homocysteine concentrations increased MMP-9 activity with mitochondrial cristae disruption and sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) pump destruction with a decrease in calcium transit that resulted in contractile dysfunction (Moshal et al., 2008; Vacek et al., 2011). Besides MMPs localization at mitochondria in cardiac myocytes, MMP-2 has also been identified at sarcomere structures associated to troponin-1 (Tn1) (Wang et al., 2002; Ali et al., 2011). This MMP is responsible for Tn1 degradation during cardiac injury (Wang et al., 2002). MMP-2 was also observed in type II fast twitch skeletal muscle fibers and its expression and enzymatic activity decreased with physical exercise (Hadler-Olsen et al., 2015).

2.2.3. MMPs zymogen forms activation

Except for MMP-23, MMPs are generated as inactive proenzymes. Their pro-peptide domain is about 80 amino acids long and has a "cysteine switch" localized in an amino acid conserved sequence between Pro100 and Asp106 (PRCGXPD), that maintains the latent form through its interaction with a zinc ion from the catalytic domain which is tetrahedrally coordinated by three conserved histidines (His147, His162, and His175), and monodentately by aspartate (Asp149) forming a structure like a sphere with a diameter of ~40 Å that prevents substrate binding (Tallant et al., 2010). Partial activation of the pro-enzyme occurs when the cysteine residue is pulled out by a conformational change of the pro-peptide with the subsequent disruption of the cysteine switch. This change in the pro-peptide conformation could be due to 3 different circumstances: (1) removal of the pro-peptide by plasmin, an important physiologic activator, trypsin and other MMPs as for instance MMP-3 and MMP-14; (2) allosteric activation without involving proteolytic cleavage of the pro-domain that occurs when substrate binds to recognition sites outside the catalytic cleft (exosites) as might happen with pro-MMP-2 and pro-MMP-9 binding to gelatin or collagens IV and VI, or pro-MMP-7 interacting with the transmembrane tetraspanin CD151; and (3) chemical modification with disruption of thiol-zinc interaction caused by reactive oxygen species (ROS), peroxynitrite, glutathione, mercurial compounds, and sodium dodecyl sulfate (SDS) (Loffek et al., 2011).

Once the MMP is partially active, it autocatalytically removes its pro-peptide obtaining full enzymatic activity (Loffek et al., 2011; Kim and Joh, 2012; Tallant et al., 2010). Noteworthy, the catalytic domain requires 2 or 3 calcium ions for its proper enzymatic activity.

Activation also occurs in some MMPs and in all the MT-MMPs with a furin recognition site (RX[KR]R) localized next to the catalytic region (Fig. 1). Furin recognition site participates in the intracellular enzymatic activation by *trans*-Golgi-associated Kex-2/furin-like convertase that leads to catalytic activation before MMPs reach their final destination in the secretory granules or the cell surface (Osenkowski et al., 2004).

On the other hand, some pro-MMPs form complexes for their activation. Pro-MMP-2 for instance, is activated by forming the pro-MMP-2/TIMP-2/MMP-14 complex on the cell surface in a 1:1:1 stoichiometric ratio (see below) (Ra and Parks, 2007). Pro-MMP-9 requires as well the formation of an activation complex with TIMP-1 and MMP-3 in which MMP-3 must be in a concentration that provokes TIMP-1 saturation to obtain full MMP-9 activation (Ogata et al., 1995).

2.2.4. Enzymatic inhibition

Active MMPs must be closely regulated since an excess in enzymatic activity may provoke pathological states related to dysregulated cell growth, inflammation, increase in cell migration and uncontrolled ECM degradation. MMPs enzymatic activity is controlled by two groups of endogenous inhibitors: α2-macrogobulin (α2M) and the tissue inhibitors of metalloproteinases (TIMPs). The α2M is a 725 kDa tetrameric glycoprotein non-specific proteinase inhibitor present in body fluids particularly in inflammation sites (Nagase et al., 1994). Its 4 subunits each of 185 kDa, form pairs connected by disulfide bonds and the complete α2M molecule is stabilized by noncovalent links. An intrachain β-cysteinyl-γ-glutamyl thioester is also present. The α2M is responsible of 95% of the anti-collagenase activity in plasma (Nagase et al., 1994). Its inhibitory function starts with the target active protease proteolytic attack to a local site known as bait region present in each α2M subunit, causing the exposition of the thioester bond of the intrachain β-cysteinyl-γ-glutamyl that is in turn subjected to a nucleophilic attack by the same protease, favoring the covalent binding of a considerable part of the enzyme to the α2M. The trapped protease can degrade small molecules but is unable of hydrolyzing large protein substrates.

While α2M is the main regulator of proteases' activity including MMPs in body fluids, TIMPs are the specific regulators of MMPs enzymatic activity in tissues. The TIMP molecule consists of about 190 amino acids with an N-terminal domain (around 125 residues long) and a C-terminal region (65 residues long), each of them stabilized by 3 disulfide bonds (Lambert et al., 2004). The N-terminal domain carries out the inhibitory activity by chelating the MMPs catalytic Zn^{2+} and forming tight noncovalent 1:1 stoichiometric complexes that are unaffected by proteolytic degradation and heat denaturation (Lambert et al., 2004). Amino acid residues next to Cys1-Cys70 disulfide bond at the N-terminal region are important for enzyme inhibition. The C-terminal domain participates in the complex formation with pro-MMPs (see below) (Baker et al., 2002; Brew and Nagase, 2010). Currently, four TIMP molecules have been characterized in mammalian tissues (Table 2). TIMP-1, a soluble glycoprotein, inhibits the enzymatic activity of almost all MMPs except for the MT-MMPs and MMP-19. This inhibitor can be found in association with pro-MMP-9. TIMP-2 is a soluble protein which has the highest affinity for pro-MMP-2 and when this MMP is in the active form, TIMP-2 can block its enzymatic activity. TIMP-3 is a partially glycosylated protein tightly bound to the ECM capable of inhibiting all MMPs including the MT-MMPs and can be associated with pro-MMP-9. TIMP-4 is also a soluble protein capable of inhibiting most MMPs and to form complexes with pro-MMP-2.

Besides inhibiting MMPs, TIMPs also abate the enzymatic activity of some ADAMs and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTs). ADAMs are enzymes coupled to the cell membrane with a desintegrin, EGF-like, cysteine rich, and transmembrane C-terminal domains, while ADAMTs are secreted proteins with desintegrin regions and thrombospondin type I motifs. From the TIMP family, only TIMP-3 is able to inhibit several ADAMs and ADAMTs (see Table 2).

Regarding TIMP-2, it builds a complex with pro-MMP-2 and MMP-14, a MT-MMP, for zymogen activation. The TIMP-2 C-terminal extreme binds to the pro-MMP-2 hemopexin region while the catalytic site of MMP-14 interacts with the TIMP-2 N-terminal domain forming a cell membrane ternary complex. The pro-enzyme requires a second MMP-14 molecule for its partial activation and MMP-2 full activity is obtained then by autocatalysis of the pro-peptide (Baker et al., 2002). Another ternary activation complex is formed among TIMP-1, pro-MMP-9, and MMP-3 (Ogata et al., 1995). The function of the association of TIMP-3 with pro-MMP-2 or pro-MMP-9, and TIMP-4 with pro-MMP-2 is unclear.

TIMPs have diverse biological roles that seems to differ from their enzyme inhibitory capacity. They are able to regulate cell proliferation, apoptosis, angiogenesis, tumorigenesis and metastasis. Promotion or inhibition of these events depends of the cell type, the TIMP molecule and their concentration (Stetler-Stevenson, 2008).

3. The metastatic journey

The metastatic cascade comprises a series of complex consecutive biological events that start with tumor cells achievement of metastatic abilities within the primary tumor microenvironment (TME) that allow them to detach from the primary tumor and establish new colonies in a suitable distant location (Fig. 2). Briefly, in the primary tumor

Table 2
General features of tissue inhibitors of metalloproteinases (TIMPs).

Feature	TIMP-1	TIMP-2	TIMP-3	TIMP-4
MW (kDa)	28	21	24/27	22
Amino acid residues	184	194	188	194
pI	8.47	6.48	9.14	7.21
Chromosomal localization	X11p11.3-11.4	17q23-25	22q12.1-q13.2	3p25
N-glycosylation sites	2	0	1	0
Protein expression	inducible	constitutive	inducible	inducible
Localization	soluble/cell surface	soluble/cell surface	ECM/cell surface	soluble/cell surface
MMPs poorly inhibited	MMP-14, MMP-15, MMP-16, MMP-19, MMP-24	none	none	none
Pro-MMP interaction	pro-MMP-9	pro-MMP-2	pro-MMP-2/-9	pro-MMP-2
ADAMS inhibition	ADAM-10	ADAM-12	ADAM-10, ADAM-12, ADAM-17, ADAM-19, ADAM-28, ADAM-33	ADAM-17, ADAM-28, ADAM-33
ADAMTS inhibition	None	none	ADAMTS-1, ADAMTS-2, ADAMTS-4, ADAMTS-5	none
Other interactions	CD63, LRP-1/MMP-9 complex	$\alpha_3\beta_1$ integrin, LRP1	EFEMP1, VEFR2, AGTR1	not known
Apoptotic effects in cancer cells	↓ Burkitt's lymphoma	↑ colorectal cancer ↓ melanoma	↑ tumor cells ↓ melanoma	not known
Cancer cells proliferation	↑	↑	↑	↑mammary ↓ Wilm's tumor cells
Tumor Angiogenesis	↑ mammary ↓ liver	↓melanoma ↓mammary	↓ melanoma	not known
Tumorigenesis	inhibits	inhibits	inhibits	inhibits
Metastasis	stimulates	not known	not known	stimulates

ADAMS, a desintegrin and metalloproteinase; ADAMTS, ADAM with thrombospondin motifs; AGTR1, type I angiotensin-II receptor; EFEMP1, epidermal growth factor-containing fibulin-like extracellular matrix protein 1; LRP1, LDL.

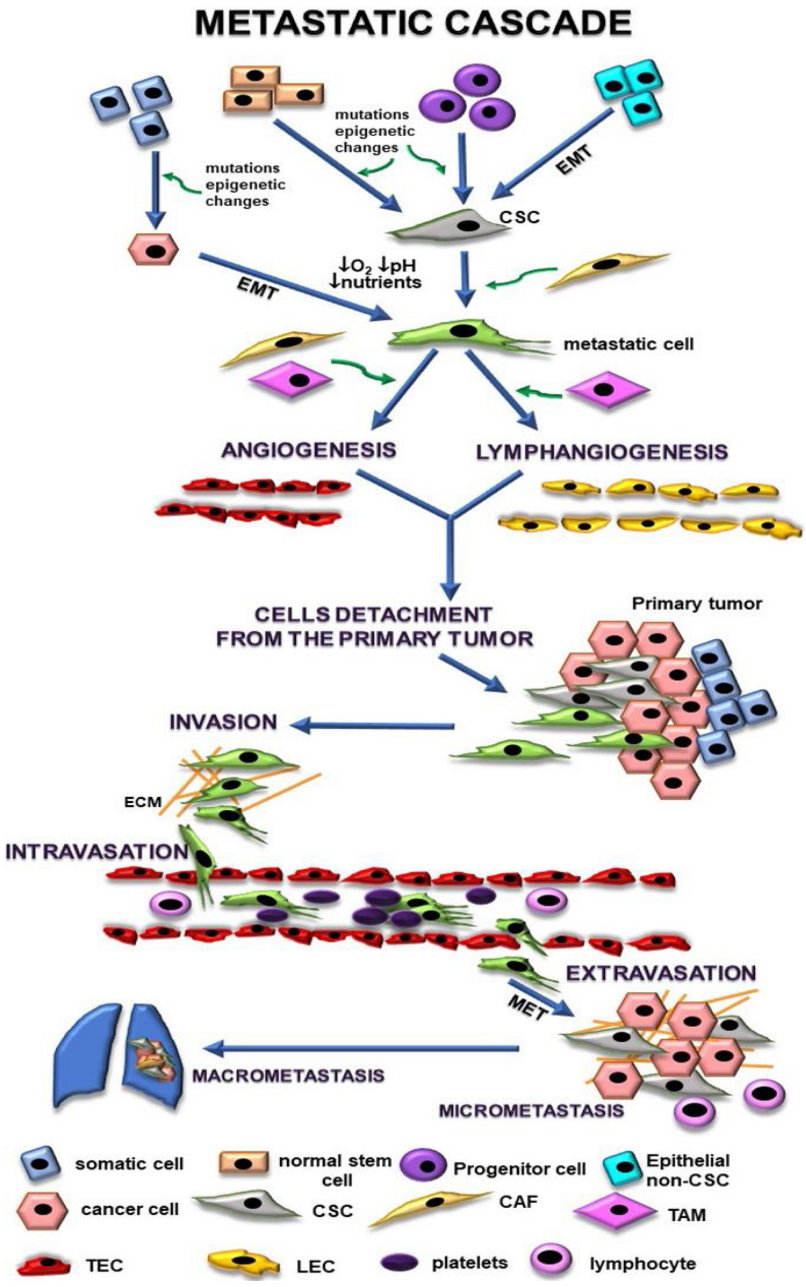

Fig. 2. The metastatic cascade. Neoplastic cells might originate from somatic cells or from CSCs derived from normal stem cells, progenitor cells or from non-stem epithelial cells. Once the primary tumor microenvironment (TME) conditions change (↓O_2, ↓ pH, ↓nutrients), neoplastic cells acquire mesenchymal cell characteristics through the EMT process. These characteristics include the induction of angiogenesis and lymphangiogenesis. Metastatic cells detach from the primary tumor and migrate (invasion) until they reach a blood or lymphatic vessel and penetrate across the vessel wall (intravasation). To survive the blood stream shear stress and avoid the immune surveillance, circulating tumor cells (CTC) form cell aggregates with platelets. Cancer cells alone or in clusters are arrested in a capillary bed in a distant organ, exit the circulation (extravasation) and invade the new tissue. In the new metastatic niche, neoplastic cells can be destroyed by the immune system, enter dormancy or adapt to the new microenvironment. In the last case, they might proliferate and establish a clinically undetectable micrometastasis that, after a while and under proper conditions, might grow and develop a macrometastasis. CAF, cancer associated fibroblast; CSC, cancer stem cell; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; LEC, lymphatic endothelial cell; MET, mesenchymal-epithelial transition; TAM, tumor associated macrophage; TEC, tumor endothelial cell.

neoplastic cells under microenvironment stress factors such as hypoxia, acidity and inflammatory cytokines, change from epithelial well differentiated cells to undifferentiated mesenchymal-like cells with migration capacities. This process known as epithelial-mesenchymal transition (EMT) allows cells to invade the surrounding tissue to reach the circulatory or lymphatic systems (Taddei et al., 2013). Cancer cells can also induce the generation of new blood or lymphatic vessels in the primary tumor, events called angiogenesis and lymphangiogenesis, respectively. Afterwards, metastatic cells cross the vascular wall (intravasation) and circulate within the blood or lymphatic stream where they need to surmount the circulation stress and evade the immune response until they are arrested in a distant capillary bed (Shibue and Weinberg, 2011). At this point, cells invade the vascular endothelium (extravasation) and migrate into the new organ in which cancer cells change from mesenchymal to the epithelial phenotype (MET), and, depending of the metastatic niche conditions, they remain dormant or proliferate establishing a metastatic colony.

MMPs actively participate in the whole metastatic journey as a consequence of their biological functions including their capacity to degrade ECM components and their ability to interact and regulate different growth factors, cytokines and chemokines.

4. Tumor cell heterogeneity

Not all neoplastic cells in a primary tumor have the same metastatic capacities.

Solid tumor cells comprise a heterogeneous cell population with differences in cell phenotype, grade of differentiation, expression of specific markers and metastatic ability (Gerdes et al., 2014). There are three theories that explain the origin of cancer cell heterogeneity. The first theory is the clonal evolution or stochastic model that considers the evolution of cancer cells like a Darwinian system based in clonal diversification and natural adaptive selection (Greaves and Maley, 2012; Marjanovic et al., 2013). In this model, somatic cells under the microenvironment pressure accumulate a series of mutations and epigenetic changes that produce cancer cell sub-clones that generate further

diversification into cancer metastatic or cancer recurrence sub-clones, or end-point sub-clones that are not able to resist competition for space and resources in the TME.

The hierarchical or cancer stem cells (CSCs) theory suggests that some cells (normal stem cells) with pluripotent capacity maintain their dedifferentiated features as they do during normal development. CSCs might derive from normal stem cells lacking cell proliferation control due to accumulative mutations or epigenetic alterations that affect oncogenes and tumor suppressor genes (O'Flaherty et al., 2012; D'Andrea et al., 2014). This model also proposes a cell hierarchical organization in which CSCs with the most tumorigenic and metastatic potential reside at the top. The CSCs might possess self-renewal capacities and generate identical cell progenies or under asymmetric division create cells with less aggressive phenotype or terminal differentiated cells.

Finally, the CSCs dynamic model postulates that non-stem cancer cells under the influence of TME conditions are able to differentiate in CSCs (Hernández-Camarero et al., 2018). In this context, CAFs and mesenchymal stem cells (MSCs) release factors as for instance IL-6, TGFβ1 and hepatocyte growth factor (HGF) and secrete exosomes containing microRNA such as miR221, that stimulate non-stem neoplastic cells to undergo EMT with the acquisition of CSCs characteristics (Hernández-Camarero et al., 2018). Interestingly, it has been suggested that cancer cells located at the tumor edges are subjected to this process during later stages of development.

Other mechanisms involved in CSCs origin have been described (Nimmakayala et al., 2018). For example, cell fusion among stem cells and somatic differentiated cancer cells producing a hybrid with CSCs or tumor-initiating cells' characteristics (Nimmakayala et al., 2018; Wang et al., 2016). Likewise, the horizontal gene transfer mechanism where a cancer cell internalizes fragmented DNA through phagocytosis or endocytosis from a mutated somatic cell that underwent apoptosis, producing a tumor cell with CSC behavior. As well, changes in metabolic conditions in the TME from oxidative phosphorylation to glycolysis, particularly in hypoxic conditions, provoke nuclear reprogramming that transforms somatic cells into pluripotent stem like cells (Folmes et al., 2011).

Similarly, CSCs can spontaneously arise from normal epithelial non-CSCs that undergo EMT cell program. CSCs generated in this way acquire essential features for cell detachment and migration from the primary tumor. Once cells go through the metastatic cascade and arrive to a distant organ, the CSCs regain their epithelial characteristics through a MET (Chang and Mani, 2013; Jolly et al., 2014).

In summary, tumors contain a heterogeneity population of CSCs subtypes each with different characteristics such as self-renewal and differentiation potential, anchorage independent growth, dormant or slow cycling behavior, resistance to apoptosis, promotion of angiogenesis and lymphangiogenesis, and resistance to conventional chemotherapy and radiotherapy (Liao et al., 2014; Li and Li, 2014). The CSCs are considered responsible for neoplasia development, initiation of metastasis and tumor recurrence; therefore, their cell nature has been associated with tumor aggressiveness and metastatic behavior.

5. Tumor microenvironment

In normal tissue, a mutual communication between the epithelial cells and the adjacent stromal cells is constantly taking place. This crosstalk is mediated by direct cell-cell contact or by soluble molecules as for example chemokines, growth factors and cytokines that maintain the tissue homeostasis. This epithelial-stroma interaction is disturbed at the early stages of the neoplastic lesion. Neoplastic cells synthesize and secrete enzymes as for instance MMP-1, MMP-2 and MMP-9 that degrade the surrounding ECM and BM. Tumor cells also produce growth factors and cytokines such as TGFβ1, TGFβ2, PDGF, FGF2, IL-1β, monocyte-chemotactic protein 1, and IL-6 that recruit and transform stromal cells such as fibroblast and macrophages (Räsänen and Vaheri, 2010; Bremnes et al., 2011; Petrella and Vincenti, 2012). The tumor associated macrophages (TAMs), adipose cells, endothelial cells, the activated CAFs, pericytes, neuroendocrine cells, the ECM and BM, deposited growth factors and signaling molecules are part of the TME that allow the evolution of the tumor (Whipple, 2015; Chen et al., 2015). Among the cells that constitute the TME, CAFs play an important role in cancer progression. CAFs derive from several cell types: resident fibroblasts via mesenchymal-mesenchymal transition (MMT), endothelial cells via endothelial-mesenchymal transition (endMT), epithelial cells via EMT, adipocytes, bone marrow originated from hematopoietic stem cells and bone marrow derived from mesenchymal stem cells (Shiga et al., 2015). Fibroblasts activation by cancer cells has been proposed to occur in a three-step sequence: (1) Fibroblast recruitment; (2) transformation from normal cells to CAFs; and (3) persistence of CAFs in the TME (Heneberg, 2016). Once CAFs are activated they release several signaling molecules to stimulate cancer cells and other cell types from the TME (Heneberg, 2016). Likewise, CAFs participate in the remodeling of the ECM secreting collagen and fibronectin, producing MMPs such as MMP-1, MMP-3, MMP-7, MMP-9 and MMP-13 that release factors as for instance VEGF from the ECM, and contract the matrix, forming tracks in which neoplastic cell migrate together with CAFs (Räsänen and Vaheri, 2010; Gaggioli et al., 2007; Eck et al., 2009; Yamaguchi and Sakai, 2015). Noteworthy, CAFs also contribute to tumor cells directional migration by organizing fibronectin fibers (Erdogan et al., 2017). Briefly, CAFs have an increase in vinculin that serves as a link between actin from cytoskeleton and non-muscle myosin II (Myo II) inside the cell. This interaction allows an augmented traction force with fibronectin through its binding to integrin $\alpha_5\beta_1$ and $\alpha_V\beta_3$ that also show higher expression in CAFs. (Erdogan et al., 2017; Attieh et al., 2017). Likewise, PDGF receptor α (PDGFRα) is overexpressed in CAFs. This molecule is involved in fibronectin fibers alignment (Erdogan et al., 2017). Fibronectin is also upregulated in cancer cells, playing a relevant role in tumor cells' proliferation and migration in the TME (Wang and Hielscher, 2017). Regardless of the cell origin, binding of fibronectin to integrin $\alpha_5\beta_1$ provokes the phosphorylation of focal adhesion kinase (FAK) which in turn activates Src (Wang and Hielscher, 2017; Meng et al., 2009). FAK and Src are required for Akt, extracellular signal-regulated kinase1/2 (ERK1/2) and PI3K phosphorylation that are involved in cell migration. Furthermore, ERK1/2 induce the expression of MMP-9 that is implicated in several steps of the metastatic process (see below), and of calpain-2 that regulates "focal adhesion dynamics" (Meng et al., 2009). Likewise, Akt/PI3K participates in the upregulation of MMP-9 and Ras homolog gene member A (RhoA) that mediates cell contraction and retraction forces (Meng et al., 2009).

Meanwhile, macrophages are recruited to the tumor by chemokines released from cancer and stromal cells. Two types of TAMs are present in TME with opposite functions: TAMs M1 with tumoricidal and immunostimulatory activities due to interferon (IFN)-γ and IL-12, and TAMs M2 that possess immunosuppressive functions through IL-10, stimulate angiogenesis and induce tumor cells MMP-1, MMP-3, MMP-10 and MMP-14 expression favoring cancer progression (Whipple, 2015; Singh et al., 2017).

Additionally, there is an accumulation of myeloid derived suppressor cells (MDSCs) in the TME. Local concentrations of growth factors and cytokines induce the activation of STAT-3 in MDSCs blocking cell apoptosis, favoring their proliferation and inhibiting their differentiation to mature cell types (Condamine and Gabrilovich, 2011).

MDSCs interfere with T cell functions through different molecular mechanisms as for instance production of peroxynitrites, ROS, TGFβ, IL-10, L-arginine metabolism and depletion of cysteine and cystine (Nagaraj and Gabrilovich, 2010). MDSCs also promote the differentiation of $FoxP3^+$ T cells involved in the blockade of the anti-tumor immune response and stimulation of tumor growth (Singh et al., 2017).

On the other hand, changes in pH, O_2 concentration, small molecules such as nitric oxide, glucose and lactate must be considered as

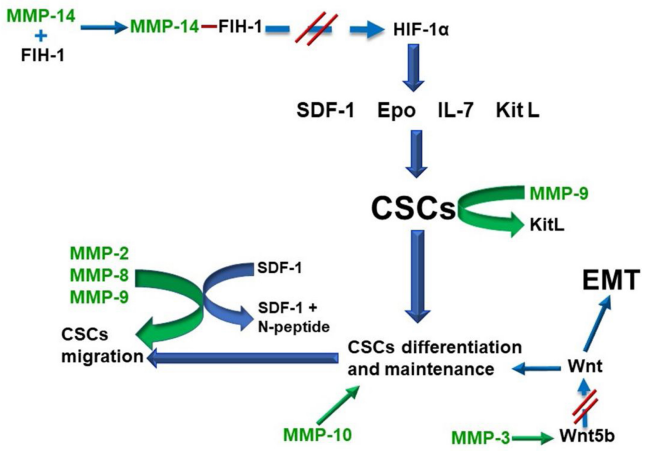

Fig. 3. MMPs in cancer stem cells evolution. Some MMPs are involved in CSCs differentiation, maintenance and migration directly modifying molecules as for instance SDF-1 (MMP-2, MMP-8 and MMP-9) or indirectly, as for example MMP-14 binding to FIH-1, preventing HIF-1α degradation. MMP-3 interaction with Wnt5b activates Wnt canonical pathway that stimulates EMT and also provokes CSCs differentiation and maintenance. CSCs, cancer stem cells; Epo, erythropoietin; FIH-1, factor inhibiting HIF-1; HIF-1α, hypoxia inducible factor-1α; IL-7, interleukin-7; Kit L, kit Ligand; SDF-1, stromal cell derived factor-1.

part of the TME. Regions of low O_2 tension (< 10 mmHg) that affect all the TME have been identified in many solid tumors (Dhani et al., 2015). In order to survive and proliferate, neoplastic cells develop genetic and adaptive changes (Sullivan and Graham, 2007). Hypoxia generates a selective pressure on cancer cells to escape the hostile hypoxic microenvironment. First, cells switch from aerobic to anaerobic glycolysis to maintain metabolic activities with an additional adaptation for energy requirements. This change produces an acidification of the extracellular space which in turn originates an adaptive cell selection for cells resistant to acidic conditions. Then cancer cells synthesize and secrete angiogenic factors for tumor neovascularization, therefore ensuring an adequate O_2 and nutrients supply for cell proliferation and migration.

