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Exosomes as a storehouse of tissue remodeling proteases and mediators of cancer progression

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Abstract
Rapidly increasing scientific reports of exosomes and their biological effects have improved our understanding of their cellular sources and their cell-to-cell communication. These nano-sized vesicles act as potent carriers of regulatory bio-macromolecules and can induce regulatory functions by delivering them from its source to recipient cells. The details of their communication network are less understood. Recent studies have shown that apart from delivering its cargo to the cells, it can directly act on extracellular matrix (ECM) proteins and growth factors and can induce various remodeling events. More importantly, exosomes carry many surface-bound proteases, which can cleave different ECM proteins and carbohydrates and can shed cell surface receptors. These local extracellular events can modulate signaling cascades, which consequently influences the whole tissue and organ. This review aims to highlight the critical roles of exosomal proteases and their mechanistic insights within the cellular and extracellular environment.

Keywords Exosomes · Nano-sized vesicles · Extracellular matrix proteases · Tumor microenvironment · Extracellular matrix

1 Introduction

Exosomes are the nano-sized endocytic origin extracellular vesicles that are secreted across the species ranging from prokaryotes to eukaryotes. Exosomes are secreted by most of the cell types and can be found in both *in vivo* and *in vitro* culture conditions [1]. Their sizes range in between 30 and 150 nm, and they are rich in bioactive molecules, which includes structural proteins, enzymes, nucleic acids, lipids, carbohydrates, and various molecules whose functions are yet to be elucidated [2]. It has been shown that exosomes are loaded with certain lipid rafts like ceramides, cholesterols, and sphingolipids [3]; these lipid moieties play a critical role in B cell and T cell immune signaling [4]. Glycomics studies have revealed the presence of specific glycan moieties in exosomes, which includes polylactosamine, branched sialic acids, high mannose N-glycans, and complex N-glycans [5]. In the cell culture model, it has been shown that N-linked glycosylation can direct protein sorting inside exosomes [6].

Nucleic acids, mainly mRNA and miRNA (microRNA), were the first macromolecules found inside the exosomes [7]; their role inside these nano-vesicles was shown as carriers of genetic material and termed as exosomes shuttle RNA (esRNA). Under normal physiological conditions, miRNA-loaded exosomes released from donor dendritic cells (DC) promote post-translational processes in acceptor DCs; further, it promotes its maturation into immunogenic antigen-presenting cells (APCs) [8]. However, in a cancerous state, tumor cells release miRNA- and mRNA-loaded exosomes, which can induce inflammatory responses *via* activating toll-like receptors in macrophages [9]. Recently, using high-throughput genome sequencing techniques, the possible existence of DNA inside the exosomes has been demonstrated [10, 11]; however, its integrity and possible mechanism of its assembly inside these vesicles are still under investigation. Comparative studies have shown that in cell culture medium, cancer-associated fibroblast-derived exosomes have more DNA content than normal fibroblast [12]. It has been reported that DNA fragments inside exosomes isolated from cancer patients have the propensity to integrate into the DNA of BRAC1-KO human fibroblasts, which results in promotion of a metastatic phenotype and cancer progression [13].

Reports suggest that secreted exosomes are internalized by the cells near its vicinity *via* endocytosis or phagocytosis or passive membrane fusion and then *via* discharging its content

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in the cytosol it influences the phenotypic properties of the recipient cell (Fig. 1) [14–16]. Exosomes can act as a vehicle to deliver genetic cargo between organs and can function as a communicating vehicle between them [17]; this kind of phenomenon reflects its relevance in the progression of metastasis. Exosomes can facilitate the formation of the pre-metastatic niche (PMN) which includes angiogenesis, extracellular matrix (ECM) remodeling, and hijacking the stromal cells for promotion of tumor-related growth factors, which is essential for cancer growth. Exosomes are loaded with various signaling molecules, growth factors, and carry potential biomarkers, which can be used as diagnostic tools in clinics. High-throughput proteomics studies of exosomes isolated from prostate cancer lines have shown a higher abundance of FASN, XPO1, and PDCD6IP; these protein molecules are potential biomarkers for prostate cancer detection [18]. Similar studies were performed with exosomes isolated from blood samples of breast cancer and ovarian cancer patients to identify novel biomarkers for prognosis and therapeutics [19]. Another very crucial group of proteins, which exist in the cargo of exosomes, are proteases and glycosidases; they promote ECM remodeling events and activate various cellular processes. In this review, we will be focusing more on the roles of these proteolytic enzymes and their effects on the cancer and its surrounding environment.