Hypoxia effects are due at least partially, to hypoxia inducible factors (HIFs) (Lu and Kang, 2010). HIF is a heterodimeric transcription factor that consists of a HIF-1α or HIF-2α and HIF-1β subunits. During normoxic states, Pro-402 and Pro-564 from HIF-α subunit are hydroxylated by HIF-1 prolyl hydroxylases in an O_2 dependent reaction. Hydroxylated HIF-α subunit binds to the von Hippled Lindau (VHL) E_3 ubiquitin ligase complex. This complex attaches ubiquitin to the HIF-α subunit which is then destroyed by the ubiquitin-proteasome system. Under hypoxic conditions, the α subunit is stabilized and can, therefore, be accumulated, translocated to the nucleus and dimerized with the β subunit (Lu and Kang, 2010). With the interaction of the coactivator CBP/p300, HIF induces the transcription of target genes. The binding of HIF to its coactivator is impaired by the factor inhibiting HIF-1 (FIH-1) that, through the hydroxylation of HIF, inhibits the transcription of the target genes (Lu and Kang, 2010).

Target genes have hypoxia responsive elements (HREs) for HIF binding that in most cases correspond to the 5′-RCGTG-3′ sequence. Most target genes have been identified to be regulated by HIF-1α, but others solely by HIF-2α. There are genes stimulated by both HIFs and it has also been pointed out that opposing activities among HIF-1α and HIF-2α exist (Keith et al., 2011). There are more than 40 genes regulated by HIFs and they can be classified in four groups: glycolysis and glucose transporters, survival and proliferation, angiogenesis, and invasion and metastasis genes (Lu and Kang, 2010; Tsai and Wu, 2012).

MMPs expression is very possibly regulated by hypoxia. There is evidence that MMP-1, MMP-2, MMP-3, MMP-7, MMP-9, MMP-10 and MMP-13 expression is increased by hypoxia in different neoplastic cells (Shyu et al., 2007; Fu et al., 2009; Choi et al., 2011; Vinothini et al., 2011). However, some authors have found contrary results. For example, MMP-2 expression is increased in glioma but not in hepatoma cells; MMP-9 synthesis was stimulated in the MDA-MB-231 breast cancer cells but not in glioma neither in hepatoma cells in hypoxic conditions (Choi et al., 2011; Miyoshi et al., 2006; Fujiwara et al., 2007). Moreover, the use of HIF-1α siRNA demonstrated that HIF-1α induces MMP-1, MMP-2, and MMP-3 synthesis (Fujiwara et al., 2007; Lin et al., 2008; Jing et al., 2012). Likewise, not all MMPs are regulated directly by HIF-1α. MMP-1 for instance, requires the chemokine receptor-4 (CXCR4) for its transcription which in turn is regulated by HIF-1α (Sun et al., 2010). The MT-MMPs expression has been also studied at different O_2 concentrations. MMP-14 expression is increased by hypoxia in hepatoma cells but not in breast and oral SCC (Miyoshi et al., 2006; Sun et al., 2010; Muñoz-Nájar et al., 2006). Furthermore, although MMP-14 is not augmented in breast cancer cells under hypoxic conditions, an increase of this MMP can be observed in the plasma membrane of invadopodia projections (Muñoz-Nájar et al., 2006). MMP-15 expression is also increased by hypoxia in pancreatic cancer cells (PANC-1) (Zhu et al., 2011). A HRE sequence for HIF-1α regulation has been identified at the −246 bp promoter site of MMP-15 that allows its direct transcription regulation by HIF. MMP-17 is indirectly regulated by HIF-1α through the induction of Slug (also known as Snail2) expression (Huang et al., 2009a). A Slug binding site has been detected in the proximal promoter (approximately −457 to −462 bp upstream from ATG) of the MMP-17 gene.

6. MMPs and cancer progression

6.1. STEM cells

MMPs are crucial molecules in the TME and their expression is induced at the very beginning of the metastatic process in neoplastic and stromal cells. They can modify ECM components, therefore changing the bioavailability of cytokines and chemokines that determine CSCs behavior (Fig. 3). In this context, studies done in bone marrow hematopoietic stem cells (HSCs) demonstrated that MMP-14 favors HIF-1α transcription genes, particularly stromal cell derived factor-1(SDF-1/CXCL12), erythropoietin (Epo), IL-7 and kit Ligand (kitL) genes which are important in HSCs maintenance and differentiation (Nishida et al., 2012). The molecular mechanism consists in the binding of MMP-14 cytoplasmic tail to FIH-1 blocking its HIF-1α inhibitory function (Sakamoto and Seiki, 2010). Likewise, MMP-9 was found to be increased in bone marrow cell supernatants from MMP-$9^{+/+}$ mice with bone marrow myelosuppression caused by 5-fluorouracile (5-FU) (Heissig et al., 2002). An increase in bone marrow cellularity and in hematopoietic cell clusters was detected in MMP-$9^{+/+}$ mice compared to MMP-$9^{-/-}$ animals in which a shortage of hematopoietic cell clusters in the vascular and osteoblastic zones after 6 days of 5-FU exposition was seen. MMP-9 seems to provoke the rapid release of kitL from the HSCs membrane promoting their differentiation (Heissig et al., 2002). Moreover, MMP-9 has the capacity to cleave the SDF-1 N-terminal region contributing to the binding of this molecule to its CXCR4 receptor allowing cells to migrate to sites containing high concentrations of SDF-1 such as LNs, lungs and bones (Klein et al., 2015; Janowski, 2009). MMP-9 ability to inactivate SDF-1 is shared by MMP-2 and MMP-8 (McQuibban et al., 2001; Steinl et al., 2013). Another MMP involved in stem cell regulation is MMP-3. Its hemopexin domain binds and inactivates Wnt5b, a ligand that inhibits the canonical Wnt signaling, consequently increasing stem cell expansion and leading to mammary stem cells maintenance (Kessenbrock et al., 2015). On the other hand, MMP-10 was observed to be overexpressed in human Kras transformed bronchioloalveolar stem cells (BSCs) participating in tumorigenesis and invasion (Justilien et al., 2012). This MMP has an important role in maintaining CSCs identity supporting their autonomous growth. Experiments with MMP-$10^{-/-}$ BSCs growing as oncospheres, showed that they lost their stem cells markers including

Table 3
Epithelial and mesenchymal cell markers in cancer EMT.

Epithelial markers	Mesenchymal markers
cdx2	β-catenin (nuclear)
Claudin-1	Collagen type I and III
Cytokeratin (CK-8, CK-18, CK19)	Fibronectin
Desmoplakin	FSPI/S100A4
E-cadherin	Integrins $\alpha_V\beta_6$, $\alpha_5\beta_1$
Mucin-1	MMPs (MMP-2, MMP-3, MMP-9)
Occludin	N-cadherin
ZO-1	Slug
	Snail
	αSMA
	Tenascin C
	TGFβ
	Thrombospondin
	Twist
	Vimentin
	Vitronectin
	ZEB1, ZEB2

cdx2, Caudal type homeobox 2; FSP1/S100A4, fibroblast specific protein 1; MMPs, matrix metalloproteinases; TGFβ, transforming growth factor-β; ZEB1/2, zinc finger E-box-binding homeobox 1/2; αSMA, smooth muscle actin; ZO-1, zonula occludens-1.

Nanong, aldehyde dehydrogenase-1 (Aldh1), CD133, Hairy/Enhancer-Of-Split related with YRPW Motif 1(Hey1) and Hey2 genes with a decrease of clonal expansion. The stem cells markers and the BSCs growth were restored with the addition of exogenous MMP-10, but the exact molecular mechanisms on how MMP-10 regulates CSCs proliferation is still unknown (Justilien et al., 2012).

6.2. EMT

As it was discussed earlier, some normal epithelial non-CSCs acquire CSCs' features through EMT process. EMT is associated with the dedifferentiation program through which cells no longer sustain cell to cell and cell-ECM interactions, modify their cytoskeletal structure and composition, lose their apico-basal and planar polarity and acquire mesenchymal cell characteristics required for cell motility and invasion (Yu and Elble, 2016). Some molecular epithelial and mesenchymal markers that carry out modified expression during EMT are shown in Table 3.

On the other hand, it is not clear yet how EMT induction factors work, but it is possible that TME conditions such as hypoxia allow cells to escape to a better microenvironment by undergoing transient EMT (Jung et al., 2015). An essential step during EMT program is the loss of E-cadherin expression (Brooks et al., 2010). E-cadherin is a transmembrane glycoprotein with a large extracellular domain that forms E-cadherin dimers that act upon another E-cadherin dimer from a neighboring cell forming cell-cell adherent junctions. Its cytoplasmic domain interacts with a protein complex containing α-, β-, and γ-catenins linked to actin filaments from the cytoskeleton (Voulgari and Pintzas, 2009). These interactions allow E-cadherin to participate in a series of signaling pathways that maintain epithelial cell polarity, adhesion and immobility (Guarino, 2007). Transcriptional factors such as Slug, Snail (also known as Snail1), E47, Twist, zinc finger E-box-binding homeobox 1 (ZEB1), ZEB2, and Krüppler-like factor 8 (KLF8) bind to E-cadherin consensus E-boxes (5′-CACCTG-3′ and 5′-CAGGTG-3′) inhibit E-cadherin transcription with the promotion of EMT (Díaz et al., 2014). The activity of these transcription repressors is regulated by cytokines and growth factors as for instance TNF-α, TGFβ and HGF that relate with other signaling pathways like Wnt, Notch and β-catenin (Huber et al., 2005). Particularly Wnt signals can be transduced by 2 different pathways, the canonical Wnt/β-catenin and the non-canonical Wnt pathway (Sherwood, 2015). In the former, Wnt signaling prevents β-catenin degradation trough the ubiquitin degradation system

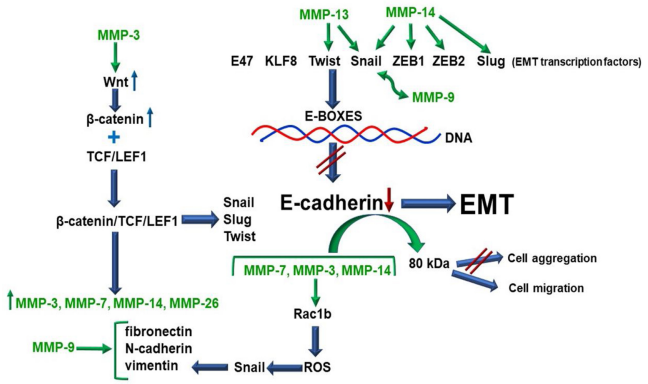

Fig. 4. MMPs role in EMT. The inhibition of E-cadherin synthesis as well as the disruption of its structure are key steps in the induction of EMT. MMPs are involved directly or indirectly through the Wnt/β-catenin signal pathway or ROS production in the upregulation of EMT transcription factors that block E-cadherin expression. MMPs as for instance MMP-3, MMP-7 and MMP-14 also disrupt E-cadherin at the cell surface releasing a fraction of the molecule that blocks E-cadherin functions in a paracrine manner. Likewise, neoplastic cells acquire mesenchymal markers as for example fibronectin, vimentin, N-cadherin and are able to synthesize collagens I and III, and several MMPs. ROS, reactive oxygen species.

destabilizing the axin-adenomatosis polyposis coli (APC) destruction complex comprised by glycogen synthase kinase 3β (GSK 3β), axin, APC, and casein kinase Iα (CKIα) (Sherwood, 2015). The disruption in β-catenin degradation provokes an increase in its cytoplasmic concentrations, saturating all binding sites that induce its translocation into the nucleus. There, it associates with the T-cell factor/Lymphoid enhancer factor1 (TCF/LEF1) promoting the expression of Wnt target genes *c-myc*, MMP-3, MMP-7, MMP-14 and MMP-26, and the upregulation of Slug, Snail and Twist involved in the induction of EMT (Fig. 4) (Blavier et al., 2010). In turn, the non-canonical Wnt pathway comprises the Wnt/Ca^{2+} or the Wnt/planar cell polarity; in the first case, Wnt signals are transduced through intracellular Ca^{2+} and in the second by small GTPases that regulate cytoskeletal remodeling (Sherwood, 2015).

There is evidence that MMPs are implicated in EMT induction (Fig. 4). MMP-3 and MMP-7 directly cut off the E-cadherin ectodomain releasing an 80 kDa fragment involved in the inhibition of epithelial cell aggregation and cell invasion induction in a paracrine manner (Noë et al., 2001). MMP-3 also participates in the regulation of the Wnt pathway (Blavier et al., 2010). MMP-3 together with Wnt3a contribute to Wnt-induced EMT enhancing Wnt-mediated signaling and β-catenin transcriptional activity, effects that are reversed by the use of the MMPs activity inhibitor AG3340 and by MMP-3 siRNA transfection (Blavier et al., 2010). Moreover, mammary epithelial cells incubated with MMP-3 express an alternatively spliced form of Rho-related C3 botulinum toxin substrate (Rac1) designated as Rac1b (Radisky et al., 2005). Rac1b induced the production and release of ROS from the mitochondria into the cytoplasm; in this context, the superoxide anion upregulates Snail expression with concomitant decrease in E-cadherin transcription and an increase in mesenchymal vimentin expression. MMP-9 also facilitates EMT by the induction of vimentin, fibronectin and N-cadherin expression (Lin et al., 2011). A feedback-loop between MMP-9 and Snail has also been identified. Snail siRNA knockdown resulted in a decrease of MMP-9 and mesenchymal markers expression; MMP-9 siRNA knockdown reduced the expression of Snail, too. The participation of MMP-14 in EMT has also been studied. Knocking down endogenous MMP-14 expression decreased the expression of vimentin, Snail, Slug and ZEB1 genes (EMT markers) with the increase of E-cadherin and zonula occludens-1 (ZO-1) (epithelial markers) in gastric cancer cells (Li et al., 2015b). Moreover, studies done in MMP-14 transfected human oral squamous cell carcinoma cells (SCC9)

demonstrated an increase in mesenchymal markers such as fibronectin and vimentin, and a down regulation of the epithelial markers E-cadherin and cytokeratin-18 (CK-18) toward the up-regulation of Twist, ZEB1 and ZEB2 gene expression (Yang et al., 2013). Likewise, MMP-14 has been implicated in the up-regulation of Wnt5a which initiates the Wnt/Ca^{2+} pathway with the induction of EMT and it is also able to shed the E-cadherin ectodomain from cell-cell junctions (Cao et al., 2008). MMP-13 also participates in the induction of EMT. Experiments done in cells from oral SSC showed that the MMP-13 knockdown with siRNA decreased vimentin, Twist and Snail expression and increased E-cadherin synthesis (Huang et al., 2016).

6.3. Anoikis resistance

Once neoplastic cells undergoing EMT detach from the ECM, they develop mechanisms that confer them anoikis resistance to survive during the next metastatic steps. Anoikis is a programmed cell death that occurs when cells lose contact with the ECM and/or they neighboring cells and prevents detached cells re-adhesion to new matrixes in incorrect tissues and their dysplastic growth (Simpson et al., 2008). Anoikis is induced through the activation of the TNF receptor superfamily of death receptors (extrinsic) and the mitochondrial (intrinsic) apoptosis pathways. EMT and anoikis resistance are associated processes (Kim et al., 2012; Frisch et al., 2013). The E-cadherin/N-cadherin switch produced during EMT generates anoikis resistance. Moreover, the loss of E-cadherin increases Twist expression inducing the synthesis of the anti-apoptotic protein B-cell lymphoma-2 (Bcl-2). Likewise, Snail downregulates the expression of the pro-apoptotic proteins BH3 interacting-domain death agonist (Bid), caspase 6 and phosphatase and tensin homolog (PTEN). The decrease in PTEN expression favors PI3K/Akt pathway activation that promotes phosphorylation and inhibition of the pro-apoptotic protein Bcl-2-associated death promoter (Bad). Furthermore, the decrease in E-cadherin and semaphorin 3F and the increase of vimentin expression induced by ZEB-1 activate the Akt pathway. These are just some interactions among anoikis and EMT (for more details see Frisch SM et al.) (Frisch et al., 2013). Besides undergoing EMT, neoplastic cells can obtain anoikis resistance by changes in integrin molecules, activation of inside-out pro-survival signals, oncogene activation, growth factors receptor overexpression and TME conditions such as hypoxia (Paoli et al., 2013). Cell detachment from ECM or modifications of ECM components induce anoikis as well. Altered fibronectin provokes a switching between α_4 integrin and the anoikis receptor nerve-glial antigen 2 (NG2) in the cell membrane (Joo et al., 2008). NG2 is a transmembrane proteoglycan that induces anoikis via downregulation of protein kinase Cα (PKCα) involved in FAK phosphorylation. The α_4 integrin also enhances FAK phosphorylation independently of PKCα. Activated FAK protects cells from apoptosis. FAK reduces caspase 3 activation and also participates in the regulation of ZEB1, ZEB2, Snail and Twist. FAK also promotes MMP-14 expression that requires the activity of MAPK and PI3K (Frisch et al., 2013; Yoon et al., 2015).

MMPs such as MMP-2, MMP-3, MMP-7, MMP-9 and MMP-11 participation in apoptotic processes is paradoxical since they have both pro- and anti-apoptotic capacities and their direct contribution to anoikis resistance is not well understood (Mannello et al., 2005). MMP-7 for example, has the ability to cleave Fas ligand (FasL) from the cell surface disturbing the initiation of the extrinsic apoptosis pathway (Vargo-Gogola et al., 2002; Wang et al., 2006). Likewise, MMP-11 increases anoikis resistance in lobular carcinoma breast cells although the molecular mechanism is unknown (Takeuchi et al., 2011). Similarly, MMP-13 has been involved in the cleavage of the NG2 extracellular domain regulating the anoikis process (Joo et al., 2014).

6.4. Angiogenesis

Tumor growth implicates the generation of new blood vessels either by vasculogenesis that consists on the creation of new vessels de novo from precursors of endothelial cells (ECs) such as circulating bone marrow progenitor cells, or by angiogenesis that implies the creation of new capillaries from the preexisting vasculature (Carmeliet and Jain, 2011; Liu et al., 2012). In this context, the new vessels may arise directly from the tumor cells through: (1) vascular co-option, in which tumor cells mesh with ECs from pre-existing vessels forming a mosaic vessel; (2) vasculogenic mimicry, that occurs when tumor cells mimic ECs and develop non-endothelial lined blood vessels; and (3) transdifferentiation of CSCs or progenitor cells in vascular ECs. Likewise, tumor cells may stimulate new vessels formation by: (1) sprouting, that comprises the development of new vessels from pre-exiting blood vessels under the stimulation of growth factors such as VEGF; (2) intussusceptive or splitting angiogenesis, which consists in the split of a blood vessel into 2 new vessels with the formation of transvascular pillars induced by angiopoietins, PDGF-B, erythropoietin-producing human hepatocellular B (EphB) receptors and Eph receptor-interacting proteins (Ephrins); and (3) vasculogenesis, in which endothelial vascular wall or bone marrow derived progenitor cells differentiate to ECs (Carmeliet and Jain, 2011; Liu et al., 2012). Interestingly, the glomeruloid, another form of angiogenesis has been reported; it consists of focal aggregates of small vessels that resemble renal glomeruli and is associated with Tp53 mutations and hypoxia (Akslen et al., 2011).

Likewise, independently of the tumor endothelial cells (TECs) origin, these cells differ from the normal ECs. TECs overexpress VEGF receptor (VEGFR), VEGF and EGFR genes, have a major response to VEGF, EGF and adrenomedullin (AM) and are more resistant to serum starvation and to some drugs such as vincristine, 5-FU and adriamycin than normal ECs (Hida et al., 2013; Tsuchiya et al., 2010). Active TECs migrate and assemble to form luminal compartments with the subsequent tube formation, capillary stabilization and maturation by BM deposition and pericytes recruitment, constructing new blood vessels (sprouting angiogenesis) (Fig. 5) (Deryugina and Quigley, 2010; Ucuzian et al., 2010).

Tumor tissue is highly vascularized but the new vessels are unorganized, tortuous, without interconnections between the TECs with a subsequent loss of normal barrier (lack of pericyte cover) that provokes blood leakiness and a chaotic blood flow allowing neoplastic cells invasion (Hida et al., 2011). This abnormalities on tumor angiogenesis are due to the imbalance among inhibiting and pro-angiogenic factors. Changes in the TME such as hypoxia, acidic pH, low nutrients availability and an increase in temperature, induce the synthesis of pro-angiogenic molecules from different cells (Lopes-Bastos et al., 2016). For instance, tumor cells produce chemokines, IL-8, HGF, bFGF, EGF, angiopoietins, placental growth factor (PIGF), AM and VEGF while CAFs synthesize VEGF, TGFβ, C-X-C motif chemokine 12 (CXL12) and galectin-1 (Hida et al., 2011; Lopes-Bastos et al., 2016; Kocemba et al., 2013). Besides VEGF that stimulates these cells in an autocrine manner, TECs produce PDGF-B that recruits pericytes to induce blood vessels stabilization (Hida et al., 2011).

Changes in the TME also produce an increase of MMPs expression from different cells that constitute the tumor niche such as stromal, tumor and immune cells. For example, MMP-9 is secreted by tumor cells, TAMs, and tumor infiltrating neutrophils (Deryugina and Quigley, 2010). This MMP releases VEGF, considered the most potent pro-angiogenic factor, from the ECM. Tumor neutrophil MMP-9 activates another angiogenic factor, the bFGF-2 (Ardi et al., 2009). Likewise, MMP-9 promotes pericyte recruitment during new vessels maturation (Chantrain et al., 2004). Besides angiogenesis, MMP-9 participates in the recruitment of bone marrow myelomonocytic cells that are involved in stabilizing tumor vasculature during vasculogenesis (Ahn and Brown, 2008). Additionally, MMP-9 cleaves Multimerin 2 (MMRN2) from the endothelial surface, promoting cell migration and angiogenesis progression (Andreuzzi et al., 2017). MMRN2 has an antitumoral effect since it disturbs the VEGF-A/VEGFR2 signaling axis interfering with ECs migration and tumor sprouting angiogenesis (Lorenzon et al.,

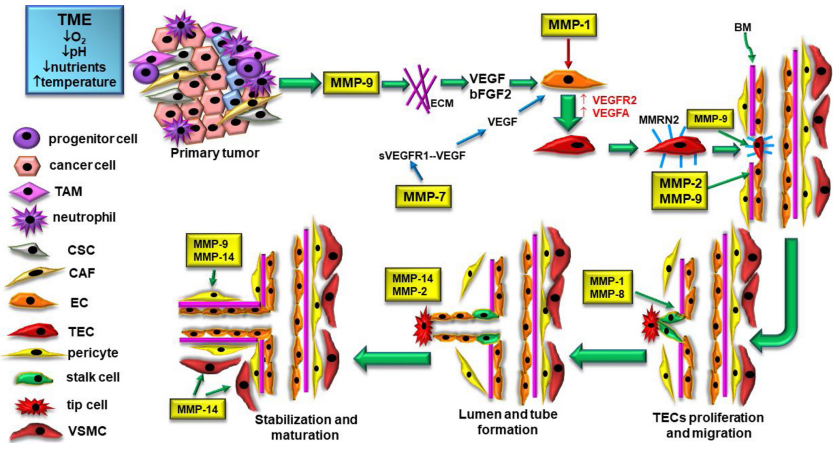

Fig. 5. MMPs participation in sprouting angiogenesis. Changes in the primary tumor TME induce the expression of pro-angiogenic molecules including MMPs from tumor cells, CAFs, TAMs and infiltrating neutrophils. These factors activate normal ECs to TECs increasing the number of VEGFRs and EGFRs. MMP-9 releases VEGF and bFGF2 from the ECM and cleaves MMRN2 present in the "hot spots" of neoangiogenesis. MMP-1 increases the expression of both VEGFA and its receptor VEGFR2. MMP-7 cleaves sVEGFR1-VEGF releasing VEGF. MMP-2 and MMP-9 degrade BM components to allow TECs migration driven by tip cells. MMP-1 and MMP-8 participate in TECs proliferation and in the acquisition of their migration capacity allowing sprout formation. MMP-14 and MMP-2 participate in tube and lumen formation. MMP-14 and MMP-9 favor pericyte recruitment to stabilize the new vessels. MMP-14 also promotes VSMCs dedifferentiation for vessels maturation. bFGF2, basic fibroblast growth factor-2; BM, basement membrane; CAFs, cancer associated fibroblasts; CSC, cancer stem cell; ECs, endothelial cells; ECM, extracellular matrix; EGFRs, epidermal growth factor receptors; MMRN2, multimerin-2; TAMs, tumor associated macrophages; TECs, tumor endothelial cells; TEM, tumor microenvironment; VEGF, vascular endothelial growth factor; VEGFRs, vascular endothelial growth factor receptors; sVEGFR1, soluble vascular endothelial growth factor receptor-1; VSMCs, vascular smooth muscle cells.

2012). Once TECs are activated, they disrupt tight, gap and adherent junctions between other ECs and perivascular cells, and degrade the vascular BM and the surrounding ECM for sprout formation with the participation of MMP-2 and MMP-9 (Ucuzian et al., 2010). TECs also show a rise in urokinase plasminogen activator receptors (uPAR) in the cell membrane surface. Binding of uPA to its receptor, produces its activation, and consequently, plasminogen cleavage to plasmin. Plasmin directly actives pro-MMPs or indirectly through the conversion of pro-galanin to galanin, a neuropeptide involved in MMP-2 and MMP-9 activation during angiogenesis (Murphy et al., 1999; Yamamoto et al., 2013b).

Additionally, TECs upregulate MMP-1, MMP-9 and MMP-14 expression (Deryugina and Quigley, 2010). MMP-1 increases VEGFR2 expression by the proteolytic activation of PAR-1 that activates the NF-κB signaling pathway involved in VEGFR2 transcription regulation (Mazor et al., 2013). The increase in VEGFR2 favors the binding of VEGFA, whose synthesis is also stimulated by MMP-1, increasing ECs proliferation (Mazor et al., 2013). Likewise, MMP-1 together with the expression of EGFR/pan-HER ligand epiregulin (EREG), MMP-2, and cyclooxygenase-2 (COX2) is associated with the development of dilated, tortuous and leaky tumor blood vessels in aggressive tumors. These proteins are synthesized by the tumor cells, but not by TECs, in a VEGF independent manner (Gupta et al., 2007). Similarly, MMP-14 increases its expression in the TECs membrane participating in pro-MMP-2 activation (Ra and Parks, 2007). MMP-14 also intervenes actively in the vascular lumen formation. This MMP favors the creation of "vascular guidance tunnels" in the ECM and TECs' aggregates to form lumens (Davis et al., 2011). There is also evidence that MMP-14 regulates vascular smooth muscle cells (VSMCs) dedifferentiation by the proteolysis of the low-density lipoprotein (LDL) receptor-related protein 1 (LRP1), that in turn activates the PDGF-BB-PDGFRβ pathway (Lehti et al., 2009). The stimulation of this pathway induces VSMC dedifferentiation allowing these cells to migrate and synthetize ECM components that contribute to vascular stabilization (Lehti et al., 2009). It is probable that this molecular mechanism is also involved in pericyte recruitment. MMP-7 also participates in angiogenesis releasing VEGF by the proteolytic degradation of soluble VEGFR-1, and therefore inducing ECs proliferation, migration and tube formation (Ito et al., 2009). MMP-8 might be also implicated in TECs proliferation since it can cleave angiotensin I to angiotensin II that upregulates platelet endothelial cell adhesion molecule-1 (PECAM1) expression allowing ECs proliferation by the induction of β-catenin expression and its nuclear accumulation (Fang et al., 2013; Biswas et al., 2003). In this manner, MMP-8 indirectly increases ECs migration through the β-catenin pathway related to the expression of Wnt genes involved in EMT (see above). Fig. 5 shows the pro-angiogenic functions of MMPs during tumor angiogenesis.

In contrast to the above cited MMPs pro-angiogenic functions, MMP-19 has been reported to have an anti-angiogenic effect (Deryugina and Quigley, 2010). Presence of early angiogenesis and tumor invasion was observed in MMP-19-deficient mice after transplantation of malignant murine keratinocytes (PDVA cells) (Jost et al., 2006). Moreover, studies done with nasopharyngeal carcinoma cells transfected with MMP-19 with a mutation in the zinc binding motif to inactivate the catalytic site of the enzyme, concluded that the catalytic MMP-19 function interferes in endothelial tube formation and in VEGF expression (Chan et al., 2011).

Besides MMPs role in vessel formation during angiogenesis, the degradation of the BM and the surrounding ECM allows the release of fragments with biological activities known as matrikines and matricryptins (Ricard-Blum and Salza, 2014). The difference among the concepts matrikine and matricryptin is a bit confusing. Momboisse JC et al. define matrikines as protein domains released from the ECM molecules while matricryptins are cryptic sites unmasked by proteolysis (Monboisse et al., 2014). Collagens, elastin, proteoglycans, laminin, fibronectin, and ECM regulators such as the MMP-2 C-terminal domain are sources of matrikines (Ricard-Blum and Salza, 2014). These peptides are able to modulate cell proliferation, migration, adhesion, apoptosis, protease synthesis, angiogenesis and matrix degradation (Monboisse et al., 2014). Matrikines considered in the present review are those with an effect on angiogenesis. In this context, activated TECs synthetized MMPs that degrade type IV collagen, the main BM component (Kalluri, 2003). Type IV collagen non-collagen domain (NCl) or triple helix degradation produces fragments with an anti-angiogenic effect (Monboisse et al., 2014). Other BM molecules that, after degradation, produce matrikines with an anti-angiogenic effect are type XV, XVIII and XIX collagens, laminin, perlecan and secreted protein acidic and rich in cysteine (SPARC)/BM-40/osteopontin (OPN) (Kalluri, 2003). Matrikines interaction with TECs inhibit cell proliferation, cell migration and tube formation, or induce apoptosis depending of the matrikines cell receptor such as integrins, chemokines or growth factors receptors. For a major review of matrikines and their receptors see Ricard-Blum S and Vallet SD (Ricard-Blum and Vallet, 2016). The MMPs involved in BM degradation are MMP-2, MMP-3, MMP-7, MMP-9, MMP-13, and MMP-20 (Ricard-Blum and Salza, 2014; Kessenbrock et al., 2010; Bellon et al., 2004). Some matrikines that participate in angiogenic regulation are included in Table 4 (Neskey et al., 2008; Cho et al., 2015; Assadian et al., 2012; Aikio et al., 2012; Hwang-Bo et al., 2016; Hwang-Bo et al., 2012; Cailhier et al., 2008; Douglass et al., 2015; Heljasvaara et al., 2005; Zhuo et al., 2011; Reiss-Pistilli et al.,

Table 4
Matrikines involved in angiogenesis inhibition.

Matrikine	MW kDa	Source	ECs proliferation inhibition	ECs migration inhibition	Tube formation inhibition	ECs apoptosis induction	Tumor growth inhibition	References
Anastellin	10	Fibronectin (III_{1C})	+	+	Not known	Not Known	+	(Neskey et al., 2008; Cho et al., 2015)
Arresten	26	NCl α(IV)	+	+	+	+	+	(Assadian et al., 2012; Aikio et al., 2012)
Canstatin	24	NCl α2(IV)	+	+	+	+	+	(Hwang-Bo et al., 2016; Hwang-Bo et al., 2012)
Endorepellin	85	Perlecan	-	+	+	-	+	(Cailhier et al., 2008; Douglass et al., 2015)
Endostatin	20	NCl α6(XVIII)	+	+	Not Known	+	+	(Heljasvaara et al., 2005; Zhuo et al., 2011; Reiss-Pistilli et al., 2017)
Hexastatin	2	NC1 α6(IV)	+	+	Not Known	Not Known	+	(Karagiannis and Popel, 2007)
Pentastatin	2.5	NCI α5(IV)	+	+	Not Known	+	+	(Koskimaki et al., 2010)
Restin	22	NCI α1(IV)	+	+	Not Known	+	+	(Ramchandran et al., 1999; Xu et al., 2002; John et al., 2005)
Tetrastatin	25	NCI α4(IV)	+	+	Not Known	Not Known	+	(Brassart-Pasco et al., 2012)
Tumstatin	27	NCI α3(IV)	+	+	+	+	+	(Boosani et al., 2010; Hwang-Bo et al., 2015)
Vastatin	18	NCI α1(VIII)	+	+	+	+	+	(Xu et al., 2001; Shen et al., 2016)

ECs, endothelial cells; MW, molecular weight; NCI, non-collagen domain.

2017; Karagiannis and Popel, 2007; Koskimaki et al., 2010; Ramchandran et al., 1999; Xu et al., 2002; John et al., 2005; Brassart-Pasco et al., 2012; Boosani et al., 2010; Hwang-Bo et al., 2015; Xu et al., 2001; Shen et al., 2016).

There are some angiogenic inhibitors that do not derive from ECM components but originate from MMPs activity such as angiostatin produced by the cleavage of plasminogen by MMP-2, MMP-9 and MMP-12 (Troyanovsky et al., 2001; Radziwon-Balicka et al., 2014).

6.5. Lymphangiogenesis

Besides disseminating through blood vessels, neoplastic cells particularly from epithelial cancers, spread through the lymphatic system. In fact, LN invasion is an early metastasis sign with a prognostic value that determines patient's treatment (Karaman and Detmar, 2014). Cancer cells access the lymphatic system by invading near preexisting lymphatic vessels (LV) or by generating new ones (lymphangiogenesis). Lymphangiogenesis consists of the development of new LV from veins or from pre-existing LV. There is some controversy about the relevance of lymphangiogenesis in metastasis since intratumoral LV are less functional due to the high intratumoral pressure compared to the pressure at the tumor periphery (Tammela and Alitalo, 2010). However, the LV structure seems to be similar inside and outside the tumor. Tumor LV have a disorganized, leaky and irregular structure that facilitates neoplastic cells invasion (Cao, 2005). Moreover, lymphatic capillaries (LC) structure is different from blood capillaries since they have a single layer of lymphatic endothelial cells (LECs) with gaps between them, little or no BM, neither a pericyte nor smooth muscular cell (SMC) layer (Tammela and Alitalo, 2010). These characteristics enhance their capacity to uptake interstitial fluid, macromolecules and cells such as tumor cells. Likewise, LECs cytoskeleton binds to interstitial type I collagen instead of to the BM through anchorage filaments mainly composed by elastic fibers facilitating LECs sprout and tubular formation (Ji, 2006; Paupert et al., 2011).

Lymphangiogenesis is crucial during initial stages of cancer invasion, distal metastasis and in immune unresponsiveness (Liu and Cao, 2016). LECs interact with tumor cells through the secretion of chemokines that attract tumor cells allowing them to pass through the lymphatic endothelium. For instance, cells that express the CCR7 receptor are attracted to the LV by the LECs chemokine CCL21, as do neoplastic cells with the CXCR4 receptor by SDF-1 (Tammela and Alitalo, 2010; Achen and Stacker, 2008). In both cases the inhibition of the interaction between the receptor and the chemokine impaired tumor cells metastases to regional LN (Achen and Stacker, 2008). Additionally, IL-6 producing tumor cells stimulate LECs to release CCL5 and VEGF inducing $CCR5^{+5}$ tumor cells recruitment, extravasation and colonization of a LN or a distant organ (Liu and Cao, 2016). LECs can also recruit immature dendritic cells and naïve T cells interfering with the immune response (Liu and Cao, 2016).

LECs are terminally differentiated cells with specific markers: (1) the lymphatic vessel endothelial hyaluronan receptor-1 (LYVE-1) that guides LECs growth; (2) the transcription factor Prospero homeobox1 (Prox1) that participates in LECs differentiation; (3) the membrane glycoprotein podoplanin that triggers platelet aggregation to block blood entrance; and (4) the VEGFR-3 implicated in the lymphangiogenesis process (Karaman and Detmar, 2014).

Neoplastic cells and TAMs release growth factors such as VEGF-C and VEGF-D that stimulate lymphangiogenesis through the activation of the VEGFR-3 localized in the LECs membrane of the LC (Karaman and Detmar, 2014). VEGFR-3 activates AKT and ERK that induce LECs proliferation and migration and protects them from apoptosis (Achen and Stacker, 2008; Zheng et al., 2014). The interaction of phosphorylated VEGFR-3 with PI3K induces LECs migration and tube formation (Zheng et al., 2014). VEGF-C and VEGF-D also interact with the axon guidance receptor neuropilin-2 (NP-2) that is internalized into the LECs. NP-2 and VEGFR-3 initiate lymphatic sprout elongation and increase

LECs sensing of the growth factors gradient (Tammela and Alitalo, 2010). VEGF-C and VEGF-D also dilate LV dilation and produce SMC remodeling, therefore increasing lymph flow in the collecting LV (Karaman and Detmar, 2014; Zheng et al., 2014). These factors also induce lymphangiogenesis in the LN even before neoplastic cells arrival, hence augmenting distant metastasis (Achen and Stacker, 2008).

Other factors directly participating in the lymphangiogenesis are sphingosine-1-phosphate (S1P) and angiopoietins (Tammela and Alitalo, 2010; Zheng et al., 2014). S1P induces LECs migration and tube formation via S1P1/$G_{(i)}$/phospholipase C/Ca^{2+} pathway while the phosphorylation of the tyrosine kinase receptor TIE2 in LECs by angiopoietin-2 provokes lymphatic growth and sprouting (Zheng et al., 2014). Growth factors as for instance HGF, PDGF-B, insulin-like growth factor-1 (IGF-1), IGF-2, FGF2 and endothelin-1 (ET-1) exert their effects on lymphangiogenesis through the stimulation of VEGF-C and VEGF-D (Tammela and Alitalo, 2010). Interestingly, ET-1 through its ET_B receptor, induced MMP-2 and MMP-9 activation during lymphatic tube formation in an in vitro Matrigel model (Spinella et al., 2010). The use of BQ788 that blocks the ET_B receptor also inhibits MMPs activation and tube formation. Likewise, MMP-2 deficiency provokes the reduction in LV formation and alters vessel branching in mice and zebrafish models (Detry et al., 2012). These results prompted the study of MMP-2 role in LECs sprouting and migration on a type I collagen matrix. Interestingly, authors found that MMP-2 behaves like an interstitial collagenase since it was able to degrade and modify type I collagen gel allowing LECs to migrate through it following a “proteolysis-driven mesenchymal migration program dependent on MMP-2” (Detry et al., 2012). Similarly, the participation of MMP-14 in lymphangiogenesis by pro-MMP-2 activation was demonstrated using a specific antibody (mAb 9E8) that selectively inhibits this MMP-14 function (Ingvarsen et al., 2013). mA9E8 inhibits LECs migration in 3-D dimensional collagen matrixes and reduces lymphatic sprouting in the “lymphatic ring assay” that uses explants from mouse thoracic ducts (Ingvarsen et al., 2013). However, MMP-14 functions in lymphangiogenesis are still controversial. It has been demonstrated that MMP-14 sheds LYVE-1 from the surface of LECs preventing the binding between LYVE-I and hyaluronan inhibiting intracellular lymphangiogenic signaling (Wong et al., 2016). MMP-14 also interferes with VEGF-C production by macrophages, the major producers of this factor during an inflammatory process; it is therefore highly probable that TAMs do the same in the tumor niche. In this regard, the results of experiments with stimulated MMP-$14^{-/-}$ macrophages revealed an increase in VEGF-C transcript and in VEGF-C protein level suggesting that MMP-14 suppress VEGF-C synthesis (Wong et al., 2016). This paper's authors propose that the non-catalytic region of MMP-14 binds to the promoter site of the PI3k transcript (*p110δ*) increasing its protein levels and inducing the inhibition of VEGF-C expression (Wong et al., 2016). All these results suggest that a molecular mechanism that regulates MMP-14 functions in lymphangiogenesis should exist. One candidate for such regulation would be MMP-16 since this enzyme degrades cell surface MMP-14 promoting lymphatic invasion (Tatti et al., 2015). MMP-16 also degrades neural L1 cell adhesion molecule (L1CAM) involved in transendothelial invasion. A shift from blood invasion to lymphatic invasion was observed in melanoma cells overexpressing MMP-16 with an increase in L1CAM shedding (Tatti et al., 2015).

MMP-13 also participates in lymphangiogenesis. This MMP has been associated with an increase of VEGF-C expression and LN metastasis in pediatric multiple myeloma (MM) (Karaman and Detmar, 2014). Furthermore, studies done in a human MM cell line (8226) showed that MMP-13 activates VEGF-C via the PI3K/Akt signaling pathway (Xu et al., 2015b). In this regard, MMP-3 and MMP-9 protein expression has been associated with an increase of LV density and LN metastasis in colorectal and breast cancer, respectively (Islekel et al., 2007; Wu et al., 2014).

6.6. Invasion

To gain access to new blood vessels or LV, neoplastic cells need to cross the ECM. The tumor stroma is particularly stiffer than normal stroma and cancer cells sense this biomechanical characteristic through their transmembrane integrins. This mechanic-sensory system allows cells to adjust their “intracellular tension trough the cytoskeletal network” as an adaptive process to their microenvironment leading them to choose among the following migration strategies: elongated-mesenchymal, rounded-amoeboid and spike mediated (Butcher et al., 2009; Lu et al., 2012; Pandya et al., 2017). For instance, when the ECM is not too stiff, cancer cells use the amoeboid migration type in which neoplastic cells move through pre-existing paths in the ECM generated by stromal cells such as CAFs that degrade the ECM components (Gaggioli et al., 2007; Yamaguchi and Sakai, 2015). Hence, cancer cells shape and motility depend on the cellular contractility and ECM stiffness, alignment, porosity and geometry. Likewise, ECM composition has an important role in cancer cell motility strategy. Neoplastic cell interactions with type I and type III collagens favor mesenchymal displacement while contact with type IV collagen induces amoeboid migration (Azorín et al., 2012). These morphologic differences are due to cytoskeletal organization and depend on the molecules implicated in focal adhesion contacts among cells and collagens. For example, adhesions with type I collagen are mediated by integrin $\alpha_2\beta_1$, are rich in vinculin and paxillin and myosin light chain kinase (MLCK) signal pathway is activated, while in the interactions with type IV collagen, intergrins α1β1 and large amounts of talin and actin are present, andRhoA dependent kinase (ROCK) pathway is induced (Azorín et al., 2012). In this way, when cells face high mechanical resistance during the invasion process, they change their behavior by increasing their synthesis of proteolytic enzymes and promoting the formation of cell membrane protrusions as has been proposed for neoplastic cell interactions with type I collagen (Azorín et al., 2012; Yamaguchi, 2012; Brown and Murray, 2015).

As well, adhesion to type IV collagen present in BM may stimulate the production of MMP-2 and MMP-9 from tumor amoeboid cells’ blebs and filopodia. Interestingly, MMP-9 can also favor rounded amoeboid cell migration through the regulation of actomyocin contractility (Orgaz et al., 2014). Moreover, MMP-9 favors cells’ rounded forms in an autocrine and/or paracrine manner via CD44 receptor (Orgaz et al., 2014). Additionally, there is evidence that amoeboid forms may use MMP-13 during the invasion process degrading type I collagen fibers (Orgaz et al., 2014). Notably, amoeboid type migration also requires MMP-14 localized in blebs and filopodia membrane structures when tumor cells migrate through natural cross-linked type I collagen gels or BM from human or mouse tissues (Sabeh et al., 2009). In this regard, more studies are needed to elucidated MMPs participation in amoeboid migration through natural ECM models.

On the other hand, cellular movement is coordinated with plasmatic membrane extensions, cell adhesion and proteolytic degradation of the ECM in the leading edge at the front and actomyocin contractility-mediated rear edge retraction on the back of the cell, driving cell movement in the locomotion direction (Pandya et al., 2017; Ridley, 2011). These membrane extensions are lamellipodia, filopodia, blebs and invadopodia, each with a different function depending on cell conditions. The most widely study membrane extension are invdopodia. Their formation is stimulated by growth factors such as TGFβ, EGF and PDGF, and the initiation phase is followed by the assembly and maturation stages; molecular mechanisms involved in these steps are well described by Jacob A. and Prekeris R. (Jacob and Prekeris, 2015). Interestingly, β_1 integrin promotes invadopodia maturation inducing Arg mediated cortactin phosphorylation. Moreover, β_1 integrin on invadopodia is also related to BM degradation since it recruits and docks MMPs such as MMP-2, MMP-9 and MMP-14 that have the capacity to

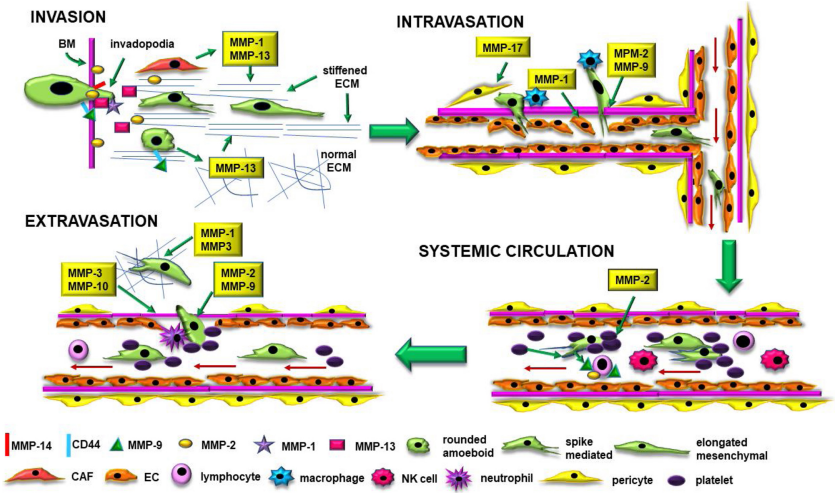

Fig. 6. MMPs participation in cancer spreading. Invasion: Tumor cells with a metastatic phenotype develop invadopodia structures containing MMP-14 that participates in pro-MMP-2 activation, and MMP-2 and MMP-9 that are responsible of degrade the BM. MMP-9 also forms a membrane complex with CD44 regulating actomyocin structure organization for cell invasion. Cells migrate through the ECM that is remodeled by MMP-1 and MMP-13 secreted by CAFs and metastatic cells. MMP-1 and MMP-13 from invadopodia may contribute to cell migration through the stiffened ECM. Intravasation: Macrophages drive tumor cells to the intravasation sites. MMP-2 and MMP-9 from invadopodia degrade the endothelial BM. MMP-1 disturbs ECs integrity increasing vascular permeability. MMP-17 from neoplastic cells provokes mural pericyte detachment enhancing vascular leakage. Systemic circulation: MMP-2 favors the formation of tumor and platelets aggregates to protect neoplastic cells from NK cells destruction. Platelets induce tumor MMP-2 and MMP-9 synthesis. These MMPs interfere with T-lymphocyte differentiation and proliferation. Extravasation: Platelets and neutrophils favor tumor cells adhesion to ECs in the extravasation site. Platelets induce the formation of invadopodia and neoplastic cells provoke platelet α-granules degranulation releasing MMP-1, MMP-2, MMP-3, and MMP-9. MMP-2 and MMP-9 from the invadopodia and platelets degrade endothelial BM while MMP-1 and MMP-3 participate in ECM remodeling in the metastatic niche. CTCs induce the synthesis of MMP-3 and MMP-10 from the pre-metastatic niche. These MMPs disrupt the endothelial layer increasing vascular permeability. BM, basement membrane; CAF, cancer associated fibroblast; CTC, circulating tumor cells; ECs, endothelial cells; ECM, extracellular matrix; NK, natural killer.

degrade type IV collagen (Jacob and Prekeris, 2015). As it was mentioned above, MMP-14 also participates in pro-MMP-2 activation at invadopodia cell membrane (Ra and Parks, 2007; Ogata et al., 1995).

Once neoplastic cells degrade the BM, they migrate through the interstitial ECM degrading some of its components. Studies done in epithelioid myeloma cells showed that MMP-13 from these cells degrades type I collagen. MMP-1 also participates in the interstitial collagen remodeling during lung adenocarcinoma invasion (Schütz et al., 2015). This MMP has been localized at invadopodia from osteogenic sarcoma cells during the invasion of an interstitial type I/type III collagen matrix. Moreover, by using this invasion model, it has been demonstrated that prenylation, a molecular mechanism that promotes protein attachment to cell membrane, is somehow involved in MMP-1 trafficking to invadopodia (Garamszegi et al., 2012).

Additionally, MMP-2 contained in cancer cell invadopodia might degrade type I collagen from the interstitial ECM as it does in LECs during lymphangiogenesis (see above) (Detry et al., 2012). In fact, MMP-2, MMP-9 and MMP-13 were identified in the invadopodia from colon cancer cells on three-dimensional type I collagen scaffolds. (Vishnubhotla et al., 2007). Furthermore, ROCK-II isoform seems to be involved in MMP-2 and MMP-13 enzymatic activity regulation at the invadopodia since ROCK-II down regulation led to a decrease of these MMPs' enzymatic activity (Vishnubhotla et al., 2007). Fig. 6 shows MMPs participation during tumor cells invasion of the surrounding tissue.