2 Exosomes and ECM remodeling enzymes

Proteomic analysis of exosomes from the cell culture medium and blood samples has revealed the presence of surface-anchored matrix-metalloproteinases (MMPs), sheddases such as a disintegrin and metalloproteinases (ADAMs), and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTs). Also, there are soluble MMPs, which are either surface-bound or soluble inside these vesicles. Along

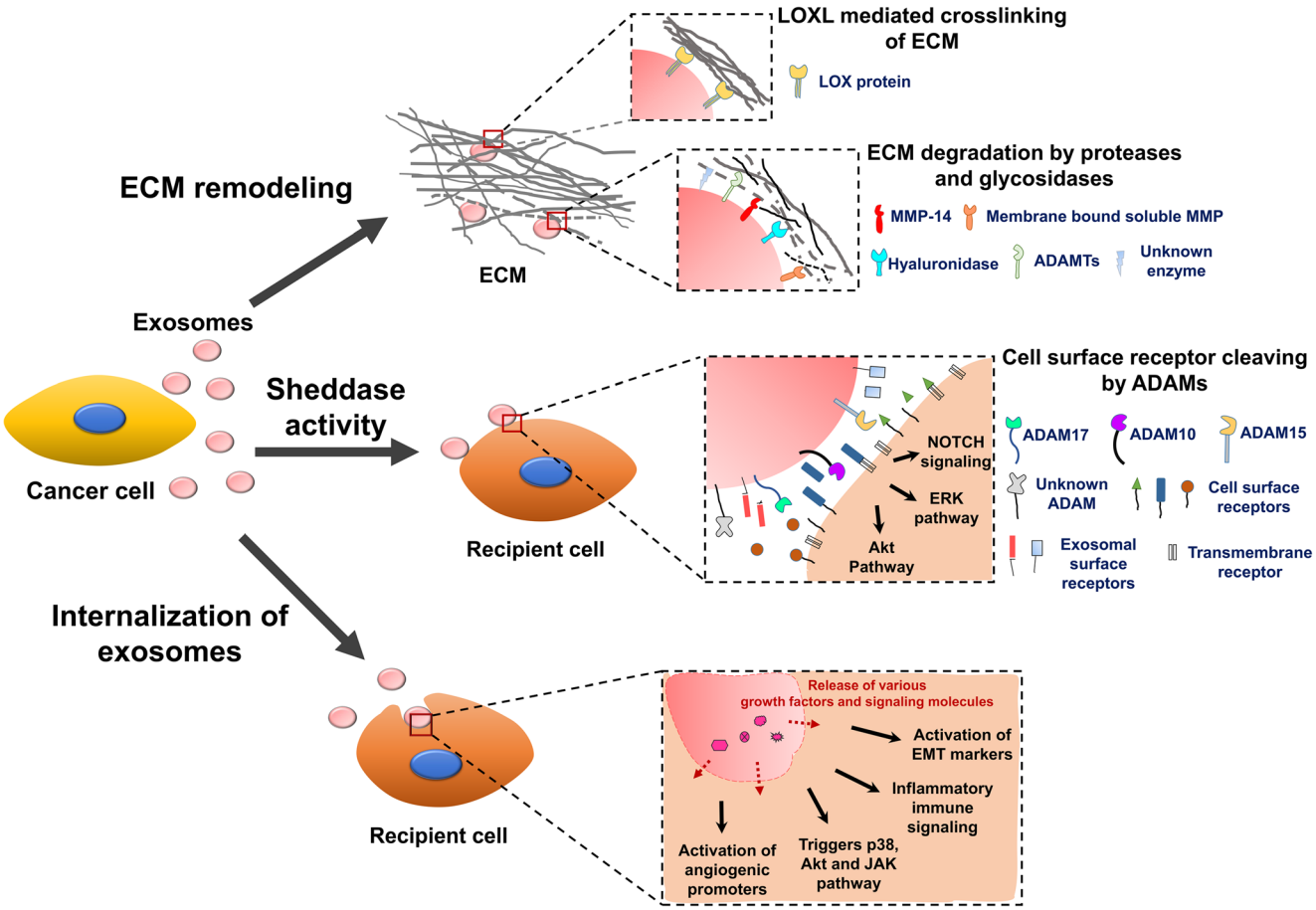

Fig. 1 Schematic illustration of the exosome-mediated changes in cancer microenvironment. ECM remodeling: exosomes secreted by cancer cells carry membrane-bound proteases and glycosidases, which can cleave the ECM components (like proteins, proteoglycans, and glycoproteins) causing ECM degradation. Along with proteases, it can also carry membrane-bound LOX enzymes that crosslinks ECM proteins. Sheddase activity: exosomes secreted by cancer cells contains surface-bound ADAMs, which can cleave various cell surface receptors and activate various signaling cascades, which includes NOTCH signaling, ERK pathway, and AKT pathway. Internalization of exosomes: exosomes contains numerous growth factors and cytokines in their lumen. Following endocytosis, these vesicles activate a myriad set of mechanisms such as epithelial-mesenchymal transition (EMT) in fibroblast, pro-inflammatory responses in macrophages, secretion of angiogenic factors, *etc.* leading to cancer promotion

with these proteases, there are glycosidases which are present on the surface or inside the lumen of exosomes (Fig. 1). Here, we are going to discuss them and their roles in matrix remodeling.