Neoplastic cells are also able to move together as multicellular streaming, tumor budding or clusters in which cell-cell adhesion is maintained (Pandya et al., 2017). Multicellular streaming migration consists in cells moving one after another ("Indian files") attracted by chemokines, morphogen gradients or ECM components. Cell-cell adhesions are weak and cytoskeleton from each cell acts independently, generating a traction force on the matrix. On the other hand, tumor budding is composed by few cells (5 cells) that emerge from the invasive front of the tumor mass as finger-like projections (Pandya et al., 2017). Separation of this buds from the tumor is associated with an increase in cytoplasmic E-cadherin stain, augmented ZEB1 expression and loss of cell polarity, all of them EMT characteristics (Bronsert et al., 2014). The presence of tumor buds has been considered a bad cancer prognosis. Likewise, clusters or collective invasion are groups of cells joined by long-lived cell-cell connections. Neoplastic cells at the front of the cell cluster or tumor mass have mesenchymal characteristics that allow the generation of a path by focal proteolysis, therefore remodeling the ECM with the secretion of MMPs; the rest of the cells move along the path (Yamaguchi, 2012). This form of migration is the slowest migration mode but has some advantages as for instance protecting inner cells from the immune response allowing cells to survive during migration into lymphatic or bloodstream circulation (Yamaguchi, 2012).

Tumor cells can modify their collective migration pattern from one type to another or from collective to single-cell migration. This adaptive plasticity of tumor cells depends on the ECM molecular and physical characteristics, weakness of cell-ECM and cell-cell junctions, proteases synthesis and secretion, tumor or mesenchymal cells' chemokines, cytokines and growth factors, membrane receptors such as β_1 integrin, and cytoskeleton organization regulated by the Rho GTPase signaling (Pandya et al., 2017).

6.7. Cancer cell intravasation

Once neoplastic cells reach a new or a pre-existing lymphatic or blood vessel, they intravasate into the systemic circulation. How cancer cells decide among the lymphatic and the hematogenous via for their dissemination is unclear.

It depends on the site of the primary tumor, tumor aggressiveness, intrinsic and extrinsic factors, lymphatic or blood vessels availability, and TME interactions with the neoplastic cells (Wong and Hynes, 2006; Chiang et al., 2016). For instance, some conditions could favor lymphatic dissemination such as lymph fluid composition that is similar to interstitial tissue fluid promoting cell survival, the discontinuous LV structure and the low shear stress of lymphatic flow conditions that favor cells intravasation and survival (Paduch, 2016). Likewise, cancer cells that are going to intravasate into LVs move in rounded-amoeboid shape since they do not need proteolytic enzymes because of the lack of BM (Wong and Hynes, 2006). Cell clusters can also penetrate trough the discontinuous structure of the LV.

In spite of the advantages that lymphatic spread provides, hematogenous dissemination seems to be the most frequent pathway for carcinoma cell metastasis to a distant organ (Valastyan and Weinberg, 2011). In fact, LVs drain eventually to the subclavian vein circulation through the left lymphatic duct known as thoracic duct, or through the right lymphatic duct (Wong and Hynes, 2006).

Hematogenous dissemination starts with tumor cell polarization toward blood vessels. Perivascular macrophages have a chemoattractant effect on cancer cells that promotes cells polarization and

migration (Wyckoff et al., 2004). A paracrine loop among macrophages with colony stimulated factor-1 (CSF-1) receptor that release EGF and tumor cells with EGF receptor which release CSF-1 has been identified (Wyckoff et al., 2007). This chemotaxis-mediated migration drives tumor cells to blood vessels and to sites of intravasation. Moreover, macrophages promote RhoA activation and the consequent development of invadopodia therefore enhancing tumor cell intravasation (Roh-Johnson et al., 2014). Invadopodia are necessary for blood vessels BM degradation by MMPs such as MMP-2 and MMP-9 allowing tumor cells intravasation (Fig. 6) (Yamaguchi, 2012; Roh-Johnson et al., 2014). Moreover, the contact of tumor cells with ECs activates the proMMP-2/MMP-14/TIMP-2 complex present in tumor cell membranes including invadopodia. Degradation of BM components opens a route for neoplastic cell migration, it also produces EC detachment inducing endothelium apoptosis-necrosis with the subsequent increase in vascular permeability (Peyri et al., 2009). Another strategy that neoplastic cells use to penetrate trough the blood vessels is the attachment of cancer cells to the endothelium. This process induces activation of signal cascades such as Src, p38 and ERK1/2 in the ECs, decreasing cell-cell adhesions and modifying ECs actin structure (Roh-Johnson et al., 2014). The disruption of EC integrity also favors cancer cells intravasation. In this context, MMP-1 is able to disrupt endothelia integrity through the activation of the protease-activated receptor 1 (PAR1) that induces actin-dependent retraction of EC, increasing endothelia permeability (Fig. 6) (Juncker-Jensen et al., 2013). Endothelial PAR1 activation by MMP-1 was also observed in a sepsis model in which PAR1 induces endothelial apoptosis. It is therefore possible that cancer cells use this mechanism to increase blood vessel permeability (Tressel et al., 2011; Zhang et al., 2017). MMP-17 from tumor cells is also involved in cancer cells intravasation (Fig. 6) (Chabottaux et al., 2009). This MMP induces enlargement of intratumoral blood vessels, detachment of mural pericytes that affect pericyte-ECs interactions augmenting vessel leakage. It seems that MMP-17 effect is related to the decrease of thrombospondin-2 (TSP-2) expression because its reduction has been associated with loss of the vascular integrity and greater permeability (Chabottaux et al., 2009).

Contrastingly, there is evidence that MMPs may have a protective effect against neoplastic cell intravasation. Sarcoma cells (HT-1080) with a low dissemination rate have high expression levels of MMP-2 (Partridge et al., 2007). Downregulation of this MMP increases HT-1080 dissemination rates and metastasis. Similar results were observed in HT-1080 cells with a high dissemination rate in which MMP-1, MMP-2 and MMP-9 downregulation increases neoplastic cell intravasation (Partridge et al., 2007). Contrary to this protective role of MMPs, radiation increased MMP-9 expression, intravasation and metastasis in in vitro and in vivo lung cancer cell models. Moreover, MMP-9 downregulation reversed radiation effects demonstrating that this MMP is necessary for cell intravasation and metastasis (Chou et al., 2012).

The number of neoplastic cells intravasated from the primary tumor into the systemic circulation can be 4×10^6 tumor cells per gram of tumor mass (Wong and Hynes, 2006). This large amount of cancer cells overcomes the inefficiency of the metastatic process since just 0.01% of the circulating tumor cells (CTCs) have the capacity to generate a metastatic colony in a distant organ.

6.8. Blood circulation and escape from immune surveillance

In the systemic circulation, CTCs travel alone or in clusters interacting with platelets or ECs that protect them from the shear stress of the blood stream and from immune surveillance (Fig. 6) (Labelle and Hynes, 2012). In this context, there is evidence that platelets protect cancer cells from natural killer (NK) cells cytotoxic effects since NK cells require direct contact with tumor cells for their destruction (Palumbo et al., 2005). Tumor cells induce the formation of platelets aggregation (TCIPA) through the activation of pro-MMP-2 by MMP-14 from both CTC and platelets, and by inducing the secretion of platelets granules that contain thromboxane A_2 (TXA_2) and adenosine diphosphate (ADP) considered as pro-aggregatory factors (Fig. 6) (Santos-Martínez et al., 2008). Moreover, MMP-2 interacts with $\alpha_{IIb}\beta_3$ integrin stimulating the expression of platelet receptors involved in TCIPA such as glycoprotein-Ib (GPIb), GPIIb/IIIa and P-selectin (Santos-Martínez et al., 2008; Gresele et al., 2017). Besides MMPs intervention in TCIPA, tumor cells also produce tissue factor (TF) that triggers the formation of thrombin, provoking coagulation and platelet activation (Labelle and Hynes, 2012). The fibrin produced in this process binds to tumor integrin $\alpha_V\beta_3$ and platelet integrin $\alpha_{IIb}\beta_3$ favoring TCIPA. P-selectins ligands from tumor cells and P-selectins from active platelets surface also participate in the formation of tumor-platelets aggregates (Labelle and Hynes, 2012). This ability of TCIPA is related to a high metastatic potential of tumor cells (Santos-Martínez et al., 2008). Furthermore, platelets induce tumor cells expression of MMP-9 and MMP-14 increasing their invasive capacity (Santos-Martínez et al., 2008; Gresele et al., 2017). On the contrary, CTC-ECs nests in which tumor cells are enveloped by ECs, are considered as a “passive metastatic route of tumor cell dissemination” with a low expression of MMP-2 (Deryugina and Quigley, 2006). This type of clusters is associated with an angiogenic capacity of the tumor cells instead of an invasive potential (Deryugina and Quigley, 2006).

On the other hand, evading the immune response is one of the major challenges that tumor cells face in their quest to establish a metastatic colony. In fact, tumor cells develop strategies to escape the immune surveillance in which MMPs are involved. For instance, MMP-9 and to a lower degree MMP-2 from tumor cells are able to cut of interleukin-2 receptor α (IL-2Rα) from the T-lymphocytes surface (Sheu et al., 2001). This receptor is necessary for T-cells proliferation. Likewise, TGFβ activation by MMP-2 and MMP-9, blocks T-cells proliferation, T-cells differentiation into cytotoxic and helper cells, and inhibits T-cells stimulatory functions on antigen presenting cells (Gorelik and Flavell, 2001; Jenkins, 2008). TGFβ also downregulates the immunoreceptor natural killer group 2D (NKG2D) on NK cells interfering with their activation (Kopp et al., 2009).

6.9. Tumor cell extravasation and tissue colonization

During blood stream circulation, CTCs alone or in clusters are arrested by the organ secondary capillary bed. To initiate extravasation, cells are arrested through 2 different mechanisms: a passive mechanical entrapping mechanism that depends on the circulation patterns and clusters size that contributes to the initial arrest, and through the interactions between tumor cells and ECs involving selectins and CD44 isoforms, and with the ECM by a mechanism implying tumor cells’ integrins (Shibue and Weinberg, 2011; Deryugina and Quigley, 2006). In this context, it has been demonstrated that the expression of CD44 variants, particularly CD44v3 and CD44v4/5 in breast cancer BT-20 cells confers them an E-selectin ligand capacity in conditions similar to those present in blood stream flow in an in vitro model (Shirure et al., 2015). Likewise, CD44v6 binding to OPN provokes neoplastic cell adhesion to ECs through $\alpha_V\beta_1$ integrin (Huang et al., 2012). Furthermore, CD44v6-OPN interaction induces tumor cells invasion to a specific tissue by enhancing their chemotaxis activity (Ma et al., 2019). Additionally, CD44v6 link to hyaluronic acid (HA) provokes the synthesis of MMP-2 and MMP-9 that disrupt the endothelial BM (Ma et al., 2019). In general terms, because CD44 isoforms are overexpressed in advanced stages of different neoplasia types, they have been considered as prognostic markers for cancer progression (Chen et al., 2018).

On the other hand, platelets and neutrophils also participate in tumor cells arrest and adhesion to the endothelium at the extravasation site (Labelle and Hynes, 2012). For instance, the interaction among tumor cells and platelets activates the NF-κB and TGFβ/Smad pathways from the neoplastic cells inducing the EMT in tumor cells including the formation of invadopodia (Labelle et al., 2011; Leong et al., 2014). In this regard, experiments done with breast cancer (MDA-MB-231LN),

human epidermoid carcinoma (HEp3) and fibrosarcoma (HT1080) cell lines showed the formation of cytoplasmic protrusions that extent between the ECs and into the extravascular stroma. These protrusions contained invadopodia components cortactin and tyrosine kinase substrate with 4 SH3 domains (Tks4), Tks5 and MMP-14 (Leong et al., 2014). Tumor cells also induce platelets degranulation provoking the release of MMP-1, MMP-2, MMP-3 and MMP-9 from their α-granules. MMP-2 and MMP-9 participate directly in cancer cell extravasation by degrading components of the vascular BM, and MMP-1 and MMP-3 promote neoplastic cell invasion of the metastatic site (Fig. 6) (Menter et al., 2014). Likewise, platelets stimulate MMPs expression from ECs and cancer cells during tumor cell extravasation (Gresele et al., 2017). Simultaneously, vascular permeability is increased by the synergic effects of MMP-3, MMP-10 and angiopoietin-2 (Fig. 6) (Huang et al., 2009b). CTC induce the expression of these MMPs via TNF-α and TGFβ1 at the pre-metastatic niche disturbing the perimatrix of the endothelial layer and degrading the endothelial BM (Huang et al., 2009b).

Tumor cells in the new tissue face a different microenvironment from the one present in the primary tumor. In such conditions, cancer cells may be destroyed by the immune system, undergo apoptosis, lie in a dormant stage or proliferate (Brooks et al., 2010). In this context, it has been proposed that neoplastic cells from the primary tumor release systemic signals such as tenascin C and lysyl oxidase (LOX), that induce organ-specific cells to create a pre-metastatic niche that supports initial tumor cell survival and growth (Valastyan and Weinberg, 2011; Gomis and Gawrzak, 2016). LOX functions as a cross linker of BM proteins including type IV collagen, changing tissue stiffness and promoting recruitment of bone marrow derived cells (BMDC) that in turn release MMP-2 that degrades collagen IV (Kessenbrock et al., 2010; Shay et al., 2015). The resulting type IV collagen peptides act as chemoattractants for BMDC and metastasizing cells. Besides its role in BM degradation, ECs MMP-9 also participates in the recruitment of BMDC through the release of soluble kit L and in the liberation of VEGF to support angiogenesis (Kessenbrock et al., 2010; Shay et al., 2015).

Interestingly, primary tumor also releases exosomes that carry molecules such as Hsp-90 that induce MMPs expression in the pre-metastatic niche (Shay et al., 2015). Moreover, exosomes that contain latent and active MMP-2 and MMP-9 have been identified in ovarian and breast cancer cells (Shay et al., 2015). The function of these exosome MMPs is not clear but perhaps they may participate in the remodeling of the pre-metastatic niche modifying the ECM structure as well as processing other exosome proteins as for instance growth factors and cytokines.

In the new tissue, cancer cells must escape the immune response and this process can be achieved by MMP-2 and MMP-9, that have the capacity to block T-cells proliferation and differentiation acting directly on T-cells or activating TGFβ in the metastatic niche (see above) (Sheu et al., 2001; Jenkins, 2008). In this context, tumor MMP-14 could activate TGFβ via integrin $\alpha_V\beta_8$ which in turn interferes with T-cell functions (Jenkins, 2008).

Likewise, neoplastic cell dormancy may result from the inability of cancer cells to induce angiogenesis, the dysregulation of apoptosis and the stimulation of cell cycle arrest, creating a balance among apoptosis and cell proliferation that maintains tumor size. The role of active immune cells in the pre-metastatic niche is to control tumor growth during cell dormancy (Gomis and Gawrzak, 2016; Almog, 2010).

Tumor cells may remain in dormancy for years or even decades. These micrometastasis cannot be detected until cancer cells escape from dormancy and acquire the capacity of generating new vessels, decreasing apoptosis and increasing cell proliferation, constituting then clinically detectable symptomatic lesions (Almog, 2010).

7. MMPs protective effects during cancer progression

Not all MMPs' functions favor cancer progression. In fact, some MMPs exert protective effects on cancer. In this context, MMP-$3^{-/-}$ mice treated with the carcinogen 1-methyl-3-nitro-1-nitroso guanidine (MMNG), had an increase in tumor growth and more metastatic lesions than MMP-3 wild type animals (McCawley et al., 2004). Moreover, a decrease in tumor infiltration by macrophages and neutrophils in MMP-$3^{-/-}$ mice compared with animals that expressed MMP-3 was observed, demonstrating that MMP-3 participates in immune surveillance (McCawley et al., 2004). Likewise, nuclear MMP-3 catalytic domain has a role in apoptosis induction in Chinese hamster ovarian cells (CHO K1) (Si-Tayeb et al., 2006). However, although there is an increase in active caspase 3, the exact mechanism by which nuclear active MMP-3 contributes to apoptosis is unclear. Similarly, cytoplasmic active MMP-3 indirectly activates caspase-9, probably through the proteolysis of Apf-1, a cytosolic protein involved in caspase-9 activation that in turn activates pro-caspase-3 in dopaminergic neuronal cells (CATH.a) (Kim et al., 2014). Although these observations were done in non-neoplastic cells, MMP-3 proapoptotic function could be part of MMP-3 protective effects against cancer progression.

MMP-8 is another MMP that might interfere with cancer evolution. Experiments done with highly metastatic melanoma cells (B16F10) that did not express MMP-8, induced lung metastasis lesions when injected in MMP-$8^{-/-}$ mice (Gutiérrez-Fernández et al., 2008). On the contrary, a reduction in lung metastasis was observed when B16F10 cells transfected with murine MMP-8 cDNA were injected into these animals (Gutiérrez-Fernández et al., 2008). In this regard, MMP-$8^{+/+}$ B16F10 cells had a decrease in their invasive capacity and an increase in cell adhesion to laminin-1 and type I collagen. Likewise, there was an association among invasive breast cancer and a negative expression of MMP-8 particularly in those patients with axillary LNs (Gutiérrez-Fernández et al., 2008). Moreover, in mobile tongue SCC, a large mortality rate was observed in those patients without MMP-8 expression compared to those in which MMP-8 was detected in tumor tissue by immunohistochemistry (Korpi et al., 2008). Interestingly, the risk to develop tongue SCC due to carcinogen 4-Nitroquinoline-N-oxide (4NQO) exposition was larger in MMP-$8^{-/-}$ female mice than in MMP-$8^{-/-}$ male mice (Korpi et al., 2008). Furthermore, this susceptibility was also observed in the increase of skin tumors in male mice, female mice treated with tamoxifen, an estrogen receptor antagonist, and animals that had their ovaries removed suggesting that this predisposition is estrogen dependent (Balbín et al., 2003). On the other hand, treatment of HSC3 tongue carcinoma cells with 17β-estradiol (E2) induced MMP-8 expression demonstrating that this MMP is hormonally regulated. However, its promoter site does not have an estrogen binding element; it contains instead the CCAAT/enhancer binding protein (C/EBP) element that forms a complex with the estrogen receptor α (ERα) promoting MMP-8 transcription (Korpi et al., 2008; Khanna-Gupta et al., 2005). MMP-8 is also able to cleave ERα regulating the estrogen-signaling pathway (Korpi et al., 2008). The MMP-8 protective effects in cancer depend on the proteolytic activity of this enzyme (Gutiérrez-Fernández et al., 2008). MMP-8 can activate decorin, an ECM protein, releasing the core protein that binds to TGFβ blocking its interaction with cell membrane receptors (Soria-Valles et al., 2014). TGFβ blockage inhibits the expression of miR-21 favoring tumor-suppressor genes expression with a reduction on tumor growth and metastasis (Soria-Valles et al., 2014).

MMP-11 seems to have a dual effect during cancer progression, since in early stages of the disease it favors tumor growth but prevents cancer dissemination. In this context, tumor developed faster in nude mice implanted with breast cancer tumor cells (MCF-7) transfected with MMP-$11^{+/+}$ in comparison with those animals transfected with MMP-$11^{-/-}$ cells (Wu et al., 2001). These tumors had a lower percentage of apoptotic cells, a fact that suggests that MMP-11 has an anti-apoptotic effect. Additionally, mouse mammary tumor virus (MMTV)-ras transgenic mice expressing MMP-11 showed an increase in primary tumors, probably because of its anti-apoptotic effect on cancer cells (Andarawewa et al., 2003). Interestingly, the number of metastatic lesions was lower in MMP-11 expressing mice in comparison to MMP-

$11^{-/-}$ animals (Andarawewa et al., 2003). These results were corroborated by intravenously injecting animals with colon carcinoma C26 cells that migrated to lung tissue (Brasse et al., 2010). As in primary tumors, there is a correlation among the presence of host MMP-11 and tumor growth rate. The neoplastic lesions in MMP-$11^{-/-}$ mice were smaller than in MMP-$11^{+/+}$ animals, and their tumors had "vascular like structures" (Brasse et al., 2010). The presence of these structures is probably related to an augmented rate of metastasis to other organs such as ovary, adrenal gland, liver and mammary gland detected in MMP-11 deficient mice in comparison with wild type animals (Brasse et al., 2010).

There is also evidence that stromal MMP-12 has a protective effect on lung tumor growth (Acuff et al., 2006). MMP-$12^{-/-}$ mice injected with Lewis lung carcinoma (LLC) cells had an increase in the number of tumors ≥ 2 mm and in the growth rate in comparison with wild type animals. The increment in growth velocity correlates with an augmented number of ECs suggesting a rise in angiogenesis (Acuff et al., 2006). MMP-12 participates in angiogenesis inhibition since this MMP cleaves plasminogen to angiostatin, an angiogenesis inhibitor (Cornelius et al., 1998). Plasma from the MMP-$12^{-/-}$ mice had a reduction of the K1-K4 forms of angiostatin and therefore an increase in tumor vascularization that favors tumor growth (Acuff et al., 2006).

MMP-13 has also protective effects during cancer progression. MMP-$13^{-/-}$ mice injected with B16BL6 melanoma cells developed more lung metastasis than the wild type animals (Fukuda et al., 2011). The localization of MMP-13 in lung tissue ECs suggested its participation in the regulation of neovascularization that was corroborated by an increase in endostatin that blocks cancer cell migration and angiogenesis (Table 4) (Fukuda et al., 2011).

Likewise, MMP-19 expression was downregulated in nasopharyngeal carcinoma (NPC) and in NPC cells lines in comparison with normal samples (Chan et al., 2011). NPC cells transfected with MMP-19 wild type or with a MMP-19 mutated in the zinc binding motif at the catalytic site were injected in athymic BALB/c *nu/nu* mice to probe the protective effect of this MMP and find out if this effect depends on the catalytic domain (Chan et al., 2011). Tumor volumes in mice injected with MMP-19 wild type cells, were less than 600 mm^3 in comparison with tumors in mice injected with mutated MMP-19. Moreover, MMP-19 effects on tumor size were due to its influence on angiogenesis. Experiments done in human umbilical vein endothelial cells (HUVEC) incubated with conditional media from MMP-19 wild type NPC cells showed a decrease in secreted VEGF and in endothelial tube formation compared with the high levels of VEGF and tube structures observed in incubations done with conditioned media from cells transfected with mutated MMP-19 (Chan et al., 2011).

On the other hand, it has been observed that MMP-26 levels change as cancer evolves with low levels in normal tissue and at the beginning of the disease, and further increase of its expression followed by a decline of its concentrations in advanced stages. In this context, there is evidence of MMP-26 proapoptotic effects preventing cancer progression. Androgen-repressed prostate cancer (ARCaP) cells transfected with sense MMP-26 cDNA as well as prostate cancer tissue samples had an increase in MMP-26 expression, Bax concentration and apoptotic cells in comparison with ARCaP cells transfected with anti-sense MMP-26 cDNA or tissue with non-neoplastic epithelium (Khamis et al., 2016). The high levels of MMP-26 decrease with prostatic cancer progression. MMP-26 also has a protective function in the early stages of breast cancer where high levels of this enzyme are considered as a favorable prognostic (Savinov et al., 2006). In breast cancer, as in other hormone-dependent tumors, MMP-26 transcription is stimulated by E2 via its interaction with ERβ, since MMP-26 has an estrogen response element in its promoter site (Savinov et al., 2006; Li et al., 2004). Moreover, as in MMP-8 transcription regulation (see above), a regulatory loop that includes MMP-26 disruption of the N-terminal region of ERβ has been identified. This MMP-26 ability could explain at least in part, its protective effect in this type of cancer (Savinov et al., 2006). However, there is also evidence that this MMP favors tumor growth, invasion and angiogenesis (Yang et al., 2012a). Breast carcinoma cells (MCF-7) transfected with sense MMP-26 cDNA had high proliferation rates together with a change in their morphologic shape from rounded to polygonal with more pseudopods increasing therefore their migration and invasion capacities (Yang et al., 2012a). Moreover, MCF-7 MMP-$26^{+/+}$ cells inoculated in nude mice provoked an increase in angiogenesis compared with mice inoculated with control MCF-7 cells. These results demonstrated the transformation effect of MMP-26 in this cancer cell line from a less malignant behavior to a highly malignant phenotype.

8. MMPs as diagnostic and prognostic markers for cancer in body fluids

The extensive participation of MMPs in all the metastatic process turns them into promising diagnostic and prognostic markers. The presence of different MMPs in cancer cells and in tissue samples, and their association with the different metastatic steps and in some cases with disease prognosis, have already been mentioned, and furthermore, MMPs can also be evaluated in body fluids. MMPs profile in blood, urine or saliva samples could be used as diagnostic and prognostic marker; it would also be useful to follow up patients' treatment since the techniques to obtain this type of samples are less invasive than for example tissue biopsies (Hadler-Olsen et al., 2013). In this context, MMPs blood concentration and enzymatic activity were used to follow up the evolution and therapy response of patients with advanced NSCLC during first line chemotherapy treatment with cis-platin alone or together with a third-generation drug (paclitaxel, vinorelbine, gemcitabine or docetaxel) (Gonzalez-Avila et al., 2012). In this study, we found a rise in blood MMP-2 and MMP-9 enzymatic activity in those patients that did not respond to treatment and had progression of the disease. Likewise, to consider MMPs blood levels as good or bad prognostic markers depends on cancer therapy and neoplasm characteristics. For instance, MMP-2 high plasma concentrations correlated with a good prognostic in glioma patients treated with bevacizumab but not when treated with a cytotoxic agent (Tabouret et al., 2014). On the contrary, changes in serum MMP-2 and MMP-9 concentrations were not related to tumor response in locally advanced breast cancer patients treated with doxorubicin, 5-FU, and cyclophosphamide (Coskun et al., 2007). However, MMP-2 high levels and MMP-9 low serum concentrations were associated with a good response to neoadjuvant therapy with bevacizumab and trastuzumab in combination with conventional chemotherapy (5-FU, epirubicin and docetaxel) before surgery in HER-2 positive non-metastatic inflammatory breast cancer (Tabouret et al., 2016).

Furthermore, the risk factor involved in the onset of a particular type of cancer could be associated with the synthesis and activity of different MMPs. In this regard, our group identified that MMP-2, MMP-9 and MMP-14 plasma concentrations and their enzymatic activity were increased in tobacco smoker patients with NSCLC in comparison with NSCLC patients exposed to wood smoke (Gonzalez-Avila et al., 2013).

On the other hand, MMPs measured in urine have also been used as prognostic markers in bladder carcinoma. MMP-9 was found to be increased in urine samples of bladder carcinoma with a poor prognosis of the disease (Offersen et al., 2010). Urine MMP-7 high concentrations have been useful as well to identify bladder cancer metastasis (Szarvas et al., 2011).

Similarly, measurement of MMPs in saliva samples has been used to establish the diagnostic of oral SCC. Saliva MMP-2, MMP-9 and MMP-13 concentrations were augmented in oral SCC patients in comparison with control subjects and individuals with oral lichen planus (OLP) (Nosratzehi et al., 2017; Peisker et al., 2017). Interestingly, MMP-1 and MMP-3 measured in the surgical drain fluid from the postoperative wound of SCC of the head and neck patients has been useful to determine recurrences with an association among the increased levels of

these MMPs and a poor prognosis of the disease (Lassig et al., 2017).

Hence, an association among increased levels of one or many MMPs in body fluids and in tissue samples, and cancer progression is evident. However, to use MMPs as accurate diagnostic and prognostic markers, we must consider which MMP or MMPs are up- and downregulated, which MMPs have a protective effect, the tissue localization of the primary tumor, paying particular attention to its histologic characteristics, and the stage of the disease, as already mentioned several times, some MMPs have a dual participation depending on the cancer stage.

9. MMPs in cancer therapy

The rapid increase in knowledge about MMPs' functions and participation in cancer development has led to the improvement of safe and effective agents and strategies trying to regulate MMPs expression, zymogen activation, secretion, and enzymatic activity. Moreover, the therapy against MMPs plus conventional chemotherapy would not only be useful for interfering with MMPs role in cancer progression, but would also help in avoiding chemoresistance since some MMPs induce it. For instants, the cytotoxic drug oxaliplatin induces tumor cell apoptosis by Fas upregulation but the MMP-7 cleavage of Fas receptor or the increase of FasL that blocks Fas, provokes oxaliplatin chemoresistance in colon cancer cells (Almendro et al., 2009). Similarly, induction of chemoresistance to cis-platin by this MMP is mediated by the upregulation of the anti-apoptotic molecule Bcl-2 in A549 lung adenocarcinoma cells (Liu et al., 2009). Likewise, pancreatic ductal adenocarcinoma cells' chemoresistance to gemcitabine is mediated by MMP-14 upregulation of the high mobility group A2 (HMGA2) (Dangi-Garimella et al., 2011). This non-histone DNA binding protein participates in pancreatic cancer cells proliferation, invasion and in the maintenance of Ras-induced EMT (Dangi-Garimella et al., 2011).

On the other hand, four molecular levels to control MMPs expression and activity can be considered: (1) the transcriptional level targeting extracellular factors such as TGFβ and EGF, transcription factors as for example HIF-1, AP-1, NF-κB, and signaling pathways like MAPK and ERK pathways; (2) the translation level with the development of antisense strategies; for instance siRNA technology to interfere with the translation of the mRNA of a specific MMP; (3) the activation of pro-MMPs level using antibodies against the specific MMP; for example an anti-MMP-14 monoclonal antibody to prevent pro-MMP-2 activation; and (4) the inhibition level of the proteolytic and non-proteolytic activities of MMPs to block MMPs functions in cancer progression. Among the strategies listed above, the inhibition of MMPs enzymatic activity as a target in cancer therapy has been extensively explored. A lot of synthetic MMP inhibitors (MMPIs) has been designed with this purpose; some of them are listed herein (Table 5) (Li et al., 2013a; Yang et al., 2016).

Table 5
MMPs enzymatic activity inhibitors.

MMPI	Specificity
Peptidomimetic	
Batimastat (BB-94)	MMP-1, MMP-2, MMP-3, MMP-7, MMP-9
Marimastat (BB-2516)	MMP-1, MMP-2, MMP-3, MMP-7, MMP-9, MMP-12, MMP-14
Non-peptidomimetic	
Prinomastat (AG3340)	MMP-2, MMP-3, MMP-7, MMP-9, MMP-13, MMP-14
Rebimastat (BMS-275291)	MMP-1, MMP-2, MMP-3, MMP-7, MMP-9, MMP-14
Tanomastat (BAY 12-9566)	MMP-2, MMP-3, MMP-9, MMP-13, MMP-14
MMI-270 (CGS27023A)	MMP-1, MMP-2, MMP-3
Chemical modified tetracycline	
Metastat (CMT-3, COL-3)	MMP-1, MMP-2, MMP-8, MMP-9, MMP-13
Doxycycline	MMP-2, MMP-9
Minocycline	MMP-1, MMP-2, MMP-3
MMPI slow inhibitor	
SB-3CT (IN 1250)	MMP-2, MMP-9
Off-target MMPI	
Zoledronic acid	MMP-2, MMP-9, MMP-14, MMP-15
Letrozole	MMP-2, MMP-9
Natural MMPIs	
Neovastat (Æ-941)	MMP-1, MMP-2, MMP-7, MMP-9, MMP-12, MMP-13
Genistein	MMP-2, MMP-9, MMP-14, MMP-15, MMP-16

MMPIs, Matrix metalloproteinase inhibitors.

9.1. Peptidomimetic MMPIs

Peptidomimetic MMP inhibitors are pseudopeptide derivates that simulate the structure of a peptide sequence identified by the target MMP as its substrate. This peptide binds to the zinc ion of the MMP catalytic domain acting as a competitive inhibitor (Li et al., 2013a). According to the chemical group that binds and chelates zinc ion, peptidomimetic MMPIs are classified into: phosphoric acid derivatives, hydro-carboxylates, carboxylates, sulfhydryls and hydroxamates (Li et al., 2013a). Among first generation MMPIs are the hydroxamates batimastat (BB-94) that inhibits MMP-1, MMP-2, MMP-3, MMP-7 and MMP-9, and marimastat (BB-2516), a major water soluble MMPI for oral administration that blocks MMP-1, MMP-2, MMP-3, MMP-7, MMP-9 and MMP-12 activity (Yang et al., 2016). Unfortunately, patients that received marimastat presented dose-related musculoskeletal pain and inflammation. These effects are probably caused by the blockade of TNF-α converting enzyme (TACE) activity and the removal of the TNF-α receptor II (TNF-RII) (Yadav et al., 2014).

9.2. Non-peptidomimetic MMPIs

These MMPIs are designed according to the 3D X-ray crystallography structures of MMPs' active site to improve specificity and oral bioavailability (Yang et al., 2016). For example, tanomastat (BAY 12-9566), inhibits the activity of MMP-2, MMP-3, MMP-9, MMP-13 and MMP-14, and prinomastat (AG3340) blocks MMP-2, MMP-3, MMP-7, MMP-9, MMP-13 and MMP-14 enzymatic activity (Yang et al., 2016). Joint and musculoskeletal symptoms such as arthralgias, stiffness and swelling have been reported for prinomastat and rebimastat (BMS-275291) in a time and dose dependent manner (Li et al., 2013a). Unfortunately, the use of non-peptidomimetic MMPIs in medical trials did not improve patients' outcome in comparison with conventional chemotherapy and placebo.

9.3. Chemically modified tetracyclines

These tetracycline derivatives have lost their antibiotic activity by the removal of the dimethyl amino group producing limited systemic toxicity (Yadav et al., 2014). They have the capacity to inhibit MMPs enzymatic activity by binding to zinc and calcium ions, interfering with the activation of the MMPs latent forms, and reducing MMPs transcription (Yang et al., 2016). Doxycycline, minocycline and metastat (CMT-3, COL-3) are part of this MMPI group. Doxycycline has already the Food and Drug Administration approval in the prevention of periodontitis in which MMP-7 and MMP-8 are involved (Li et al., 2013a). Doxycycline prevents MMP-2 and MMP-9 secretion and also works as a noncompetitive inhibitor of the enzymatic activity of these MMPs (Yang et al., 2016). Metastat inhibits MMP-1, MMP-2, MMP-3, MMP-7, MMP-9 and MMP-12 activity (Yang et al., 2016). This MMPI has been used in Kaposi's sarcoma with a 40% overall response rate with a decrease in MMP-2 serum levels (Sapadin and Fleischmajer, 2006). Dose dependent toxicities of metastat are headache, cutaneous phototoxicity, nausea, vomiting, anorexia, anemia and increase of liver enzyme levels (Li et al., 2013a).

9.4. SB-3CT a MMPI slow inhibitor

The SB-3CT (IN 1250, MMP-2/MMP-9 Inhibitor IV) is a competitive

inhibitor of MMP-2 and MMP-9 activity and its inhibitory mechanism consists on an enzyme-catalyzed ring opening of the thiirane that produces stable zinc-thiolate species (Li et al., 2013a). The direct interaction of the zinc ion with the sulfur atom from the inhibitor generates a conformational change around the catalytic site that is very difficult to reverse (Meisel and Chang, 2017). SB-3CT behaves as a slow inhibitor of MMP-2 and MMP-9 resulting in long residence times that allows major duration of the pharmacological effects (Meisel and Chang, 2017). This inhibitor promotes apoptosis increasing caspase-3 and caspase-9 synthesis, and downregulates the anti-apoptotic molecules Bcl-XL and Bcl-2 expression. It also stimulates cell cycle arrest and blocks cell proliferation (Li et al., 2016).

9.5. Off target inhibitors of MMPs

This kind of drugs was not designed to target MMPs but has a beneficial effect by diminishing MMPs enzymatic activities. Such is the case of bisphosphonates, pyrophosphate (PPi) analogs that were developed to inhibit bone resorption and for the treatment of osteoporosis. These drugs have the ability of inhibiting MMP-1, MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-12, MMP-13, MMP-14 and MMP-15 (Yang et al., 2016; Gialeli et al., 2011). They also indirectly inhibit MMP-2 secretion via TIMP-2 (Yadav et al., 2014). For example, zoledronic acid downregulates the expression of MMP-2, MMP-9, MMP-14 and MMP-15 in breast cancer cells, and MMP-2 and MMP-9 in nasopharyngeal carcinoma cells (Dedes et al., 2013; Li et al., 2012). The use of zoledronic acid has improved patients' outcome in advanced breast and prostate cancer not just for its effects preventing bone metastasis but also by interfering in cancer cell growth and invasion (Coleman et al., 2011).

Likewise, a non-steroidal agent used for hormone therapy in breast cancer but with inhibitor effects on MMPs is letrozole. Letrozole suppresses MMP-2 and MMP-9 release from breast cancer cells in a dose dependent manner limiting their invasion potential (Mitropoulou et al., 2003).

9.6. Natural MMPIs

Natural MMPIs are used in cancer treatment to avoid the toxic effects of the synthetic inhibitors. Neovastat (Æ-941) is a shark cartilage extract with antiangiogenic and antimetastatic activities due to its capacity to inhibit VEGF and MMP-2, MMP-9, MMP-12 and serine elastase enzymatic activities (Gingras et al., 2001). Neovastat has been tolerated by patients but has side effects such as rash, constipation, diarrhea, flatulence, nausea, and vomiting (Li et al., 2013a). Phase III trials where Neovastat was used together with chemoradiotherapy in stage III NSCLC patients, demonstrated no differences in comparison with the use of conventional treatment (Lu et al., 2010).

Another natural MMPI is the soy isoflavonoid genistein; its structure resembles estradiol and interferes with the synthesis and activity of MMP-2, MMP-9, MMP-14, MMP-15 and MMP-16 (Gialeli et al., 2011). Genistein also downregulates genes implicated in cell cycle and cell proliferation, promotes apoptosis, inhibits NF-κB and decreases Akt protein levels, downregulates androgen-mediated carcinogenesis and has antioxidant effects (Yang et al., 2012b). All these attributes make genistein a candidate for cancer chemoprevention and treatment. However, results in medical trials evaluating its efficacy are inconsistent because of its low oral bioavailability (Yang et al., 2012b).

10. MMPs visualization in tumor tissue

MMPs identification in a particular tumor tissue is crucial to decide patient's therapy and to follow up, through MMPs enzymatic activity, the response to a drug during treatment. With this intention novel non-invasive imaging techniques have been developed.

MMPs activity based probes (ABP) have been designed to react only with active forms of MMPs (Deu et al., 2012). ABP include a warhead that links covalently to the MMPs catalytic cleft, a peptide sequence that targets the ABP to a specific MMP, and a fluorophore/quencher as for instance tetramethylrhodamine (TMR) or fluorescein that become fluorescent on activation allowing the localization of a particular MMP and its activity in the tumor tissue (Deu et al., 2012). The use of two fluorophores defines MMPs activity and the monitoring of the probe concentration. Magnetic resonance imaging (MIR) contrast agents such as gadolinium (Gd) chelates and superparamagnetic iron oxide particles are also useful to localize MMP activity but this technology has a low sensitivity because of the contrast agent solubility (Lebel et al., 2008). The addition of a solubility switch cleaved by a MMP such as MMP-2 reduces contrast agent solubility increasing its accumulation in the cells and therefore enhancing its sensitivity. Another interesting alternative is the use of radioisotopes with the ABPs and its visualization through photon emission tomography (PET) or single photon emission computed tomography (SPECT) (Matusiak et al., 2013).

Likewise, activatable cell penetrating peptides (ACPPs) were developed to improve cell specific uptake and increase sensitivity. ACPPs consist of a MMPs substrate inserted between a polycationic cell penetrating peptide conjugated with an image label, and a polyanionic peptide that reduces the net charge almost to zero preventing unspecific cell adhesion and penetration (Aguilera et al., 2009). When the linker (substrate) is cleaved by a specific MMP such as MMP-2 or MMP-9, the polyanionic peptide is released allowing cell adhesion and uptake of the image label. Moreover, dendrimeric nanoparticles coated by ACPPs, labeled with Cy5 for fluorescence or Gd for MIR have been used to increase sensitivity because of the increase of nanoparticles deposited in the tissue that overexpress the target MMP (Olson et al., 2010). The signal is more intense since a dendrimeric nanoparticle is covalently attached to the polycationic segment of around 6 ACPPs. When the linker substrate is cleaved by a MMP, 6 polyanionic segments are released increasing the image label signal that enters into the cell.

11. MMPs in the theranostic approach

Targeting a specific treatment to a specific site is a challenge in cancer therapy. A new strategy known as theranostic approach emerges to overcome this problem (Roy Chowdhury et al., 2016). The theranostic approach consists in the integration of specific targeted therapy with a specific targeted diagnostic test allowing diagnosis, drug delivery and treatment response monitoring in a single agent with less toxic side effects. Nanotechnology offers a good option to develop delivery nanosystems for theranostic proposes (Xie et al., 2011). Nanoparticles (NPs) most frequently used are: (1) ion oxide NP (IONP) made from magnetite or hematite; (2) quantum dots (QD) which are light-emitting nanocrystals made from semiconductor materials; (3) gold and silver NPs; (4) carbon nanotubes (CNTs); (5) silica NPs; and (6) protein-based NPs (Xie et al., 2011; Ren et al., 2011). The accumulation of NPs in neoplastic cells is due to their size scale that permits achievement of the enhanced-permeability-and-retention (EPR) effects (Xie et al., 2011). The inclusion of polymers as for instance polyethylene-glycol (PEG) to NPs surface enhanced circulation half-life to ensure that the nanosystem reaches their tumor target. The delivery system can be conjugated covalently or non-covalently to biological and therapeutic agents such as siRNA or chemotherapy drugs, image probes, and targeting ligands such as antibodies against specific biomarkers overexpressed in the cancer cells surface to guide the delivery system to its target (Roy Chowdhury et al., 2016). Furthermore, to avoid toxic side effects, the treatment is delivered as a pro-drug that activates at the TME by a specific process of cancer cells metabolism. In this context, pro-drugs with a peptide sequence that is cleaved by a specific MMP overexpressed in the target tumor cells have been designed. Once the peptide is disrupted the drug is internalized into the cells. For instance, the NPs copolymer methoxy-PEG-polycaprolactone (mPEG-PCL) has been modified with the insertion of the peptide PVGLIG (mPEG-

peptide-PCL) which is cleaved by MMP2/MMP-9; this nanosystem is conjugated with docetaxel (Doc) (Gel-Doc-NPs) (Li et al., 2013b). The uptake and cytotoxic effects were more effective in cancer cells treated with Gel-Doc-NPs in comparison with cells treated with DOC or non-modified NPs alone (Li et al., 2013b). Likewise, to increase paclitaxel solubility and cell intake, more complex NPs were constructed using a MMP-2 degradable peptide (GPLGIAGQ), PEG 2000-paclitaxel conjugate as a pro-drug, the cell penetrating enhancer transactivating transcriptional activator peptide PEG1000-phosphoethanolamine (TATp-PEG1000-PE), and a nanocarrier building block (PEG1000-PE) (Zhu et al., 2013). This delivery system lowers risk of premature release/leakage, enhances tumor targeting and drug internalization, and increases drug cytotoxic effects.

12. Conclusions and future perspectives

Because MMPs are main actors in each step of the metastatic cascade and since most cancer deaths are consequence of metastatic lesions, the interest in MMPs as diagnostic and prognostic markers has grown. Likewise, the development of new therapeutic approaches to block MMPs' functions to control the evolution of the disease is a particularly attractive proposal. However, phase III clinical trials have demonstrated that MMPIs were not useful to improve cancer patients' survival and moreover, some patients that received them had reduced survival rates in comparison with those that received a placebo. Furthermore, MMPIs treatment produces toxic effects that limit the maximun-tolerated dose interfering with MMPIs efficacy. Additionally, some MMPs are anti-targets, and when these MMPs are inhibited, there is a loss of their host protective effects and of their essential functions for the cell resulting in the onset of toxic side effects, and/or worsening of the disease (Dufour and Overall, 2013). Likewise, ADAMS and ADAMTS are also MMPIs anti-target molecules and their inhibition interferes with membrane protein shedding, regulation of growth factors availability, cell adhesion and cell-matrix interactions (Wong et al., 2013). To improve the efficacy of MMPIs, several factors need to be considered: (1) MMPs are implicated in a lot of normal physiological events that maintain the ECM homeostasis; (2) MMPs regulate molecular processes and cell pathways through the metabolism of growth factors, cytoskeletal proteins, cytokines, cell adhesion proteins, and chemokines; (3) some MMPs have protective effects that prevent cancer dissemination; (4) most MMPIs were designed to interfere with MMPs catalytic activity without considering that MMPs have no-proteolytic functions involved in cancer progression; and (5) MMPs expression and activity are specific to the different cancer stages.

Clearly, new strategies must be developed taking into account the clinical results of the use of MMPIs and MMPs roles in cancer progression: (1) identify the precise set of MMPs that are active in a specific tumor and stage using techniques such as microarrays, differentiating which MMPs have a protective function; (2) use more specific MMPIs, targeting both the catalytic site and the MMPs exosites; (3) develop monoclonal antibodies to specific MMPs such as the DX-2400 that joins the active site of MMP-14 (Devy et al., 2009); (4) design specific siRNA to block MMPs translation; (5) combined administration of chemotherapy plus MMPIs, siRNA or antibodies to avoid chemoresistance; (6) employ image techniques to determine MMPs concentration and activity, and to monitor treatment response; and (7) use nanotechnology to construct nano-delivery-systems that include MMPIs, siRNA, anti-MMPs monoclonal antibodies, pro-drugs, image probes, and specific targeting antibodies to guide the system to the corresponding cancer cells.

In summary, most cancer deaths are due to metastasis, mainly, because many patients arrive to the clinical services with advanced stages of the disease and second because the establishment of a pre-metastatic niche occurs in the early stages of cancer progression. MMPs have an important role during the whole disease development; the knowledge on how they participate in every one of the phases of the metastatic cascade considering the different stages of a particular cancer may help develop a specific therapy that, besides inhibiting MMPs synthesis and functions, allows the improvement of other treatments that increase overall patients' survival and quality of life.

Conflict of interest

The authors declare that they have no conflict of interest to disclose.

Disclosure

All authors had a substantial participation in the elaboration of this manuscript

GGA: Participated in the conception, design, acquisition and analysis of the information, writing of the manuscript, final edition of the figures, critical review of the manuscript and revision of the final version to be submitted.

BS: Participated in the writing of the manuscript, critical review of the manuscript and revised the final version to be submitted.

DAMP: Participated in the acquisition and analysis of the information, writing of the manuscript and revised the final version to be submitted.

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References

Achen, M.G., Stacker, S.A., 2008. Molecular control of lymphatic metastasis. Ann. N. Y. Acad. Sci. 1131, 225–234.

Acuff, H.B., Sinnamon, M., Fingleton, B., Boone, B., Levy, S.E., Chen, X., et al., 2006. Analysis of host- and tumor- derived proteinase using a custom dual species microarray reveals a protective role for stromal matrix metalloproteinase-12 in non-small cell lung cancer. Cancer Res. 66 (16) 7968-7795.

Aguilera, T.A., Olson, E.S., Timmers, M.M., Jiang, T., Tsien, R.Y., 2009. Systemic in vivo distribution of activatable cell penetrating peptides is superior to that of cell penetrating peptides. Integr. Biol. (Camb.) 1 (5–6), 371–381.

Ahn, G.O., Brown, J.M., 2008. Matrix metalloproteinase-9 is required for tumor vasculogenesis but not for angiogenesis: role of bone marrow-derived myelomonocytic cells. Cancer Cell 13 (3), 193–205.

Aikio, M., Alahuhta, I., Nurmenniemi, S., Suojanen, J., Palovuori, R., Teppo, S., et al., 2012. Arresten, a collagen-derived angiogenesis inhibitor, suppresses invasion of squamous cell carcinoma. PLoS One 7 (12), e51044. https://doi.org/10.1371/journal.pone.0051044.

Akool, el-S., Kleinert, H., Hamada, F.M., Abdelwahab, M.H., Förstermann, U., Pfeilschifter, J., et al., 2003. Nitric oxide increases the decay of matrix metalloproteinase 9 mRNA by inhibiting the expression of mRNA-stabilizing factor HuR. Mol. Cell. Biol. 23 (14), 4901–4916.

Akslen, L.A., Straume, O., Geisler, S., Sørlie, T., Chi, J.T., Aas, T., et al., 2011. Glomeruloid microvascular proliferation is associated with lack of response to chemotherapy in breast cancer. Br. J. Cancer 105 (1), 9–12.

Aldonyte, R., Brantly, M., Block, E., Patel, J., Zhang, J., 2009. Nuclear localization of active matrix metalloproteinase-2 in cigarette smoke-exposed apoptotic endothelial cells. Exp. Lung Res. 35 (1), 59–75.

Ali, M.A., Fan, X., Schulz, R., 2011. Cardiac sarcomeric proteins: novel intracellular targets of matrix metalloproteinase-2 in heart disease. Trends Cardiovasc. Med. 21 (4), 112–118.

Almendro, V., Ametller, E., García-Recio, S., Collazo, O., Casas, I., Augé, J.M., et al., 2009. The role of MMP7 and its cross-talk with the FAS/FASL system during the acquisition of chemoresistance to oxaliplatin. PLoS One 4 (3), e4728. https://doi.org/10.1371/journal.pone.0004728.