Matrix-metalloproteinases (MMPs) One of the most clinically relevant families of molecules identified inside the exosomes are MMPs. Members of this family are zinc-dependent proteolytic enzymes which can cleave the ECM fibers, mainly collagen, fibronectin, and laminins. Apart from ECM proteins, they can also cleave various cytokines and growth factors and proteolytically activate them [2, 20, 21]. MMPs are upregulated in multiple cancer, which includes breast cancer, pancreatic cancer, prostate cancer, ovarian cancer, and melanoma. They promote cancer progression and proliferation by altering the physical properties of ECM [22–27]. In normal conditions, stromal cells, fibroblasts, and some immune cells secrete basal level of MMPs, which is counter-balanced by TIMPs (tissue inhibitors of metalloproteinases) and tissue homeostasis is maintained. However, in cancerous conditions, significant upregulation of both soluble and membrane-bound MMPs is observed in cancer cells and cancer-supporting stromal cells, leading to extensive tissue destruction and disruption of normal physiological processes. Considering the fact that exosomes secreted by most cancer cells are loaded with MMPs, upon delivery, they can release these proteases and can cause ECM degradation on-site. Its mode of action and biochemical details are yet to be mapped out. Apart from cleaving ECM fibers, exosomal-MMPs can cleave the prodomain of surface-bound receptors, resulting in the activation of various cancer-promoting signaling cascades. Here, we have listed secreted exosomal enzymes and their various roles in cancer progression (Table 1).

Previously, metastatic murine melanoma cells secreted tiny vesicles into the cell culture medium showed the capability to degrade collagen and gelatin. Further characterization of these vesicles revealed the presence of MMPs, which have the affinity for Gly-Ile bonds in substrates like collagen, gelatin etc. [27, 31]. Similarly, in the culture medium of a human rectal carcinoma cell line, exosomes like vesicles termed glycocalyceal bodies of size ranging from 20 to 100 nm were observed, analysis revealing that these membrane-bound vesicles could degrade collagen molecule and facilitate cancer cell invasion [61]. The exosomes secreted by HT-1080 fibrosarcoma cells, shown to have membrane-bound pro and active form of MMP-9 and MMP-2, it can degrade ECM proteins and promote invasive behavior [28, 29]. Immunoelectron microscopic analysis of vesicles secreted by 8701-BC breast carcinoma cells revealed the presence of various cell surface-related proteins, which includes integrin β1, lymphocyte antigen type 1, and MMP-9 [30]. The existence of these proteins in these vesicles helps tumor cells to adhere, degrade, and escape from immune cell attack. Recent evidence in corneal fibroblast exosomes suggests that these vesicles employ their surface-bound MMP-14 to recruit active MMP-2 in its lumen [35]. Similar results were observed in cancer cells where surface-bound exosomal MMP-14 was shown to cleave Pro-MMP2 and activate it to degrade gelatin and collagen type I [36]. In tumorous conditions, hypoxia can induce secretion of exosomal membrane-associated C4.4A, which gets associated with α6β4 integrins and MMP-14 and in combination contributes to an invasive phenotype [37]. Likewise, in nasopharyngeal carcinoma, hypoxia-induced exosomes were shown to promote cancer invasion by surface-expressed MMP-13 [39]. Clinical studies of ovarian and breast cancer patient exosomes revealed the presence of active MMP-2 and MMP-9, which can degrade ECM proteins [32–34].

Comparative analysis of exosomes secreted by different grades of cancer cells, which includes MDA-MB-231, MCF-7, HT-1080, 8701-BC, and regular epithelial mammary cell MCF-10A, suggests that the exosomal content and its proteolytic activity depend on the aggressiveness of cancer cell [62–64]. Using a chick CAM (chorioallantois membrane) tumor model, Weaver and co-workers have demonstrated the capability of cancer cell-exosome-mediated cleavage of fibronectin into fragments; further, their results suggest the role of these fragments in inducing chemotactic cell migration and metastasis [38]. Taken together, all these reports suggest the crucial role of exosome-MMPs in the degradation of ECM proteins, which further promotes cancerous growth and invasion *via* various molecular mechanisms associated with MMP substrate specificity and activity.

A disintegrin and metalloproteinases (ADAM) ADAMs are the single-pass transmembrane endopeptidases, which consist of the cysteine-rich extracellular domain, a disintegrin, and metalloprotease. Upon cleavage of its prodomain, it can cleave extracellular ectodomain and regulate various cellular processes; active ADAMs were classified as sheddases. So far, 24 ADAMs are known to exist in humans, out of which 13 were found to have proteolytic activity, and eight non-proteolytic [65]. Among these, ADAM10 and ADAM17 were the most studied and found to have clinical relevance in normal and cancerous conditions [66, 67]. ADAM17's role as a sheddase on specific cell receptors and further its effect on downstream signaling cascades are well documented; in human uterine epithelial cells, ADAM17 was identified as MUC1 sheddase; this process is essential for creating a microenvironment for embryo implantation in the uterine wall [68]. ADAM17 sheddase activity on macrophage colony-stimulating receptor downregulates the activity of macrophages [69]. During sepsis or severe bacterial infection, overexpression of ADAM17 leads to excessive cleavage of L-selectin and CXCR2, which impairs the normal rolling motion and trans-endothelial migration of neutrophils [70]. The role of ADAM17 in regulating signaling cascade *via* processing of

Table 1 List of exosomal ECM remodeling enzymes and their roles in cancer progression

Exosomal enzymes	Cell type/functions
MMP 2, MMP 9	Promotes invasive behavior in HT1080 cancer cells [28, 29], 8701-BC breast carcinoma [30], melanoma cells [27, 31], clinical samples of ovarian and breast cancer patients [32–34]
MMP 14	Cleavage and packaging of MMP2 in corneal fibroblast [35]. Matrix degradation in fibrosarcoma and melanoma cells [36]. Promote invasive phenotype in metastatic cells [37, 38].
MMP 13	Cancer invasion in nasopharyngeal carcinoma [39]
ADAM17	A549 tumor cells, LPS treated monocyte and primary endothelial cells [20, 40], and malignant ovarian carcinoma [41]. Prostate cancer cell-surface protein TROP2 shedding and cancer progression [42, 43], colorectal cancer cell invasion [44]
ADAM10	TIMP-knock out fibroblast and promotes cancer invasion [45]. Shedding lymphoma-related growth factors in Hodgkin lymphoma [46]. Induce EMT markers in MDCK cells [47]. Present in NSCLC exosomes [48]. Leading front of glioma cells and induce cell migration [21, 49], colorectal cancer cell invasion [44], blood plasma of breast cancer and ovarian cancer patients [50]
ADAM15	Anti-cancerous effects on ovarian MDAH2774 cancer cells and breast MCF-7 cancer cells [51].
ADAM9	DU145 prostate cancer cells [52].
ADAMTS5	Promotes IL-6 overexpression and inflammation [53]
ADAMTS1, ADAMTS8	Rat pancreatic adenocarcinoma cells line, ASML [54]
Hyaluronidases	Prostate Cancer cells [55], HEK293T cells [56]
Elastase	Neutrophils in COPD murine model [57]
Insulin-degrading enzyme	N2a Neuroblastoma cells [58, 59]
Heparanases	Melanoma cells [60]
Sialidases	LPS treated microglial cells [60]

TNFα is well established in regulation of immune cells [71]; studies have shown that ADAM17-deficient mice are not viable due to compromised immune signaling [72].

Recently, phorbol-12-myristate-13-acetate (PMA)-treated lung epithelial A549 tumor cells were shown to secrete exosomes with mature ADAM17 on its surface; the same group demonstrated that lipopolysaccharide-treated primary endothelial cells and monocytes secrete exosomal membrane-bound active ADAM17 [20, 40], which are capable of similar sheddase activity as found on regular cell surface. In malignant ovarian carcinoma, cancer cells secrete exosomes with surface-bound ADAM17 and CD44 and L1 cytoplasmic cleave fragments in its lumen [41], these findings suggest a dual role played by these vesicles, cell surface sheddase and carrier of active biomolecules. Prostate cancer cell-surface protein TROP2 is cleaved by ADAM17 before being secreted by exosomes; cleavage and secretion of TROP2 cell surface protein promote cancerous phenotype and are considered as a promising biomarker in prostate cancer diagnostics [42, 43]. Clinical analysis of exosomes isolated from colorectal cancer (CLC) patient serum revealed the abundance of surface-bound ADAM10 and ADAM17 [44]; their presence might be an indication of circulatory tumor cells in non-metastatic patients.

ADAM10 is another class of sheddase; it regulates various essential biological functions in humans. Knockout studies in mice have shown that its deficiency leads to numerous problems in the central nervous system and circulatory system [73]. The role of ADAM10 in shedding and activation of highly conserved NOTCH signaling is well established; this highly conserved signaling cascade regulates cell fate and tissue development [74]. Researchers have shown the clinical relevance of ADAM10 in breast cancer progression, its overexpression and involvement in shedding activity of various transmembrane proteins which includes HER2, E-cadherin, CD44, L1, EGFR, and betacellulin, induces cancer-promoting effects [67, 75]. RNA interference-mediated suppression of ADAM10 expression in MDA-MB-231 breast cancer cells showed its inhibitory effects on cancer cell invasion and metastasis [76]. Increased expression of ADAM10 after trastuzumab treatment was positively correlated with the development of drug resistance in HER2-positive breast cancer cells [77]. Recent reports revealed that ADAM10-mediated cleavage of APPα (amyloid precursor protein) can induce proliferation and migration of breast cancer cells *via* PKA, Akt and FAK pathway (Fig. 1) [78].