Almog, N., 2010. Molecular mechanisms underlying tumor dormancy. Cancer Lett. 294 (2), 139–146.
Amălinei, C., Căruntu, I.D., Giuşcă, S.E., Bălan, R.A., 2010. Matrix metalloproteinases involvement in pathologic conditions. Rom. J. Morphol. Embryol. 51 (2), 215–228.
Andarawewa, K.L., Boulay, A., Masson, R., Mathelin, C., Stoll, I., Tomasetto, C., et al., 2003. Dual stromelysin-3 function during natural mouse mammary tumor virus-ras tumor progression. Cancer Res. 63 (18), 5844–5849.
Andreuzzi, E., Colladel, R., Pellicani, R., Tarticchio, G., Cannizzaro, R., Spessotto, P., et al., 2017. The angiostatic molecule Multimerin 2 is processed by MMP-9 to allow sprouting angiogenesis. Matrix Biol. 64, 40–53.
Ardi, V.C., Van den Steen, P.E., Opdenakker, G., Schweighofer, B., Deryugina, E.I., Quigley, J.P., 2009. Neutrophil MMP-9 proenzyme, unencumbered by TIMP-1, undergoes efficient activation in vivo and catalytically induces angiogenesis via a basic fibroblast growth factor (FGF-2)/FGFR-2 pathway. J. Biol. Chem. 284 (38), 25854–25866.
Assadian, S., El-Assaad, W., Wang, X.Q., Gannon, P.O., Barrès, V., Latour, M., et al., 2012. p53 inhibits angiogenesis by inducing the production of Arresten. Cancer Res. 72 (5), 1270–1279.
Attieh, Y., Clark, A.G., Grass, C., Richon, S., Pocard, M., Mariani, P., et al., 2017. Cancer-associated fibroblasts lead tumor invasion thorugh integrin-β3-dependent fibronectin assembly. J. Cell Biol. 216 (11), 3509–3520.
Azorín, E., Solano-Agama, C., Mendoza-Garrigo, M.E., 2012. The invasión mode of GH(3) cells is conditioned by collagen subtype, and its efficiency depends on cell-cell adhesion. Arch. Biochem. Biophys. 528 (2), 148–155.
Baker, A.H., Edwards, D.R., Murphy, G., 2002. Metalloproteinase inhibitors: biological actions and therapeutic opportunities. J. Cell Sci. 115 (Pt19), 3719–3727.
Balbín, M., Fueyo, A., Tester, A.M., Pendás, A.M., Pitiot, A.S., Astudillom, A., et al., 2003. Loss of collagenase-2 confers increased skin tumor susceptibility to male mice. Nat. Genet. 35 (3), 252–257.
Bellon, G., Martiny, L., Robinet, A., 2004. Matrix metalloproteinases and matrikines in angiogenesis. Crit. Rev. Oncol. Hematol. 49 (3), 203–220.
Biswas, P., Canosa, S., Schoenfeld, J., Schoenfeld, D., Tucker, A., Madri, J.A., 2003. PECAM-1 promotes beta-catenin accumulation and stimulates endothelial cell proliferation. Biochem. Biophys. Res. Commun. 303 (1), 212–218.
Blavier, L., Lazaryev, A., Shi, X.H., Dorey, F.J., Shackleford, G.M., DeClerck, Y.A., 2010. Stromelysin-1 (MMP-3) is a target and a regulator of Wnt1-induced epithelial-mesenchymal transition (EMT). Cancer Biol. Ther. 10 (2), 198–208.
Boosani, C.S., Varma, A.K., Sudhakar, A., 2010. Validation of different systems for Tumstatin expression and its in-vitro and iv-vivo activities. J. Cancer Sci. Ther. 2009, 8–18.
Brassart-Pasco, S., Sénéchal, K., Thevenard, J., Ramont, L., Devy, J., Di Stefano, L., et al., 2012. Tetrastatin, the NC1 domain of the α4(IV) collagen chain: a novel potent anti-tumor matrikine. PLoS One 7 (4), e29587. https://doi.org/10.1371/journal.pone.0029587.
Brasse, D., Mathelin, C., Leroux, K., Chenard, M.P., Blaise, S., Stoll, I., et al., 2010. Matrix metalloproteinase 11/stromelysin 3 exerts both activator and repressor functions during the hematogenous metastatic process in mice. Int. J. Cancer 127 (6), 1347–1355.
Bremnes, R.M., Dønnem, T., Al-Saad, S., Al-Shibli, K., Andersen, S., Sirera, R., et al., 2011. The role of tumor stroma in cancer progression and prognosis: emphasis on carcinoma-associated fibroblasts and non-small cell lung cancer. JTO 6 (1), 209–217.
Brew, K., Nagase, H., 2010. The tissue inhibitors of metalloproteinases (TIMPs): an ancient family with structural and functional diversity. Biochim. Biophys. Acta 1803 (1), 55–71.
Bronsert, P., Enderle-Ammour, K., Bader, M., Timme, S., Kuehs, M., Csanadi, A., et al., 2014. Cancer cell invasion and EMT marker expression: a three-dimensional study of the human cancer-host interface. J. Pathol. 234 (3), 410–422.
Brooks, S.A., Lomax-Browne, H.J., Carter, T.M., Kinch, C.E., Hall, D.M., 2010. Molecular interactions in cancer cell metastasis. Acta Histochem. 112 (1), 3–25.
Brown, G.T., Murray, G.I., 2015. Current mechanistic insights into the roles of matrix metalloproteinases in tumour invasion and metastasis. J. Pathol. 237 (3), 273–281.
Butcher, D.T., Alliston, T., Weaver, V.M., 2009. A tense situation: forcing tumour progression. Nat. Rev. Cancer 9 (2), 108–122.
Cailhier, J.F., Sirois, I., Laplante, P., Lepage, S., Raymond, M.A., Brassard, N., et al., 2008. Caspase-3 activation triggers extracellular cathepsin L release and endorepellin proteolysis. J. Biol. Chem. 283 (40), 27220–27229.
Cao, Y., 2005. Opinion: emerging mechanisms of tumour lymphangiogenesis and lymphatic metastasis. Nat. Rev. Cancer 5 (9), 735–743.
Cao, J., Chiarelli, C., Richman, O., Zarrabi, K., Kozarekar, P., Zucker, S., 2008. Membrane type 1 matrix metalloproteinase induces epithelial-to-mesenchymal transition in prostate cancer. J. Biol. Chem. 283 (10), 6232–6240.
Carmeliet, P., Jain, R.K., 2011. Molecular mechanisms and clinical applications of angiogenesis. Nature 473 (7347), 298–307.
Cauwe, B., Opdenakker, G., 2010. Intracellular substrate cleavage: a novel dimension in the biochemistry, biology and pathology of matrix metalloproteinases. Crit. Rev. Biochem. Mol. Biol. 45 (5), 351–423.
Chabottaux, V., Ricaud, S., Host, L., Blacher, S., Paye, A., Thiry, M., et al., 2009. Membrane-type 4 matrix metalloproteinase (MT4-MMP) induces lung metastasis by alteration of primary breast tumour vascular architecture. J. Cell. Mol. Med. 13 (9B), 4002–4013.
Chan, K.C., Ko, J.M., Lung, H.L., Sedlacek, R., Zhang, Z.F., Luo, D.Z., et al., 2011. Catalytic activity of matrix metalloproteinase-19 is essential for tumor suppressor and anti-angiogenic activities in nasopharyngeal carcinoma. Int. J. Cancer 129 (8), 1826–1837.
Chang, J.T., Mani, S.A., 2013. Sheep, wolf or werewolf: cancer stem cells and the epithelial-to-mesenchymal transition. Cancer Lett. 341 (1), 16–23.
Chantrain, C.F., Shimada, H., Jodele, S., Groshen, S., Ye, W., Shalinsky, D.R., et al., 2004. Stromal matrix metalloproteinase-9 regulates the vascular architecture in neuroblastoma by promoting pericyte recruitment. Cancer Res. 64 (5), 1675–1686.
Chen, F., Zhuang, X., Lin, L., Yu, P., Wang, Y., Shi, Y., et al., 2015. New horizons in tumor microenvironment biology: challenges and opportunities. BMC Med. 13, 45. https://doi.org/10.1186/s12916-015-0278-7.
Chen, C., Zhao, S., Karnad, A., Freeman, J.W., 2018. The biology and role of CD44 in cancer progression: therapeutic implications. J. Hematol. Oncol. 11 (1), 64. https://doi.org/10.1186/s13045-018-0605-5.
Chiang, S.P., Cabrera, R.M., Segall, J.E., 2016. Tumor cell intravasation. Am. J. Physiol. Cell Physiol. 311 (1), C1–C14.
Cho, C., Kelsh-Lasher, R., Ambesi, A., McKeown-Longo, P.J., 2015. Cryptic activity within the Type III_1 domain of fibronectin regulates tissue inflammation and angiogenesis. Curr. Top. Pep. Protein Res. 16, 37–47.
Choi, D.H., Kim, E.M., Son, H.J., Joh, T.H., Kim, Y.S., Kim, D., et al., 2008. A novel intracellular role of matrix metalloproteinase-3 during apoptosis of dopaminergic cells. J. Neurochem. 106 (1), 405–415.
Choi, J.Y., Jang, Y.S., Min, S.Y., Song, J.Y., 2011. Overexpression of MMP-9 and HIF-1α in breast cancer cells under hypoxic conditions. J. Breast Cancer 14 (2), 88–95.
Chou, C.H., Teng, C.M., Tzen, K.Y., Chang, Y.C., Chen, J.H., Cheng, J.C., 2012. MMP-9 from sublethally irradiated tumor promotes Lewis lung carcinoma cell invasiveness and pulmonary metastasis. Oncogene 31 (4), 458–468.
Clark, I.M., Swingler, T.E., Sampieri, C.L., Edwards, D.R., 2008. The regulation of matrix metalloproteinases and their inhibitors. Int. J. Biochem. Cell Biol. 40 (6–7), 1362–1378.
Coleman, R., Cook, R., Hirsh, V., Major, P., Lipton, A., 2011. Zoledronic acid use in cancer patients: more than just supportive care? Cancer 117 (1), 11–23.
Condamine, T., Gabrilovich, D.I., 2011. Molecular mechanisms regulating myeloid-derived suppressor cell differentiation and function. Trends Immunol. 32 (1), 19–25.
Cornelius, L.A., Nehring, L.C., Harding, E., Bolanowski, M., Welgus, H.G., Kobayashi, D.K., et al., 1998. Matrix metalloproteinases generate angiostatin: effects on neovascularization. J. Immunol. 161 (12), 6845–6852.
Coskun, U., Yamac, D., Gulbahar, O., Sancak, B., Karaman, N., Ozkan, S., 2007. Locally advanced breast carcinoma treated with neoadjuvant chemotherapy: are the changes in serum levels of YKL-40, MMP-2 and MMP-9 correlated with tumor response? Neoplasma 54 (4), 348–352.
Cuadrado, E., Rosell, A., Borrell-Pagès, M., García-Bonilla, L., Hernández-Guillamon, M., Ortega-Aznar, A., et al., 2009. Matrix metalloproteinase-13 is activated and is found in the nucleus of neural cells after cerebral ischemia. J. Cereb. Blood Flow Metab. 29 (2), 398–410.
Cui, N., Mm, Hu, Khalil, R.A., 2017. Biochemical and biological attributes of matrix metalloproteinases. Prog. Mol. Transl. Sci. 147, 1–73.
D'Andrea, V., Guarino, S., Di Matteo, F.M., Maugeri-Sacca, M., De Maria, R., 2014. Cancer stem cells in surgery. G. Chir. 35 (11–12), 257–259.
Dangi-Garimella, S., Krantz, S.B., Barron, M.R., Shields, M.A., Heiferman, M.J., Grippo, P.J., et al., 2011. Three-dimensional collagen I promotes gemcitabine resistance in pancreatic cancer through MT1-MMP-mediated expression of HMGA2. Cancer Res. 71 (3), 1019–1028.
Davis, G.E., Stratman, A.N., Sacharidou, A., Koh, W., 2011. Molecular basis for endothelial lumen formation and tubulogenesis during vasculogenesis and angiogenic sprouting. Int. Rev. Cell Mol. Biol. 288, 101–165.
Dedes, P.G., Kanakis, I., Gialeli, Ch., Theocharis, A.D., Tsegenidis, T., Kletsas, D., et al., 2013. Preclinical evaluation of zoledronate using an in vitro mimetic cellular model for breast cancer metastatic bone disease. Biochim. Biophys. Acta 1830 (6), 3625–3634.
Delany, A.M., Canalis, E., 2001. The metastasis-associated metalloproteinase stromelysin-3 is induced by transforming growth factor-beta in osteoblasts and fibroblasts. Endocrinology 42 (4), 1561–1566.
Deryugina, E.I., Quigley, J.P., 2006. Matrix metalloproteinases and tumor metastasis. Cancer Metastasis Rev. 25 (1), 9–34.
Deryugina, E.I., Quigley, J.P., 2010. Pleiotropic roles of matrix metalloproteinases in tumor angiogenesis: contrasting, overlapping and compensatory functions. Biochim. Biophys. Acta 1803 (1), 103–120.
Detry, B., Erpicum, C., Paupert, J., Blacher, S., Maillard, C., Bruyère, F., et al., 2012. Matrix metalloproteinase-2 governs lymphatic vessel formation as an interstitial collagenase. Blood 119 (21), 5048–5056.
Deu, E., Verdoes, M., Bogyo, M., 2012. New approaches for dissecting protease functions to improve probe development and drug discovery. Nat. Struct. Mol. Biol. 19 (1), 9–16.
Devy, L., Huang, L., Naa, L., Yanamandra, N., Pieters, H., Frans, N., et al., 2009. Selective inhibition of matrix metalloproteinase-14 blocks tumor growth, invasion, and angiogenesis. Cancer Res. 69 (4), 1517–1526.
Dhani, N., Fyles, A., Hedley, D., Milosevic, M., 2015. The clinical significance of hypoxia in human cancers. Semin. Nucl. Med. 45 (2), 110–121.
Díaz, V.M., Viñas-Castells, R., García de Herreros, A., 2014. Regulation of the protein stability of EMT transcription factors. Cell Adhes. Migr. 8 (4), 418–428.
Douglass, S., Goyal, A., Iozzo, R.V., 2015. The role of perlecan and endorepellin in the control of tumor angiogenesis and endothelial cell autophagy. Connect. Tissue Res. 56 (5), 381–391.
Dufour, A., Overall, C.M., 2013. Missing the target: matrix metalloproteinase antitargets in inflammation and cancer. Trends Pharmacol. Sci. 34 (4), 233–242.
Eck, S.M., Côté, A.L., Winkelman, W.D., Brinckerhoff, C.E., 2009. CXCR4 and matrix metalloproteinase-1 are elevated in breast carcinoma-associated fibroblasts and in normal mammary fibroblasts exposed to factors secreted by breast cancer cells. Mol. Cancer Res. 7 (7), 1033–1044.
Eguchi, T., Kubota, S., Kawata, K., Mukudai, Y., Uehara, J., Ohgawara, T., et al., 2008.

Novel transcription-factor-like function of human matrix metalloproteinase 3 regulating the CTGF/CCN2 gene. Mol. Cell. Biol. 28 (7), 2391–2413.
Erdogan, B., Ao, M., White, L.M., Means, A.L., Brewer, B.M., Yang, L., et al., 2017. Cancer associated fibroblasts promote directional cancer cell migration by aligning fibronectin. J. Cell Biol. 216 (11), 3799–3816.
Fang, C., Wen, G., Zhang, L., Lin, L., Moore, A., Wu, S., et al., 2013. An important role of matrix metalloproteinase-8 in angiogenesis in vitro and in vivo. Cardiovasc. Res. 99 (1), 146–155.
Folmes, C.D., Nelson, T.J., Martinez-Fernandez, A., Arrell, D.K., Lindor, J.Z., Dzeja, P.P., et al., 2011. Somatic oxidative bioenergetics transitions into pluripotency-dependent glycolysis to facilitate nuclear reprogramming. Cell Metab. 14 (2), 264–271.
Frisch, S.M., Schaller, M., Cieply, B., 2013. Mechanisms that link the oncogenic epithelial-mesenchymal transition to suppression of anoikis. J. Cell Sci. 126 (Pt1), 21–29.
Fu, O.Y., Hou, M.F., Yang, S.F., Huang, S.C., Lee, W.Y., 2009. Cobalt chloride-induced hypoxia modulates the invasive potential and matrix metalloproteinases of primary and metastatic breast cancer cells. Anticancer Res. 29 (8), 3131–3138.
Fujiwara, S., Nakagawa, K., Harada, H., Nagato, S., Furukawa, K., Teraoka, M., et al., 2007. Silencing hypoxia-inducible factor-1alpha inhibits cell migration and invasion under hypoxic environment in malignant gliomas. Int. J. Oncol. 30 (4), 793–802.
Fukuda, H., Mochizuki, S., Abe, H., Okano, H.J., Hara-Miyauchi, C., Okano, H., et al., 2011. Host-derived MMP-13 exhibits a protective role in lung metastasis of melanoma cells by local endostatin production. Br. J. Cancer 105 (10), 1615–1624.
Gaggioli, C., Hooper, S., Hidalgo-Carcedo, C., Grosse, R., Marshall, J.F., Harrington, K., et al., 2007. Fibroblast-led collective invasion of carcinoma cells with differing roles for RhoGTPases in leading and following cells. Nat. Cell Biol. 9 (12), 1392–1400.
Garamszegi, N., Garamszegi, S.P., Scully, S.P., 2012. Matrix metalloproteinase-1 contribution to sarcoma cell invasion. J. Cell. Mol. Med. 16 (6), 1331–1341.
Gerdes, M.J., Sood, A., Sevinsky, C., Pris, A.D., Zavodszky, M.I., Ginty, F., 2014. Emerging understanding of multiscale tumor heterogeneity. Front. Oncol. 4, 366. https://doi.org/10.3389/fonc.2014.00366.
Gialeli, C., Theocharis, A.D., Karamanos, N.K., 2011. Roles of matrix metalloproteinases in cancer progression and their pharmacological targeting. FEBS J. 278 (1), 16–27.
Gingras, D., Batist, G., Béliveau, R., 2001. AE-941 (Neovastat): a novel multifunctional antiangiogenic compound. Expert Rev. Anticancer Ther. 1 (3), 341–347.
Gomis, R.R., Gawrzak, S., 2016. Tumor cell dormancy. Mol. Oncol. https://doi.org/10.1016/j.molonc.2016.09.009. pii: S1574-7891(16)30109-0.
Gonzalez-Avila, G., Sommer, B., Mendoza-Posada, D.A., Delgado, J., Aquino-Galvez, A., Ramos, C., 2012. Gelatinase activity of matrix metalloproteinases during first-line chemotherapy in lung adenocarcinoma patients: an initial approach. Lung 190 (1), 99–104.
Gonzalez-Avila, G., Delgado, J., Mendoza-Posada, D.A., Sommer, B., Ramos, C., Aquino-Galvez, A., et al., 2013. Differences in plasma MMPs and TIMPs protein expression and chemotherapy response in patients with tobacco- or wood-smoke-induced lung cancer. Respiration 85 (4), 281–288.
Gorelik, L., Flavell, R.A., 2001. Immune-mediated eradication of tumors through the blockade of transforming growth factor-beta signaling in T cells. Nat. Med. 7 (10), 1118–1122.
Greaves, M., Maley, C.C., 2012. Clonal evolution in cancer. Nature 481 (7381), 306–313.
Gresele, P., Falcinelli, E., Sebastiano, M., Mommi, S., 2017. Matrix metalloproteinases and platelet function. Prog. Mol. Biol. Transl. Sci. 147, 133–165.
Guarino, M., 2007. Epithelial-mesenchymal transition and tumour invasion. Int. J. Biochem. Cell Biol. 39 (12), 2153–2160.
Gupta, G.P., Nguyen, D.X., Chiang, A.C., Bos, P.D., Kim, J.Y., Nadal, C., et al., 2007. Mediators of vascular remodelling co-opted for sequential steps in lung metastasis. Nature 446 (7137), 765–770.
Gutiérrez-Fernández, A., Fueyo, A., Folgueras, A.R., Garabaya, C., Pennington, C.J., Pilgrim, S., et al., 2008. Matrix metalloproteinas-8 functions as a metastasis suppressor through modulation of tumor cell adhesion and invasion. Cancer Res. 68 (8), 2755–2763.
Hadler-Olsen, E., Winberg, J.O., Uhlin-Hansen, L., 2013. Matrix metalloproteinases in cancer: their value as diagnostic and prognostic markers and therapeutic targets. Tumour Biol. 34 (4), 2041–2051.
Hadler-Olsen, E., Solli, A.I., Hafstad, A., Winberg, J.O., Uhlin-Hansen, L., 2015. Intracellular MMP-2 activity in skeletal muscle is associated with type II fibers. J. Cell. Physiol. 230 (1), 160–169.
Hegde, R.S., Bernstein, H.D., 2006. The surprising complexity of signal sequences. Trends Biochem. Sci. 31 (10), 563–571.
Heissig, B., Hattori, K., Dias, S., Friedrich, M., Ferris, B., Hackett, N.R., et al., 2002. Recruitment of stem and progenitor cells from the bone marrow niche requires MMP-9 mediated release of kit-ligand. Cell 109 (5), 625–637.
Heljasvaara, R., Nyberg, P., Luostarinen, J., Parikka, M., Heikkilä, P., Rehn, M., et al., 2005. Generation of biologically active endostatin fragments from human collagen XVIII by distinct matrix metalloproteases. Exp. Cell Res. 307 (2), 292–304.
Heneberg, P., 2016. Paracrine tumor signaling induces transdifferentiation of surrounding fibroblasts. Crit. Rev. Oncol. Hematol. 97, 303–311.
Hernández-Camarero, P., Jiménez, G., López-Ruiz, E., Barungi, S., Marchal, J.A., Perán, M., 2018. Revisiting the dynamic cancer stem cell model: importance of tumour edges. Crit. Rev. Oncol. Hematol. 131, 35–45.
Hida, K., Kawamoto, T., Ohga, N., Akiyama, K., Hida, Y., Shindoh, M., 2011. Altered angiogenesis in the tumor microenvironment. Pathol. Int. 61 (11), 630–637.
Hida, K., Ohga, N., Akiyama, K., Maishi, N., Hida, Y., 2013. Heterogeneity of tumor endothelial cells. Cancer Sci. 104 (11), 1391–1395.
Huang, C.H., Yang, W.H., Chang, S.Y., Tai, S.K., Tzeng, C.H., Kao, J.Y., et al., 2009a. Regulation of membrane-type 4 matrix metalloproteinase by SLUG contributes to hypoxia-mediated metastasis. Neoplasia 11 (12), 1371–1382.
Huang, Y., Song, N., Ding, Y., Yuan, S., Li, X., Cai, H., et al., 2009b. Pulmonary vascular destabilization in the premetastatic phase facilitates lung metastasis. Cancer Res. 69 (19), 7529–7537.
Huang, J., Pan, C., Hu, H., Zheng, S., Ding, L., 2012. Osteopontin-enhanced hepatic metastasis of colorectal cancer cells. PLoS One 7 (10), e47901. https://doi.org/10.1371/journal.pone.00447901.
Huang, S.H., Law, C.H., Kuo, P.H., Hu, R.Y., Yang, C.C., Chung, T.W., et al., 2016. MMP-13 is involved in oral cancer cell metastasis. Oncotarget 7 (13), 17144–17161.
Huber, M.A., Kraut, N., Beug, H., 2005. Molecular requirements for epithelial-mesenchymal transition during tumor progression. Curr. Opin. Cell Biol. 17 (5), 548–558.
Huwiler, A., Akool, el-S., Aschrafi, A., Hamada, F.M., Pfeilschifter, J., Eberhardt, W., 2003. ATP potentiates interleukin-1 beta-induced MMP-9 expression in mesangial cells via recruitment of the ELAV protein HuR. J. Biol. Chem. 278 (51), 51758–51769.
Hwang-Bo, J., Yoo, K.H., Park, J.H., Jeong, H.S., Chung, I.S., 2012. Recombinant canstatin inhibits angiopoietin-1-induced angiogenesis and lymphangiogenesis. Int. J. Cancer 131 (2), 298–309.
Hwang-Bo, J., Park, J.H., Chung, I.S., 2015. Tumstatin induces apoptosis mediated by Fas signaling pathway in oral squamous cell carcinoma SCC-VII cells. Oncol. Lett. 10 (2), 1016–1022.
Hwang-Bo, J., Park, J.H., Bae, M.G., Chung, I.S., 2016. Recombinant canstatin inhibits VEGF-A-induced lymphangiogenesis and metastasis in an oral squamous cell carcinoma SCC-VII animal model. Cancer Med. 5 (10), 2977–2988.
Ingvarsen, S., Porse, A., Erpicum, C., Maertens, L., Jürgensen, H.J., Madsen, D.H., et al., 2013. Targeting a single function of the multifunctional matrix metalloprotease MT1-MMP: impact on lymphangiogenesis. J. Biol. Chem. 288 (15), 10195–10204.
International Agency for Research on Cancer (IARC), 2018. GLOBOCAN 2018. Cancer Today: Estimated number of new cases in 2018, worldwide, both sexes, all ages. IARC Cancer Base, Lyon France Available at http://gco.iarc.fr. Accessed February 4, 2019.
Ip, Y.C., Cheung, S.T., Fan, S.T., 2007. Atypical localization of membrane type 1-matrix metalloproteinase in the nucleus is associated with aggressive features of hepatocellular carcinoma. Mol. Carcinog. 46 (3), 225–230.
Islekel, H., Oktay, G., Terzi, C., Canda, A.E., Füzün, M., Küpelioğlu, A., 2007. Matrix metalloproteinase-9, -3 and tissue inhibitor of matrix metalloproteinase-1 in colorectal cancer: relationship to clinicopathological variables. Cell Biochem. Funct. 25 (4), 433–441.
Ito, T.K., Ishii, G., Saito, S., Yano, K., Hoshino, A., Suzuki, T., et al., 2009. Degradation of soluble VEGF receptor-1 by MMP-7 allows VEGF access to endothelial cells. Blood 113 (10), 2363–2369.
Jackson, B.C., Nebert, D.W., Vasiliou, V., 2010. Update of human and mouse matrix metalloproteinase families. Hum. Genomics 4 (3), 194–201.
Jacob, A., Prekeris, R., 2015. The regulation of MMP targeting to invadopodia during cancer metastasis. Front. Cell Dev. Biol. 3, 4. https://doi.org/10.3389/fcell.2015.00004.
Jacob, A., Jing, J., Lee, J., Schedin, P., Gilbert, S.M., Peden, A.A., et al., 2013. Rab40b regulates trafficking of MMP2 and MMP9 during invadopodia formation and invasion of breast cancer cells. J. Cell Sci. 126 (Pt 20), 4647–4658.
Janowski, M., 2009. Functional diversity of SDF-1 splicing variants. Cell Adhes. Migr. 3 (3), 243–249.
Jenkins, G., 2008. The role of proteases in transforming growth factor-beta activation. Int. J. Biochem. Cell Biol. 40 (6–7), 1068–1078.
Ji, R.C., 2006. Lymphatic endothelial cells, lymphangiogenesis, and extracellular matrix. Lymphat. Res. Biol. 4 (2), 83–100.
Jing, S.W., Wang, Y.D., Kuroda, M., Su, J.W., Sun, G.G., Liu, Q., et al., 2012. HIF-1α contributes to hypoxia-induced invasion and metastasis of esophageal carcinoma via inhibiting E-cadherin and promoting MMP-2 expression. Acta Med. Okayama 66 (5), 399–407.
John, H., Radtke, K., Ständker, L., Forssmann, W.G., 2005. Identification and characterization of novel endogenous proteolytic forms of the human angiogenesis inhibitors restin and endostatin. Biochim. Biophys. Acta 1747 (2), 161–170.
Jolly, M.K., Huang, B., Lu, M., Mani, S.A., Levine, H., Ben-Jacob, E., 2014. Towards elucidating the connection between epithelial-mesenchymal transitions and stemless. J. R. Soc. Interface 11 (101), 20140962. https://doi.org/10.1098/rsif.2014.0962.
Joo, N.E., Watanabe, T., Chen, C., Chekenya, M., Stallcup, W.B., Kapila, Y.L., 2008. NG2, a novel proapoptotic receptor, opposes integrin alpha4 to mediate anoikis through PKCalpha-dependent suppression of FAK phosphorylation. Cell Death Differ. 15 (5), 899–907.
Joo, N.E., Miao, D., Bermúdez, M., Stallcup, W.B., Kapila, Y.L., 2014. Shedding of NG2 by MMP-13 attenuates anoikis. DNA Cell Biol. 33 (12), 854–862.
Jost, M., Folgueras, A.R., Frérart, F., Pendas, A.M., Blacher, S., Houard, X., et al., 2006. Earlier onset of tumoral angiogenesis in matrix metalloproteinase-19-deficient mice. Cancer Res. 66 (10), 5234–5241.
Juncker-Jensen, A., Deryugina, E.I., Rimann, I., Zajac, E., Kupriyanova, T.A., Engelholm, L.H., et al., 2013. Tumor MMP-1 activates endothelial PAR1 to facilitate vascular intravasation and metastatic dissemination. Cancer Res. 73 (14), 4196–4211.
Jung, H.Y., Fattet, L., Yang, J., 2015. Molecular pathways: linking tumor microenvironment to epithelial-mesenchymal transition in metastasis. Clin. Cancer Res. 21 (5), 962–968.
Justilien, V., Regala, R.P., Tseng, I.C., Walsh, M.P., Batra, J., Radisky, E.S., et al., 2012. Matrix metalloproteinase-10 is required for lung cancer stem cell maintenance, tumor initiation and metastatic potential. PLoS One 7 (4), e35040. https://doi.org/10.1371/journal.pone.0035040.
Kalluri, R., 2003. Basement membranes: structure, assembly and role in tumour angiogenesis. Nat. Rev. Cancer 3 (6), 422–433.
Kang, T., Yi, J., Guo, A., Wang, X., Overall, C.M., Jiang, W., et al., 2001. Subcellular distribution and cytokine- and chemokine-regulated secretion of leukolysin/MT6-MMP/MMP-25 in neutrophils. J. Biol. Chem. 276 (24), 21960–21968.