ADAM10-enriched exosomes were frequently detected in diseases and cancerous conditions; studies have shown that TIMP-knock out fibroblasts secrete ADAM10-rich exosomes, which can induce cell migration *via* activating RhoA-mediated cell contractility and promotes Notch signaling in cancer cells [45]. In Hodgkin lymphoma, functionally active ADAM10 is secreted in the vesicles that can shed lymphoma-related growth factors and reduce the efficacy of immune therapy [46]. Proteomics analysis of Madin-Darby Canine Kidney (MDCK) cell-derived exosomes revealed the presence of

ADAM10 and growth factors in its cargo; *in vitro* results suggest that it can induce EMT in recipient cells [47]. In the blood plasma samples of breast cancer and ovarian cancer patients, higher expression of ADAM10 in CD9-positives exosomes and CD24-positive exosomes suggests the implication of ADAM10 in the cancer development process [50]. Proteomic analysis of non-small cell lung carcinoma (NSCLC)-secreted exosomes revealed more prevalence of ADAM10 on its surface compared to other proteases [48]. In glioma cells, shedding of surface-expressed exosomal CD171 by ADAM10 at the cell-leading front promotes cell migration and invasion *via* upregulation of FAK, integrins, and matrix-degrading enzymes [21, 49].

Recently, evidence of other exosomal ADAM proteins apart from ADAM10 and ADAM 17 has been revealed; cell culture medium of human embryonic kidney (HEK) cells contains exosomal ADAM15, whose sheddase activity can promote anti-cancer effects [79]. Macrophage-secreted exosomal ADAM15 was shown to inhibit ovarian cancer cell, MDAH2774, and breast cancer cell, MCF-7, metastatic phenotype *via* blocking its integrin-mediated interaction with fibronectin [51]. High-throughput SOMAscan proteomics analysis of exosomes isolated from DU145 prostate cancer cells revealed the presence of ADAM9 on its surface [52]. However, its functionality and implication are yet to be explained. Collectively, all these reports suggest that exosomes carry surface-bound ADAMs, and ADAM17 and ADAM10 are more frequently detected (Fig. 1). However, recent proteomic screening results have exposed the presence of other ADAM proteins in exosomes, mainly ADAM15 and ADAM9; knowledge about their roles in cancer progression are still at an early stage. The molecular basis of how the cell membrane-bound ADAM enzymes are bound to exosomes remains to be discovered and rationalized. It is unclear if these enzymes are activated and presented on the surface of exosomes or whether they are stored in their activated form inside the exosomes.

2.1 A disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS)

Unlike the ADAMs, these secreted soluble proteases ADAMTs can cleave various ECM proteins that include aggrecan, versican, brevican, and neurocan [80] and can promote maturation of ECM proteins like pro-collagen and von Willebrand factors [80]. ADAMTS' have a thrombospondin-like motif in place of the transmembrane and cytoplasmic domain. So far, 19 ADAMTS-like proteins were identified in humans. Studies have shown their essential roles in connective tissue homeostasis, angiogenesis, inflammation, and cell migration [80–82]. ADAMTS extracellular proteolytic activity and non-proteolytic activity have been shown to promote both pro/anti-cancer effects [81]. It can cleave a wide range of ECM proteins, can bind to various regulatory components in the tumor microenvironment, and can induce angiogenesis, cancer cell migration, and proliferation. Reports suggest that ADAMTS9-mediated ECM degradation is crucial for focal adhesion assembly and cytoskeletal organization in smooth muscle cells; in a murine model, its role was demonstrated in parturition [83]. Recently, exosomes isolated from IL-1β stimulated human synovial fibroblasts have shown elevated levels of ADAMTS5. Further results revealed its role in transmitting pathogenic signals across cell types in osteoarthritis-affected joints [53]. Exosomes isolated from the rat pancreatic adenocarcinoma cell line, ASML, have shown the presence of ADAMTS1 and ADAMTS8, along with other proteases and growth factors [54]. Exosomal ADAMTS-mediated regulation of the cancer microenvironment is still very naive; however, with more accumulating evidence, its role will become more clear in the near future.

Hyaluronidases (Hyal) This is a crucial glycosidase, which can degrade hyaluronic acid (HA), and certain chondroitin and its sulfates, which are classified as endoglycosidases which can digest β-N-acetyl-D-glucosaminidic linkages [54]. Recently, overexpression of hyaluronidases in cancer and other diseases has been documented [84, 85]. Many research groups are actively trying to understand their roles in cancer progression and in other disease conditions. Clinical studies revealed that elevated levels of HA in prostate cancer stroma promote increased expression of Hyal and together it can lead to the relapse of prostate cancer, which ultimately affects the survival rates of patients [86]. Identical results were observed in bladder cancer where Hyal overexpression is considered as a cancer diagnostic marker [85]. In breast cancer, Hyal overexpression induces a metastatic phenotype and anchorage-independent growth in cell culture conditions [87].

Recently, Hyal has been detected in exosomes isolated from prostate tumor cells, where it can promote stromal cell migratory potential *via* excessive phosphorylation of pFAK and overexpression of integrin β1 at the cell front [55]. Exosomes harboring the active form of PH20 Hyal shows HA degrading capabilities; this enhances their penetration rate inside solid tumors and promotes higher infiltration of T cells [56]. These exosomes could find application in the design of cancer therapeutic drugs.

Other proteases and glycosidases in exosomes Apart from above mentioned proteases, there are other proteolytic enzymes which are found in the cargo of exosomes, including elastase, insulin-degrading enzymes, sialidase, and heparanases [59]. Recently, in COPD (chronic obstructive pulmonary disease) murine models, PMN-secreted (polymorphonuclear leukocytes) exosomal neutrophil elastase was shown to cause extensive alveolar destruction by its

collagenase activity, making the alveolar more prone to emphysema and bronchopulmonary like conditions [57]. In an Alzheimer's murine model, neuroblastoma cells were shown to secrete exosomal insulin-degrading enzymes; these enzymes can degrade Aβ-peptides in amyloid plaques [58, 59]. Melanoma cancer cells secrete heparanase-loaded exosomes that can degrade heparan sulfate and release various active biomolecules embedded in ECM; these active molecules promote cancer progression and metastasis [60]. Lipopolysaccharide-treated microglial cells secrete sialidases on the surface of its exosomes, which can cleave polysialic acid and release growth factors that can promote neural growth and differentiation [60].

3 Exosomes' cellular sources and the tumor microenvironment

Tumors are not just random cluster of cells, it is a more complex microenvironment that is composed of different extracellular matrix proteins, growth factors, and many cell types, all of which work in tandem to regulate various dynamic processes that aid in growth and proliferation of cancer tissue. With the evidence of exosomes inside the tumor microenvironment and their roles in transferring bioactive molecules between cancer cells and other stromal cells, the importance of these tiny vesicles in the maintenance of cancer stroma is becoming more evident (Fig. 1). Here in this section, we will highlight some recent findings of exosome-mediated regulation of the tumor microenvironment.

Exosomes and angiogenesis Cancer cell-secreted exosomes and their implication in angiogenesis have been an area of interest for cancer biologists. In solid tumors, sprouting of new blood vessels is essential for its growth and proliferation. Reports suggest that circulating exosomes isolated from cancer patients can modulate endothelial cells to secrete vascular endothelial growth factor (VEGF) or similar growth factors, to promote angiogenesis [88]. Under hypoxia-like conditions, multiple myeloma cell-secreted exosomes promote hypoxia-inducible factors (HIF-1) and VEGF-like angiogenic factors in endothelial cells, and collectively, they promote myeloma cell growth and proliferation [89]. Mesenchymal stem cell (MSC)-derived exosomes were shown to downregulate angiogenesis in murine breast cancer cells [90]; if similar studies could be shown in human breast cancer cells, then these MSC-derived nanovesicles might find application in clinical studies. MDCK cells undergoing oncogenic epithelial to mesenchymal transition (EMT) can induce angiogenesis in its neighboring endothelial cells *via* secreting exosomal Rac1/PAK2, an angiogenic promoter [91]. Exosomes play a prominent role in pre-metastatic niche formation. Recently, it has been shown that tumor cell-secreted exosomal surface-bound programmed death-ligand (PD-L1) can bind to the PD-1 receptor on T cells, and then induce apoptosis and T cell inactivation [92]. Through this mechanism tumor cells, lying at a distant place can cause apoptotic and immunomodulatory effects on any targeted organ, thereby pre-conditioning the microenvironment for metastasis. In CRC cells, exosomal miR-25-3p was shown to promote angiogenesis and leaky vascularization, increasing the tendency of the cancer cell to metastasize in the liver and lungs [93]. Ovarian cancer cells were shown to secrete 80 kDa soluble E-cadherin in its exosomal cargo, *in vivo* and clinical results demonstrated that these soluble E-cadherin fragments could induce angiogenesis *via* activation of β-catenin and NFκB signaling [94]. These results point towards a novel angiogenic promoting biomarker for future clinical studies. Altogether, these studies suggest a critical role of cancer cell exosomes in mediating the process of angiogenesis.

Exosomes and stromal cells Stromal cells are present in the connective tissue of any organ; these cells play an essential role in the maintenance of tissue homeostasis. Primarily, fibroblast and mesenchymal stem cells (MSCs) are found in the stromal tissue. MSCs can differentiate into osteoblast, myocytes, adipocytes, and neurons; its lineage differentiation fate depends on tissue-specific growth factors and mechanical signals. In cancerous conditions, the interaction between stromal cells and tumor cells has been shown to be crucial for cancer growth, proliferation, and survival [95]. Studies have shown that cancer cell-secreted exosomes can modulate the local microenvironment by inducing stromal cells to secrete cancer-promoting growth factors [96]. Recently, in chronic lymphocyte leukemia, cancer cell-secreted exosomes internalized by stromal cells were shown to exhibit a cancer-associated fibroblast (CAF) like phenotype; further, these cells secrete leukemia-related growth factors which promote the lymphoid tumor microenvironment [97]. Exosomes isolated from chronic myelogenous leukemia (CML) patients showed an elevated level of amphiregulin (AREG). These AREG-enriched exosomes interact with the epidermal growth receptor (EGF) of stromal cells and lead to downstream activation of EMT-like markers, mainly MMP-9 and MMP-2 [98]. Along similar lines, bone marrow stromal cell-secreted exosomal fibroblast growth factor 2 (FGF2) was shown to be endocytosed by leukemia cells, shielding them from tyrosine kinase inhibitory drugs [99]. These results point to a possible combinatorial therapy option against leukemia. Inhibitors against FGF2 will reduce exosomal FGF2 secretion and will increase drug efficacy of tyrosine kinase inhibitors in white blood cells. Myeloma cell derived exosomal fibronectin-heparin sulfate complexes were shown to interact with surrounding cells *via* the fibronectin ligand; these interactions promote p38 and pERK signaling in myeloma cells resulting in a more aggressive phenotype [100]. Another