Karagiannis, E.D., Popel, A.S., 2007. Identification of novel short peptides derived from the alpha 4, alpha 5, and alpha 6 fibrils of type IV collagen with anti-angiogenic properties. Biochem. Biophys. Res. Commun. 354 (2), 434–439.
Karaman, S., Detmar, M., 2014. Mechanisms of lymphatic metastasis. J. Clin. Invest. 124 (3), 922–928.
Keith, B., Johnson, R.S., Simon, M.C., 2011. HIF1α and HIF2α: sibling rivalry in hypoxic tumour growth and progression. Nat. Rev. Cancer 12 (1), 9–22.
Kessenbrock, K., Plaks, V., Werb, Z., 2010. Matrix metalloproteinases: regulators of the tumor microenvironment. Cell 141 (1), 52–67.
Kessenbrock, K., Wang, C.Y., Werb, Z., 2015. Matrix metalloproteinases in stem cell regulation and cancer. Matrix Biol. 44–46, 184–190.
Khamis, Z.I., Iczkowski, K.A., Man, Y.G., Bou-Dargham, M.J., Sang, Q.X., 2016. Evidence for a proapoptotic role of matrix metalloproteinase-26 in human prostate cancer cells and tissues. J. Cancer 7 (1), 80–87.
Khanna-Gupta, A., Zibello, T., Idone, V., Sun, H., Lekstrom-Himes, J., Berliner, N., 2005. Human neutrophil collagenase expression is C/EBP-dependent during myeloid development. Exp. Hematol. 33 (1), 42–52.
Kim, Y.S., Joh, T.H., 2012. Matrix metalloproteinases, new insights into the understanding of neurodegenerative disorders. Biomol. Ther. (Seoul) 20 (2), 133–143.
Kim, Y.N., Koo, K.H., Sung, J.Y., Yun, U.J., Kim, H., 2012. Anoikis resistance: an essential prerequisite for tumor metastasis. Int. J. Cell Biol. 2012, 306879. https://doi.org/10.1155/2012/306879.
Kim, E.M., Shin, E.J., Lee, J.A., Son, H.J., Choi, D.H., Han, J.M., et al., 2014. Caspase-9 activation and Apaf-1 cleavage by MMP-3. Biochem. Biophys. Res. Commun. 453 (3), 563–568.
Klein, G., Schmal, O., Aicher, W.K., 2015. Matrix metalloproteinases in stem cell mobilization. Matrix Biol. 44–46, 175–183.
Kocemba, K.A., van Andel, H., de Haan-Kramer, A., Mahtouk, K., Versteeg, R., Kersten, M.J., et al., 2013. The hypoxia target adrenomedullin is aberrantly expressed in multiple myeloma and promotes angiogenesis. Leukemia 27 (8), 1729–1737.
Kopp, H.G., Placke, T., Salih, H.R., 2009. Platelet-derived transforming growth factor-beta down-regulates NKG2D thereby inhibiting natural killer cell antitumor reactivity. Cancer Res. 69 (19), 7775–7783.
Korpi, J.T., Kervinen, V., Mäklin, H., Väänänen, A., Lahtinen, M., Läärä, E., et al., 2008. Collagenase-2 (matrix metalloproteinase-8) plays a protective role in tongue cancer. Br. J. Cancer 98 (4), 766–775.
Koskimaki, J.E., Karagiannis, E.D., Tang, B.C., Hammers, H., Watkins, D.N., Pili, R., et al., 2010. Pentastatin-1, a collagen IV derived 20-mer peptide, suppresses tumor growth in a small cell lung cancer xenograft model. BMC Cancer 10, 29. https://doi.org/10.1186/1471-2407-10-29.
Kwan, J.A., Schulze, C.J., Wang, W., Leon, H., Sariahmetoglu, M., Sung, M., et al., 2004. Matrix metalloproteinase-2 (MMP-2) is present in the nucleus of cardiac myocytes and is capable of cleaving poly (ADP-ribose) polymerase (PARP) in vitro. FASEB J. 18 (6), 690–692.
Labelle, M., Hynes, R.O., 2012. The initial hours of metastasis: the importance of cooperative host-tumor cell interactions during hematogenous dissemination. Cancer Discov. 2 (12), 1091–1099.
Labelle, M., Begum, S., Hynes, R.O., 2011. Direct signaling between platelets and cancer cells induces an epithelial-mesenchymal-like transition and promotes metastasis. Cancer Cell 20 (5), 576–590.
Lambert, E., Dassé, E., Haye, B., Petitfrère, E., 2004. TIMPs as multifacial proteins. Crit. Rev. Oncol. Hematol. 49 (3), 187–198.
Lassig, A.A.D., Joseph, A.M., Lindgren, B.R., Yueh, B., 2017. Association of oral cavity and oropharyngeal cancer biomarkers in surgical drain fluid with patient outcomes. JAMA Otolaryngol. Head Neck Surg. 143 (7), 670–678.
Lebel, R., Jastrzebska, B., Therriault, H., Cournoyer, M.M., McIntyre, J.O., Escher, E., et al., 2008. Novel solubility-switchable MRI agent allows the noninvasive detection of matrix metalloproteinase-2 activity in vivo in a mouse model. Magn. Reson. Med. 60 (5), 1056–1065.
Lee, H.J., Yun, C.H., Lim, S.H., Kim, B.C., Baik, K.G., Kim, J.M., et al., 2007. SRF is a nuclear repressor of Smad3-mediated TGF-beta signaling. Oncogene 26 (2), 173–185.
Lehti, K., Rose, N.F., Valavaara, S., Weiss, S.J., Keski-Oja, J., 2009. MT1-MMP promotes vascular smooth muscle dedifferentiation through LRP1 processing. J. Cell Sci. 122 (Pt1), 126–135.
Leong, H.S., Robertson, A.E., Stoletov, K., Leith, S.J., Chin, C.A., Chien, A.E., et al., 2014. Invadopodia are required for cancer cell extravasation and are a therapeutic target for metastasis. Cell Rep. 8 (5), 1558–1570.
Li, S., Li, Q., 2014. Cancer stem cells and tumor metastasis. Int. J. Oncol. 44 (6), 1806–1812.
Li, W., Savinov, A.Y., Rozanov, D.V., Golubkov, V.S., Hedayat, H., Postnovam, T.I., et al., 2004. Matrix metalloproteinase-26 is associated with estrogen-dependent malignancies and targets alpha1-antitrypsin serpin. Cancer Res. 64 (23), 8657–8665.
Li, X.Y., Lin, Y.C., Huang, W.L., Hong, C.Q., Chen, J.Y., You, Y.J., et al., 2012. Zoledronic acid inhibits proliferation and impairs migration and invasion through down-regulating VEGF and MMPs expression in human nasopharyngeal carcinoma cells. Med. Oncol. 29 (2), 714–720.
Li, W., Saji, S., Sato, F., Noda, M., Toi, M., 2013a. Potential clinical applications of matrix metalloproteinase inhibitors and their future prospects. Int. J. Biol. Markers 28 (2), 117–130.
Li, R., Wu, W., Liu, Q., Wu, P., Xie, L., Zhu, Z., et al., 2013b. Intelligently targeted drug delivery and enhanced antitumor effect by gelatinase-responsive nanoparticles. PLoS One 8 (7), e69643. https://doi.org/10.1371/journal.pone.0069643.
Li, J., Wang, H., Ke, H., Ni, S., 2015a. MiR-129 regulates MMP9 to control metastasis of non-small cell lung cancer. Tumor Biol. 36 (8), 5785–5790.
Li, W., Li, S., Deng, L., Yang, S., Li, M., Long, S., et al., 2015b. Decreased MT1-MMP in gastric cancer suppressed cell migration and invasion via regulating MMPs and EMT. Tumor Biol. 36 (9), 6883–6889.
Li, H., Li, L., Zheng, H., Yao, X., Zang, W., 2016. Regulatory effects of ΔFosB on proliferation and apoptosis of MCF-7 breast cancer cells. Tumour Biol. 37 (5), 6053–6063.
Liao, W.T., Ye, Y.P., Deng, Y.J., Bian, X.W., Ding, Y.Q., 2014. Metastatic cancer stem cells: from the concept to therapeutics. Am. J. Stem Cells 3 (2), 46–62.
Limb, G.A., Matter, K., Murphy, G., Cambrey, A.D., Bishop, P.N., Morris, G.E., et al., 2005. Matrix metalloproteinase-1 associates with intracellular organelles and confers resistance to lamin A/C degradation during apoptosis. Am. J. Pathol. 166 (5), 1555–1563.
Lin, J.L., Wang, M.J., Lee, D., Liang, C.C., Lin, S., 2008. Hypoxia-inducible factor-1alpha regulates matrix metalloproteinase-1 activity in human bone marrow-derived mesenchymal stem cells. FEBS Lett. 582 (17), 2615–2619.
Lin, C.Y., Tsai, P.H., Kandaswami, C.C., Lee, P.P., Huang, C.J., Hwang, J.J., et al., 2011. Matrix metalloproteinase-9 cooperates with transcription factor Snail to induce epithelial-mesenchymal transition. Cancer Sci. 102 (4), 815–827.
Liu, Y., Cao, X., 2016. Characteristics and significance of the pre-metastatic niche. Cancer Cell 30 (5), 668–681.
Liu, H., Zhang, T., Wu, B., Huang, J., Zhou, Y., Zhu, J., 2009. Chronic exposure to exogenous matrilysin induces chemoresistance and enhances Bcl-2 expression in A549 lung adenocarcinoma cells. Mol. Biol. Rep. 36 (8), 2099–2109.
Liu, J., Huang, J., Yao, W.Y., Ben, Q.W., Chen, D.F., He, X.Y., et al., 2012. The origins of vascularization in tumors. Front. Biosci. (Landmark Ed) 17, 2559–2565.
Loffek, S., Schilling, O., Franzke, C.W., 2011. Biological role of matrix metalloproteinases: a critical balance. Eur. Respir. J. 38 (1), 191–208.
Lopes-Bastos, B.M., Jiang, W.G., Cai, J., 2016. Tumour-endothelial cell communications: Important and indispensable mediators of tumour angiogenesis. Anticancer Res. 36 (3), 1119–1126.
Lorenzon, E., Colladel, R., Andreuzzi, E., Marastoni, S., Todaro, F., Schiappacassi, M., et al., 2012. MULTIMERIN2 impairs tumor angiogenesis and growth by interfering with VEGF-A/VEGFR2 pathway. Oncogene 31 (26), 3136–3147.
Loreto, C., Leonardi, R., Musumeci, G., Pannone, G., Castorina, S., 2013. An ex vivo study on immunohistochemical localization of MMP-7 and MMP-9 in temporomandibular joint discs with internal derangement. Eur. J. Histochem. 57 (2), e12.
Lu, X., Kang, Y., 2010. Hypoxia and hypoxia-inducible factors: master regulators of metastasis. Clin. Cancer Res. 16 (24), 5928–5935.
Lu, C., Lee, J.J., Komaki, R., Herbst, R.S., Feng, L., Evans, W.K., et al., 2010. Chemoradiotherapy with or without AE-941 in stage III non-small cell lung cancer: a randomized phase III trial. J. Natl. Cancer Inst. 102 (12), 859–865.
Lu, P., Weaver, V.M., Werb, Z., 2012. The extracellular matrix: a dynamic niche in cancer progression. J. Cell Biol. 196 (4), 395–406.
Ma, L., Dong, L., Chang, P., 2019. CD44v6 engages in colorectal cancer progression. Cell Death. Dis. 10 (1), 30. https://doi.org/10.1038/s41419-018-1265-7.
Mannello, F., Medda, V., 2012. Nuclear localization of matrix metalloproteinases. Prog. Histochem. Cytochem. 47 (1), 27–58.
Mannello, F., Luchetti, F., Falcieri, E., Papa, S., 2005. Multiple roles of matrix metalloproteinases during apoptosis. Apoptosis 10 (1), 19–24.
Marjanovic, N.D., Weinberg, R.A., Chaffer, C.L., 2013. Cell plasticity and heterogeneity in cancer. Clin. Chem. 59 (1), 168–179.
Mastenbroek, T.G., Feijge, M.A., Kremers, R.M., van den Bosch, M.T., Swieringa, F., De Groef, L., et al., 2015. Platelet-associated matrix metalloproteinases regulate thrombus formation and exert local collagenolytic activity. Arterioscler. Thromb. Vasc. Biol. 35 (12), 2554–2561.
Matusiak, N., van Waarde, A., Bischoff, R., Oltenfreiter, R., van de Wiele, C., Dierckx, R.A., et al., 2013. Probes for non-invasive matrix metalloproteinase-targeted imaging with PET and SPECT. Curr. Pharm. Des. 19 (25), 4647–4672.
Mazor, R., Alsaigh, T., Shaked, H., Altshuler, A.E., Pocock, E.S., Kistler, E.B., et al., 2013. Matrix metalloproteinase-1-mediated up-regulation of vascular endothelial growth factor-2 in endothelial cells. J. Biol. Chem. 288 (1), 598–607.
McCawley, L.J., Crawford, H.C., King Jr., L.E., Mudgett, J., Matrisian, L.M., 2004. A protective role for matrix metalloproteinase-3 in squamous cell carcinoma. Cancer Res. 64 (19), 6965–6972.
McQuibban, G.A., Butler, G.S., Gong, J.H., Bendall, L., Power, C., Clark-Lewis, I., et al., 2001. Matrix metalloproteinase activity inactivates the CXC chemokine stromal cell-derived factor-1. J. Biol. Chem. 276 (47), 43503–43508.
Meisel, J.E., Chang, M., 2017. Selective small-molecule inhibitors as chemical tools to define the roles of matrix metalloproteinases in disease. Biochim. Biophys. Acta. https://doi.org/10.1016/j.bbamcr.2017.04.011. pii: S0167-4889(17)30105-2.
Meng, X.N., Jin, Y., Bai, J., Liu, G.Y., Zhu, J., Zhao, Y.Z., et al., 2009. Characterization of fibronectin-mediated FAK signaling pathways in lung cancer cell migration and invasion. Br. J. Cancer 101 (2), 327–334.
Menter, D.G., Tucker, S.C., Kopetz, S., Sood, A.K., Crissman, J.D., Honn, K.V., 2014. Platelets and cancer: a casual or causal relationship: revisited. Cancer Metastasis Rev. 33 (1), 231–269.
Mitropoulou, T.N., Tzanakakis, G.N., Kletsas, D., Kalofonos, H.P., Karamanos, N.K., 2003. Letrozole as a potent inhibitor of cell proliferation and expression of metalloproteinases (MMP-2 and MMP-9) by human epithelial breast cancer cells. Int. J Cancer 104 (2), 155–160.
Mittal, R., Patel, A.P., Debs, L.H., Nguyen, D., Patel, K., Grati, M., et al., 2016. Intricate functions of matrix metalloproteinases in physiological and pathological conditions. J. Cell Physiol. 231 (12), 2599–2621.
Miyata, S., Nakatani, Y., Hayashi, N., Nakashima, T., 2005. Matrix-degrading enzymes tissue plasminogen activator and matrixmetalloprotease-3 in the hypothalamo-neurohypophysial system. Brain Res. 1058 (1–2), 1–9.
Miyoshi, A., Kitajima, Y., Ide, T., Ohtaka, K., Nagasawa, H., Uto, Y., et al., 2006. Hypoxia accelerates cancer invasion of hepatoma cells by upregulating MMP expression in an

HIF-1alpha-independent manner. Int. J. Oncol. 29 (6), 1533–1539.
Mohammad, G., Kowluru, R.A., 2011. Novel role of mitochondrial matrix metalloproteinase-2 in the development of diabetic retinopathy. Invest. Ophthalmol. Vis. Sci. 52 (6), 3832–3841.
Monboisse, J.C., Oudart, J.B., Ramont, L., Brassart-Pasco, S., Maquart, F.X., 2014. Matrikines from basement membrane collagens: a new anti-cancer strategy. Biochim. Biophys. Acta 1840 (8), 2589–2598.
Moshal, K.S., Tipparaju, S.M., Vacek, T.P., Kumar, M., Singh, M., Frank, I.E., et al., 2008. Mitochondrial matrix metalloproteinase activation decreases myocyte contractility in hyperhomocysteinemia. Am. J. Physiol. Heart Circ. Physiol. 295 (2), H890–H897.
Muñoz-Nájar, U.M., Neurath, K.M., Vumbaca, F., Claffey, K.P., 2006. Hypoxia stimulates breast carcinoma cell invasion through MT1-MMP and MMP-2 activation. Oncogene 25 (16), 2379–2392.
Murphy, G., Nagase, H., 2008. Progress in matrix metalloproteinase research. Mol. Aspects Med. 29 (5), 290–308.
Murphy, G., Stanton, H., Cowell, S., Butler, G., Knäuper, V., Atkinson, S., et al., 1999. Mechanisms for pro matrix metalloproteinase activation. APMIS 107 (1), 38–44.
Nagaraj, S., Gabrilovich, D.I., 2010. Myeloid-derived suppressor cells in human cancer. Cancer J. 16 (4), 348–353.
Nagase, H., Itoh, Y., Binner, S., 1994. Interaction of alpha 2-macroglobulin with matrix metalloproteinases and its use for identification of their active forms. Ann. N. Y. Acad. Sci. 732, 294–302.
Neskey, D.M., Ambesi, A., Pumiglia, K.M., McKeown-Longo, P.J., 2008. Endostatin and anastellin inhibit distinct aspects of the angiogenic process. J. Exp. Clin. Cancer Res. 27, 61. https://doi.org/10.1186/1756-9966-27-61.
Nimmakayala, R.K., Batra, S.K., Ponnusamy, M.P., 2018. Unraveling the journey of cancer stem cells from origin to metastasis. Biochim. Biophys. Acta Rev. Cancer 1871 (1), 50–63.
Nishida, C., Kusubata, K., Tashiro, Y., Gritli, I., Sato, A., Ohki-Koizumi, M., et al., 2012. MT1-MMP plays a critical role in hematopoiesis by regulating HIF-mediated chemokine/cytokine gene transcription within niche cells. Blood 119 (23), 5405–5416.
Noë, V., Fingleton, B., Jacobs, K., Crawford, H.C., Vermeulen, S., Steelant, W., et al., 2001. Release of an invasion promoter E-cadherin fragment by matrilysin and stromelysin-1. J. Cell Sci. 114 (Pt1), 111–118.
Nosratzehi, T., Alijani, E., Moodi, M., 2017. Salivary MMP-1, MMP-2, MMP-3 and MMP-13 levels in patients with oral lichen planus and squamous cell carcinoma. Asian Pac. J. Cancer Prev. 18 (7), 1947–1951.
O'Flaherty, J.D., Varr, M., Fennell, D., Richard, D., Reynolds, J., O'Leary, J., et al., 2012. The cancer stem-cell hypothesis. Its emerging role in lung cancer biology and its relevance for future therapy. JTO 7 (12), 1880–1890.
Offersen, B.V., Knap, M.M., Horsman, M.R., Verheijen, J., Hanemaaijer, R., Overgaard, J., 2010. Matrix metalloproteinase-9 measured in urine from bladder cancer patients is an independent prognostic marker of poor survival. Acta Oncol. 49 (8), 1283–1287.
Ogata, Y., Itoh, Y., Nagase, H., 1995. Steps involved in activation of the pro-matrix metalloproteinase 9 (progelatinase B)-tissue inhibitor of metalloproteinases-1 complex by 4-aminophenylmercuric acetate and proteinases. J. Biol. Chem. 270 (31), 18506–18511.
Olson, E.S., Jiang, T., Aguilera, T.A., Nguyen, Q.T., Ellies, L.G., Scadeng, M., et al., 2010. Activatable cell penetrating peptides linked to nanoparticles as dual probes for in vivo fluorescence and MR imaging of proteases. Proc. Natl. Acad. Sci. U.S.A. 107 (9), 4311–4316.
Orgaz, J.L., Pandya, P., Dalmeida, R., Karagiannis, P., Sanchez-Laorden, B., Viros, A., et al., 2014. Diverse matrix metalloproteinase functions regulate cancer amoeboid migration. Nat. Commun. 5, 4255. https://doi.org/10.1038/ncomms5255.
Osenkowski, P., Toth, M., Fridman, R., 2004. Processing, shedding, and endocytosis of membrane type 1-matrix metalloproteinase (MT1-MMP). J. Cell. Physiol. 200 (1), 2–10.
Overall, C.M., Wrana, J.L., Sodek, J., 1991. Transcriptional and post-transcriptional regulation of 72-kDa gelatinase/type IV collagenase by transforming growth factor-beta 1 in human fibroblasts. Comparisons with collagenase and tissue inhibitor of matrix metalloproteinase gene expression. J. Biol. Chem. 266 (21), 14064–14071.
Paduch, R., 2016. The role of lymphangiogenesis and angiogenesis in tumor metastasis. Cell. Oncol. (Dordr) 39 (5), 397–410.
Palumbo, J.S., Talmage, K.E., Massari, J.V., La Jeunesse, C.M., Flick, M.J., Kombrinck, K.W., et al., 2005. Platelets and fibrin(ogen) increase metastatic potential by impeding natural killer cell-mediated elimination of tumor cells. Blood 105 (1), 178–185.
Pandya, P., Orgaz, J.L., Sanz-Moreno, V., 2017. Modes of invasion during tumour dissemination. Mol. Oncol. 11 (1), 5–27.
Paoli, P., Giannoni, E., Chiarugi, P., 2013. Anoikis molecular pathways and its role in cancer progression. Biochim. Biophys. Acta 1833 (12), 3481–3498.
Partridge, J.J., Madsen, M.A., Ardi, V.C., Papagiannakopoulos, T., Kupriyanova, T.A., Quigley, J.P., et al., 2007. Functional analysis of matrix metalloproteinases and tissue inhibitors of metalloproteinases differentially expressed by variants of human HT-1080 fibrosarcoma exhibiting high and low levels of intravasation and metastasis. J. Biol. Chem. 282 (49), 35964–35977.
Paupert, J., Sounni, N.E., Noël, A., 2011. Lymphangiogenesis in post-natal tissue remodeling: lymphatic endothelial cell connection with its environment. Mol. Aspects Med. 32 (2), 146–158.
Peisker, A., Raschke, G.F., Fahmy, M.D., Guentsch, A., Roshanghias, K., Hennings, J., et al., 2017. Salivary MMP-9 in the detection of oral squamous cell carcinoma. Med. Oral Patol. Oral Cir. Bucal 22 (3), 270–275.
Petrella, B.L., Vincenti, M.P., 2012. Interleukin-1β mediates metalloproteinase-dependent renal cell carcinoma tumor cell invasion through the activation of CCAAT enhancer binding protein β. Cancer Med. 1 (1), 17–27.
Peyri, N., Berard, M., Fauvel-Lafeve, F., Trochon, V., Arbeille, B., Lu, H., et al., 2009. Breast tumor cells transendothelial migration induces endothelial cell anoikis through extracellular matrix degradation. Anticancer Res. 29 (6), 2347–2355.
Ra, H.J., Parks, W.C., 2007. Control of matrix metalloproteinase catalytic activity. Matrix Biol. 26 (8), 587–596.
Radisky, D.C., Levy, D.D., Littlepage, L.E., Liu, H., Nelson, C.M., Fata, J.E., et al., 2005. Rac1b and reactive oxygen species mediate MMP-3-induced EMT and genomic instability. Nature 436 (7047), 123–127.
Radziwon-Balicka, A., Ramer, C., Moncada de la Rosa, C., Zielnik-Drabik, B., Jurasz, P., 2014. Angiostatin inhibits endothelial MMP-2 and MMP-14 expression: a hypoxia specific mechanism of action. Vascul. Pharmacol. 58 (4), 280–291.
Ramchandran, R., Dhanabal, M., Volk, R., Waterman, M.J., Segal, M., Lu, H., et al., 1999. Antiangiogenic activity of restin, NC10 domain of human collagen XV: comparison to endostatin. Biochem. Biophys. Res. Commun. 255 (3), 735–739.
Räsänen, K., Vaheri, A., 2010. Activation of fibroblasts in cancer stroma. Exp. Cell Res. 316 (17), 2713–2722.
Reiss-Pistilli, M.L., Schuppan, D., Barroso, M.M., Assunção-Miranda, I., Farias, S., Lery, L., et al., 2017. An extracellular proteasome releases endostatin from human collagen XVIII. Angiogenesis 20 (1), 125–137.
Ren, D., Kratz, F., Wang, S.W., 2011. Protein nanocapsules containing doxorubicin as a pH-responsive delivery system. Small 7 (8), 1051–1060.
Ricard-Blum, S., Salza, R., 2014. Matricryptins and matrikines: biologically active fragments of the extracellular matrix. Exp. Dermatol. 23 (7), 457–463.
Ricard-Blum, S., Vallet, S.D., 2016. Matricryptins network with matricellular receptors at the surface of endothelial and tumor cells. Front. Pharmacol. 7, 11. https://doi.org/10.3389/fphar.2016.00011.
Ridley, A.J., 2011. Life at the leading edge. Cell 145 (7), 1012–1022.
Roh-Johnson, M., Bravo-Cordero, J.J., Patsialou, A., Sharma, V.P., Guo, P., Liu, H., et al., 2014. Macrophage contact induces RhoA GTPase signaling to trigger tumor cell intravasation. Oncogene 33 (33), 4203–4212.
Roy Chowdhury, M., Schumann, C., Bhakta-Guha, D., Guha, G., 2016. Cancer nanotheranostics: Strategies, promises and impediments. Biomed. Pharmacother. 84, 291–304.
Sabeh, F., Shimizu-Hirota, R., Weiss, S.J., 2009. Protease-dependent versus-independent cancer cell invasion programs: three-dimensional amoeboid movement revisted. J. Cell Biol. 185 (1), 11–19.
Sakamoto, T., Seiki, M., 2010. A membrane protease regulates energy production in macrophages by activating hypoxia-inducible factor-1 via a non-proteolytic mechanism. J. Biol. Chem. 285 (39), 29951–29964.
Santos-Martínez, M.J., Medina, C., Jurasz, P., Radomski, M.W., 2008. Role of metalloproteinases in platelet function. Thromb. Res. 121 (4), 535–542.
Sapadin, A.N., Fleischmajer, R., 2006. Tetracyclines: nonantibiotic properties and their clinical implications. J. Am. Acad. Dermatol. 54 (2), 258–265.
Savinov, A.Y., Remacle, A.G., Golubkov, V.S., Krajewska, M., Kennedy, S., Duffy, M.J., et al., 2006. Matrix metalloproteinase 26 proteolysis of the NH2-terminal domain of the estrogen receptor beta correlates with the survival of breast cancer patients. Cancer Res. 66 (5), 2716–2724.
Sbai, O., Ould-Yahoui, A., Ferhat, L., Gueye, Y., Bernard, A., Charrat, E., et al., 2010. Differential vesicular distribution and trafficking of MMP-2, MMP-9, and their inhibitors in astrocytes. Glia 58 (3), 344–366.
Schütz, A., Röser, K., Klitzsch, J., Lieder, F., Aberger, F., Gruber, W., et al., 2015. Lung adenocarcinomas and lung cancer cell lines show association of MMP-1 expression with STAT3 activation. Transl. Oncol. 8 (2), 97–105.
Shay, G., Lynch, C.C., Fingleton, B., 2015. Moving targets: Emerging roles for MMPs in cancer progression and metastasis. Matrix Biol. 44–46, 200–206.
Shen, Z., Yao, C., Wang, Z., Yue, L., Fang, Z., Yao, H., et al., 2016. Vastatin, an endogenous antiangiogenesis polypeptide that is lost in hepatocellular carcinoma, effectively inhibits tumor metastasis. Mol. Ther. 24 (8), 1358–1368.
Sherwood, V., 2015. WNT signaling: an emerging mediator of cancer cell metabolism? Mol. Cell. Biol. 35 (1), 2–10.
Sheu, B.C., Hsu, S.M., Ho, H.N., Lien, H.C., Huang, S.C., Lin, R.H., 2001. A novel role of metalloproteinase in cancer-mediated immunosuppression. Cancer Res. 61 (1), 237–242.
Shibue, T., Weinberg, R.A., 2011. Metastatic colonization: settlement, adaptation and propagation of tumor cells in a foreign tissue environment. Semin. Cancer Biol. 21 (2), 99–106.
Shiga, K., Hara, M., Nagasaki, T., Sato, T., Takahashi, H., Takeyama, H., 2015. Cancer-associated fibroblasts: their characteristics and their roles in tumor growth. Cancers (Basel) 7 (4), 2443–2458.
Shirure, V.S., Liu, T., Delgadillo, L.F., Cuckler, C.M., Tees, D.F., Benecia, F., et al., 2015. CD44 variant isoforms expressed by breast cancer cells are functional E-selectin ligands under flow conditions. Am. J. Cell Physiol. 308 (1), C68–C78.
Shyu, K.G., Hsu, F.L., Wang, M.J., Wang, B.W., Lin, S., 2007. Hypoxia-inducible factor 1alpha regulates lung adenocarcinoma cell invasion. Exp. Cell Res. 313 (6), 1181–1191.
Simpson, C.D., Anyiwe, K., Schimmer, A.D., 2008. Anoikis resistance and tumor metastasis. Cancer Lett. 272 (2), 177–185.
Singh, S., Mehta, N., Lilan, J., Budhthoki, M.B., Chao, F., Yong, L., 2017. Initiative action of tumor-associated macrophages during tumor metastasis. Biochim. Open 4, 8–18.
Si-Tayeb, K., Monvoisin, A., Mazzocco, C., Lepreux, S., Decossas, M., Cubel, G., et al., 2006. Matrix metalloproteinase 3 is present in the cell nucleus and is involved in apoptosis. Am. J. Pathol. 169 (4), 1390–1401.
Soehnlein, O., Zernecke, A., Weber, C., 2009. Neutrophils launch monocyte extravasation by release of granule proteins. Thromb. Haemost. 102 (2), 198–205.
Somerville, R.P., Oblander, S.A., Apte, S.S., 2003. Matrix metalloproteinases: old dogs with new tricks. Genome Biol. 4 (6), 216.
Soria-Valles, C., Gutiérrez-Fernández, A., Guiu, M., Mari, B., Fueyo, A., Gomis, R.R., et al.,

2014. The anti-metastatic activity of collagenase-2 in breast cancer cells is mediated by a signaling pathway involving decorin and miR-21. Oncogene 33 (23), 3054–3063.
Spinella, F., Caprara, V., Garrafa, E., Di Castro, V., Rosanò, L., Natali, P.G., et al., 2010. Endothelin axis induces metalloproteinase activation and invasiveness in human lymphatic endothelial cells. Can. J. Physiol. Pharmacol. 88 (8), 782–787.
Steinl, C., Essl, M., Schreiber, T.D., Geiger, K., Prokop, L., Stevanović, S., et al., 2013. Release of matrix metalloproteinase-8 during physiological trafficking and induced mobilization of human hematopoietic stem cells. Stem Cells Dev. 22 (9), 1307–1318.
Stetler-Stevenson, W.G., 2008. Tissue inhibitors of metalloproteinases in cell signaling: metalloproteinase-independent biological activities. Sci. Signal. 1 (27), re6. https://doi.org/10.1126/scisignal.127re6.
Sullivan, R., Graham, C.H., 2007. Hypoxia-driven selection of the metastatic phenotype. Cancer Metastasis Rev. 26 (2), 319–331.
Sun, X., Wei, L., Chen, Q., Terek, R.M., 2010. CXCR4/SDF1 mediate hypoxia induced chondrosarcoma cell invasion through ERK signaling and increased MMP1 expression. Mol. Cancer 9, 17. https://doi.org/10.1186/1476-4598-9-17.
Szarvas, T., Singer, B.B., Becker, M., Vom Dorp, F., Jäger, T., Szendroi, A., et al., 2011. Urinary matrix metalloproteinase-7 level is associated with the presence of metastasis in bladder cancer. BJU Int. 107 (7), 1069–1073.
Tabouret, E., Boudouresque, F., Barrie, M., Matta, M., Boucard, C., Loundou, A., et al., 2014. Association of matrix metalloproteinase 2 plasma level with response and survival in patients treated with bevacizumab for recurrent high-grade glioma. Neuro Oncol. 16 (3), 392–399.
Tabouret, E., Bertucci, F., Pierga, J.Y., Petit, T., Levy, C., Ferrero, J.M., et al., 2016. MMP2 and MMP9 serum levels are associated with favorable outcome in patients with inflammatory breast cancer treated with bevacizumab-based neoadjuvant chemotherapy in the BEVERLY-2 study. Oncotarget 7 (14), 18531–18540.
Taddei, M.L., Giannoni, E., Comito, G., Chiarugi, P., 2013. Microenvironment a tumor cell plasticity: an easy way out. Cancer Lett. 341 (1), 80–96.
Takeuchi, T., Adachi, Y., Nagayama, T., Furihata, M., 2011. Matrix metalloproteinase-11 overexpressed in lobular carcinoma cells of the breast promotes anoikis resistance. Virchows Arch. 459 (3), 291–297.
Tallant, C., Marrero, A., Gomis-Rüth, F.X., 2010. Matrix metalloproteinases: Fold and function of their catalytic domains. Biochim. Biophys. Acta 1803 (1), 20–28.
Tammela, T., Alitalo, K., 2010. Lymphangiogenesis: Molecular mechanisms and future promise. Cell 140 (4), 460–476.
Tatti, O., Gucciardo, E., Pekkonen, P., Holopainen, T., Louhimo, R., Repo, P., et al., 2015. MMP16 mediates a proteolytic switch to promote cell-cell adhesion, collagen alignment, and lymphatic invasion in melanoma. Cancer Res. 75 (10), 2083–2094.
Tressel, S.L., Kaneider, N.C., Kasuda, S., Foley, C., Koukos, G., Austin, K., et al., 2011. A matrix metalloprotease-PAR1 system regulates vascular integrity, systemic inflammation and death in sepsis. EMBO Mol. Med. 3 (7), 370–384.
Troyanovsky, B., Levchenko, T., Månsson, G., Matvijenko, O., Holmgren, L., 2001. Angiomotin: an angiostatin binding protein that regulates endothelial cell migration and tube formation. J. Cell Biol. 152 (6), 1247–1254.
Tsai, Y.P., Wu, K.J., 2012. Hypoxia-regulated target genes implicated in tumor metastasis. J. Biomed. Sci. 19, 102. https://doi.org/10.1186/1423-0127-19-102.
Tsuchiya, K., Hida, K., Hida, Y., Muraki, C., Ohga, N., Akino, T., et al., 2010. Adrenomedullin antagonist suppresses tumor formation in renal cell carcinoma through inhibitory effects on tumor endothelial cells and endothelial progenitor mobilization. Int. J. Oncol. 36 (6), 1379–1386.
Ucuzian, A.A., Gassman, A.A., East, A.T., Greisler, H.P., 2010. Molecular mediators of angiogenesis. J. Burn Care Res. 31 (1), 158–175.
Vacek, T.P., Metreveli, N., Tyagi, N., Vacek, J.C., Pagni, S., Tyagi, S.C., 2011. Electrical stimulation of cardiomyocytes activates mitochondrial matrix metalloproteinase causing electrical remodeling. Biochem. Biophys. Res. Commun. 404 (3), 762–766.
Valastyan, S., Weinberg, R.A., 2011. Tumor metastasis: Molecular insights and evolving paradigms. Cell 147 (2), 275–292.
Vargo-Gogola, T., Fingleton, B., Crawford, H.C., Matrisian, L.M., 2002. Matrilysin (matrix metalloproteinase-7) selects for apoptosis-resistant mammary cells in vivo. Cancer Res. 62 (19), 5559–5563.
Villeneuve, J., Block, A., Le Bousse-Kerdilès, M.C., Lepreux, S., Nurden, P., Ripoche, J., et al., 2009. Tissue inhibitors of matrix metalloproteinases in platelets and megakaryocytes: a novel organization for these secreted proteins. Exp. Hematol. 37 (7), 849–856.
Vinothini, G., Aravindraja, C., Chitrathara, K., Nagini, S., 2011. Correlation of matrix metalloproteinases and their inhibitors with hypoxia and angiogenesis in premenopausal patients with adenocarcinoma of the breast. Clin. Biochem. 44 (12), 969–974.
Vishnubhotla, R., Sun, S., Huq, J., Bulic, M., Ramesh, A., Guzman, G., et al., 2007. ROCK-II mediates colon cancer invasion via regulation of MMP-2 and MMP-13 at the site of invadopodia as revealed by multiphoton imaging. Lab. Invest. 87 (11), 1149–1158.
Voulgari, A., Pintzas, A., 2009. Epithelial-mesenchymal transition in cancer metastasis: mechanisms, markers and strategies to overcome drug resistance in the clinic. Biochim. Biophys. Acta 1796 (2), 75–90.
Wang, J., Hielscher, A., 2017. Fibronectin: How its aberrant expression in tumors may improve therapeutic targeting. J. Cancer 8 (4), 674–682.
Wang, W., Schulze, C.J., Suarez-Pinzon, W.L., Dyck, J.R., Sawicki, G., Schulz, R., 2002. Intracellular action of matrix metalloproteinase-2 accounts for acute myocardial ischemia and reperfusion injury. Circulation 106 (12), 1543–1549.
Wang, W.S., Chen, P.M., Wang, H.S., Liang, W.Y., Su, Y., 2006. Matrix metalloproteinase-7 increases resistance to Fas-mediated apoptosis and is a poor prognostic factor of patients with colorectal carcinoma. Carcinogenesis 27 (5), 1113–1120.
Wang, H., Zhu, Y., Zhao, M., Wu, C., Zhang, P., Tang, L., et al., 2013. miRNA-29c suppresses lung cancer cell adhesion to extracellular matrix and metastasis by targeting integrin β1 and matrix metalloproteinase2 (MMP2). PLoS One 8 (8), e70192. https://doi.org/10.1371/journal.pone.0070192.
Wang, H.Y., Tu, Y.S., Long, J., Zhang, H.Q., Qi, C.L., Xie, X.B., et al., 2015. SRF-miR-29b-MMP2 axis inhibits NSCLC invasion and metastasis. Int. J. Oncol. 47 (2), 641–649.
Wang, R., Chen, S., Li, C., Ng, K.T., Kong, C.W., Cheng, J., et al., 2016. Fusion with stem cell makes the hepatocellular carcinoma cells similar to liver tumor-initiating cells. BMC Cancer 16, 56. https://doi.org/10.1186/s12885-016-2094-7.
Whipple, C.A., 2015. Tumor talk: understanding the conversation between the tumor and its microenvironment. Cancer Cell Microenviron. 2 (2), e773. https://doi.org/10.14800/ccm.773.
Wong, S.Y., Hynes, R.O., 2006. Lymphatic or hematogenous dissemination: how does a tumor cell decide? Cell Cycle 5 (8), 812–817.
Wong, M.S., Sidik, S.M., Mahmud, R., Stanslas, J., 2013. Molecular targets in the discovery and development of novel antimetastatic agents: current progress and future prospects. Clin. Exp. Pharmacol. Physiol. 40 (5), 307–319.
Wong, H.L., Jin, G., Cao, R., Zhang, S., Cao, Y., Zhou, Z., 2016. MT1-MMP sheds LYVE-1 on lymphatic endothelial cells and suppresses VEGF-C production to inhibit lymphangiogenesis. Nat. Commun. 7, 10824. https://doi.org/10.1038/ncomms10824.
Wu, E., Mari, B.P., Wang, F., Anderson, I.C., Sunday, M.E., Shipp, M.A., 2001. Stromelysin-3 suppresses tumor cell apoptosis in a murine model. J. Cell. Biochem. 82 (4), 549–555.
Wu, Q.W., Yang, Q.M., Huang, Y.F., She, H.Q., Liang, J., Yang, Q.L., et al., 2014. Expression and clinical significance of matrix metalloproteinase-9 in lymphatic invasiveness and metastasis of breast cancer. PLoS One 9 (5), e97804. https://doi.org/10.1371/journal.pone.0097804.
Wyckoff, J., Wang, W., Lin, E.Y., Wang, Y., Pixley, F., Stanley, E.R., et al., 2004. A paracrine loop between tumor cells and macrophages is required for tumor cell migration in mammary tumors. Cancer Res. 64 (19), 7022–7029.
Wyckoff, J.B., Wang, Y., Lin, E.Y., Li, J.F., Goswami, S., Stanley, E.R., et al., 2007. Direct visualization of macrophage-assisted tumor cell intravasation in mammary tumors. Cancer Res. 67 (6), 2649–2656.
Xie, J., Lee, S., Chen, X., 2011. Nanoparticle-based theranostic agents. Nano Lett. 11 (2), 814–819.
Xu, M., Wang, Y.Z., 2013. miR-133a suppresses cell proliferation, migration and invasion in human lung cancer by targeting MMP-14. Oncol. Rep. 30 (3), 1398–1404.
Xu, R., Yao, Z.Y., Xin, L., Zhang, Q., Li, T.P., Gan, R.B., 2001. NC1 domain of human type VIII collagen (alpha 1) inhibits bovine aortic endothelial cell proliferation and causes cell apoptosis. Biochem. Biophys. Res. Commun. 289 (1), 264–268.
Xu, R., Xin, L., Fan, Y., Meng, H.R., Li, Z.P., Gan, R.B., 2002. Mouse restin inhibits bovine aortic endothelial cell proliferation and causes cell apoptosis. Acta Biochim. Biophys. SINICA 34 (2), 138–142.
Xu, T., Jing, C., Shi, Y., Miao, R., Peng, L., Kong, S., et al., 2015a. microRNA-20a enhances the epithelial-to-mesenchymal transition of colorectal cancer cells by modulating matrix metalloproteinases. Exp. Ther. Med. 10 (2), 683–688.
Xu, L., Sun, K., Xia, M., Li, X., Lu, Y., 2015b. MMP13 Regulates aggressiveness of pediatric multiple myeloma through VEGF-C. Cell. Physiol. Biochem. 36 (2), 509–516.
Yadav, L., Puri, N., Rastogi, V., Satpute, P., Ahmad, R., Kaur, G., 2014. Matrix metalloproteinases and cancer - roles in threat and therapy. Asian Pac. J. Cancer Prev. 15 (3), 1085–1091.
Yamaguchi, H., 2012. Pathological roles of invadopodia in cancer invasion and metastasis. Eur. J. Cell Biol. 91 (11–12), 902–907.
Yamaguchi, H., Sakai, R., 2015. Direct interaction between carcinoma cells and cancer associated fibroblasts for the regulation of cancer invasion. Cancers (Basel) 7 (4), 2054–2062.
Yamamoto, A., Kasamatsu, A., Ishige, S., Koike, K., Saito, K., Kouzu, Y., et al., 2013a. Exocyst complex component Sec8: a presumed component in the progression of human oral squamous-cell carcinoma by secretion of matrix metalloproteinases. J. Cancer Res. Clin. Oncol. 139 (4), 533–542.
Yamamoto, H., Okada, R., Iguchi, K., Ohno, S., Yokogawa, T., Nishikawa, K., et al., 2013b. Involvement of plasmin-mediated extracellular activation of progalanin in angiogenesis. Biochem. Biophys. Res. Commun. 430 (3), 999–1004.
Yan, C., Boyd, D.D., 2007. Regulation of matrix metalloproteinase gene expression. J. Cell. Physiol. 211 (1), 19–26.
Yang, H., Wang, Y., Li, Y., Zhang, L., Deng, Y., Qi, D., et al., 2012a. Roles of matrix metalloproteinase-26 in the growth, invasion and angiogenesis of breast cancer. Oncol. Lett. 4 (4), 832–836.
Yang, Z., Kulkarni, K., Zhu, W., Hu, M., 2012b. Bioavailability and pharmacokinetics of geninistein: mechanistic studies on its ADME. Anticancer Agents Med. Chem. 12 (10), 1264–1280.
Yang, C.C., Zhu, L.F., Xu, X.H., Ning, T.Y., Ye, J.H., Liu, L.K., 2013. Membrane Type 1 Matrix Metalloproteinase induces an epithelial to mesenchymal transition and cancer stem cell-like properties in SCC9 cells. BMC Cancer 13, 171. https://doi.org/10.1186/1471-2407-13-171.
Yang, J.S., Lin, C.W., Su, S.C., Yang, S.F., 2016. Pharmacodynamic considerations in the use of matrix metalloproteinase inhibitors in cancer treatment. Expert Opin. Drug Metab. Toxicol. 12 (2), 191–200.
Yeghiazaryan, M., Żybura-Broda, K., Cabaj, A., Włodarczyk, J., Sławińska, U., Rylski, M., et al., 2012. Fine-structural distribution of MMP-2 and MMP-9 activities in the rat skeletal muscle upon training: a study by high-resolution in situ zymography. Histochem. Cell Biol. 138 (1), 75–87.
Yoon, H., Dehart, J.P., Murphy, J.M., Lim, S.T., 2015. Understanding the roles of FAK in cancer: inhibitors, genetic models, and new insights. J. Histochem. Cytochem. 63 (2), 114–128.
Yu, Y., Elble, R.C., 2016. Homeostatic signaling by cell-cell junctions and its dysregulation during cancer progression. J. Clin. Med. 5 (2). https://doi.org/10.3390/jcm5020026. pii: E26.

Yu, X., Wei, F., Yu, J., Zhao, H., Jia, L., Ye, Y., et al., 2015. Matrix metalloproteinase 13: a potential intermediate between low expression of microRNA-125b and increasing metastatic potential of non-small cell lung cancer. Cancer Genet. 208 (3), 76–84.
Zhang, S., Liu, Y., Wang, Z., Liu, J., Gu, Z., Xu, Q., et al., 2017. PAR1-mediated c-Jun activation promotes heat stress-induced early stage apoptosis of human umbilical vein endothelial cells. Mol. Med. Rep. 15 (5), 2595–2603.
Zheng, W., Aspelund, A., Alitalo, K., 2014. Lymphangiogenic factors, mechanisms, and applications. J. Clin. Invest. 124 (3), 878–887.
Zhou, H.Z., Ma, X., Gray, M.O., Zhu, B.Q., Nguyen, A.P., Baker, A.J., et al., 2007. Transgenic MMP-2 expression induces latent cardiac mitochondrial dysfunction. Biochem. Biophys. Res. Commun. 358 (1), 189–195.
Zhu, S., Zhou, Y., Wang, L., Zhang, J., Wu, H., Xiong, J., et al., 2011. Transcriptional upregulation of MT2-MMP in response to hypoxia is promoted by HIF-1α in cancer cells. Mol. Carcinog. 50 (10), 770–780.
Zhu, L., Wang, T., Perche, F., Taigind, A., Torchilin, V.P., 2013. Enhanced anticancer activity of nanopreparation containing a MMP2-sensitive PEG-drug conjugate and cell-penetrating moiety. Proc. Natl. Acad. Sci. U.S.A. 110 (42), 17047–17052.
Zhuo, W., Chen, Y., Song, X., Luo, Y., 2011. Endostatin specifically targets both tumor blood vessels and lymphatic vessels. Front. Med. 5 (4), 336–340.