important cell type inside the cancer stroma is immune cells, mainly macrophages which play a vital role in the upregulation of cancer-related inflammation [101]. They can secrete various pro/anti-cancerous growth factors and modulate tumor microenvironment [102]. Studies on clinical samples have shown the higher abundance of tumor-associated macrophages (TAMs) in cancer stroma [102]. In a murine breast cancer model, endocytosis of E0771 cancer cell-secreted exosomes was shown to promote IL-6 overexpression in macrophages [102]. Exosomes secreted by oral squamous cell carcinoma demonstrated activation of the p38, Akt, and JNK pathways in tissue-resident macrophages leading to their polarization and differentiation [103]. These results suggest the crucial role of cancerous exosomes in the creation of a pre-metastatic niche by corrupting immune cells. Surprisingly, in low-grade metastatic melanoma, cancer cell-secreted exosomes were shown to stimulate innate immune cells and circulatory monocytes, which induce anti-cancerous effects and lead to clearance of tumor cells in metastatic sites [104]. Collectively, all these studies highlight the importance of cancer cell-stromal cell interactions and its implication in cancer progression.

Exosomes and cell migration Cancer cell migration is necessary for metastasis and recolonization in the pre-metastatic niche. Prior to metastasis, the cancer microenvironment undergoes dynamic tissue reorganization which includes excessive ECM deposition and linearization of collagen fibers. Experimentally, it has been shown that cancer cells can treat these linearized bundled collagen fibers as highways and which can guide them towards blood vessels where they can undergo intravasation and finally metastasize [105–108]. Studies have shown that the induction of hypoxia is frequently observed in densely packed cancer microenvironment [109]. Recently in solid tumors, endothelial cells were shown to secrete lysyl oxidase 2 (LOXL2) in their exosomes [110]; LOXL2 proteins can induce tissue stiffening and cancer progression. Similar results were seen in hepatocellular carcinoma cells (HCC), where secreted exosomal LOXL4 was shown to promote cancer progression *via* the FAK/src pathway [111]. Exosomal MMPs, mainly MMP-14, released at the leading front of invadopodia can cause matrix degradation and promote cancer cell invasion [112]. Human gastric cancer cell lines, BGC-823 and MGC80-3, were shown to secrete exosomes, which can promote inflammatory proteins in neutrophils; by corrupting surrounding neutrophils, the gastric cancer cell maintains its migratory phenotype [113, 114]. Clinical studies revealed that patients suffering from AIDS/HIV1 have a higher incidence of non-AIDS defining cancers (NADCs). Their results demonstrated that HIV-infected T cells secreted exosomes can promote cell migration and cancerous growth in lung and oral tissue [115]. Interestingly, in prostate cancer cells, secreted exosomal αvβ6 integrins were shown to be internalized by healthy prostate cells, resulting in enhanced migratory potential in recipient cells [116], implying exosome-mediated direct transfer of phenotypic effects from cancer cells to healthy cells.

Microbiome and outer-membrane vesicles The existence of the microbiome in cancer tissue has redefined our understanding of the cancer microenvironment [117–119]. Its possible role in chemoresistance [120] and modulation of immune signaling for cancer growth and survival [121] has been reported. Presently, detailed mechanism of their interaction with stromal cells, ECM proteins, and various other roles inside cancer tissue is not known. In-depth proteomic analysis of bacterial exosomes, also referred to as outer membrane vesicles (OMVs), revealed the presence of DNA, RNA, proteins, and various active biomolecules [122]. Like exosomes, OMVs also have the capability to induce phenotypic/genotypic modifications in recipient cells [123]. With the availability of robust sequence analysis tools, evidence of lateral gene transfer between prokaryotes and eukaryotes are being revealed [124]. Studies have shown the presence of bacterial DNA in the chromosome of stomach adenocarcinoma cells [125, 126]. How this integration might have happened is still an open question, but researchers suggest that bacterial OMVs might be responsible for this lateral transfer of genetic material. Recently, OMVs secreted by *B. fragilis* were shown to deliver polysaccharide A to intestinal dendritic cells, which results in inflammation of intestinal cells due to overexpression of $CD4^+$ $IL10^+$T regulatory cells [125, 126]. Group B streptococcus secreted OMVs were to shown to degrade the maternal uterine wall *via* its collagenase activity, leading to poor implantation of the embryo and causing premature birth [127]. High throughput protein sequence analysis of colorectal cancer cell secreted exosomes revealed sequence similarity with gastrointestinal tract microbiome [128]. These results suggest a possible exchange of proteinous content between cancer cells and commensal bacteria. Although the mode of this exchange is unclear, it could be hypothesized that bacterial OMVs might mediate this process.

Chemoexosomes Exosomes secreted by cancer cells after surviving chemotherapy is termed as "chemoexosomes." Chemotherapy can eliminate the majority of the cancer cells but not all them. After a certain period, survivors or drug-resistant cells can lead to relapse and in some cases, may end up as more aggressive tumors, which ultimately leads to cancer-related mortality. Studies have shown that in acute myeloid leukemia (AML), chemotherapeutic agents induce certain mutations in the cancer cell genome, which make them resistant to these drugs [129, 130]. Recently, chemotherapy-exposed melanoma cells were shown to secrete a lot of heparanase abundant exosomes, which were involved in the degradation of ECM proteins and induction of ERK activation

and overexpression of TNFα in macrophages [131]. On similar lines, another study has shown that these exosomes carry heparanase-1 and heparanase-2 in its cargo; the former promoting tumor growth and invasion, while the latter has inhibitory functions [132]. How, in combination, they promote drug resistance and cancer growth is less understood. Right now knowledge about the chemoexosome is minimal, but its importance in cancer relapse and poor prognosis cannot be overlooked. It is predicted that soon it will become one of the critical mediators of cancer drug resistance.

4 Exosomes in high mortality cancers

Cancer-related mortality depends on detection stage and its relapse after chemotherapy, detection at a very late stage usually leading to cancer-related fatality. However, with the advancement in medical science and improved diagnostic tools, survival rates for most cancers have improved, but not in the case of pancreatic cancer and brain cancer. National Cancer Institute's (NCI) cancer statistical data from 2009 to 2015 suggests that survival rates in patients with pancreatic cancer are only 9.5% and in brain-related cancer, it is only about 30%, and it is not improving. Thus to shed more light into this matter, herein we discuss these cancers focusing on their secreted exosomal contents and clinical significance.

Pancreatic cancer Pancreatic ductal adenocarcinoma (PDAC) has a dismal 5-year survival rate and continues to be an unmet diagnostic and therapeutic challenge. The vast majority of treated patients show tumor recurrence [133]. PDAC is characterized by extensive desmoplasia and overcoming the stromal barrier for effective drug delivery remains a major obstacle [134]. Early dissemination of PDAC cells to distant metastases sites and concomitant preparation of distant sites for colonization is suspected [134]. Keeping in mind the unique challenges, an urgent search for early detection biomarkers and prognostic markers is ongoing. Exosomes are one of the predominant soluble factors shed from pancreatic tumors. PDAC-derived exosomes were shown to express the macrophage migration inhibitory factor (MIF), which helped them selectively promote liver metastasis. These exosomes were found in turn to induce fibrosis in hepatic sites by upregulating transforming growth factorβ (TGFβ) [134]. The hepatocyte-specific organ tropism to liver is a result of αvβ5 integrin on their surface [135]. These PDAC exosomes are even suspected of inducing characteristic weight loss *via* adrenomedullin (ADM), a lipolysis factor that induces lipolysis in adipose tissue *via* the adrenomedullin receptor (ADMR) [136]. Exosomes from CAFs induce the chemoresistance-inducing factor, Snail in recipient epithelial cells, which results in increased proliferation and drug resistance. This chemo resistance provided by CAFs is countered when the release of exosomes from CAFs are curtailed using GW4869—an exosome release inhibitor [135]. PDAC-derived exosomes were shown to regulate TLR4 of dendritic cells which can influence TNF-α and IL-12 activity downstream [137]. PDAC exosomal Sox2 was shown to promote EMT and stem cell-like properties in neighboring cells by downstream activation of Sox2 signaling, these results suggest Sox2 as a good candidate PDAC biomarker [138]. Hypoxic exosomes derived from PDAC cells were shown to activate the M2 macrophage phenotype in a HIF1a or HIF2a dependent manner, in which changes were positively correlated with invasion, lymph node metastasis, and poor prognosis of pancreatic cancer [139].

Exosomes and their cargo can also influence the developments of the tumor microenvironment. PDAC-derived exosomes were found to activate various gene expressions in human umbilical vein endothelial cells (HUVECs) and promoted Akt and ERK1/2 signaling pathways and tube formation *via* dynamin-dependent endocytosis in HUVECs [140], suggesting a possible role of pancreatic cancer exosomes in the induction of neoangiogenesis. Mass spectrometric analysis of PDAC exosomes revealed a cell surface proteoglycan called glypican-1 (GPC1) [141], which was previously identified as both an early stage and late-stage marker for cancer diagnostics. Its abundance in exosomes raised its possibility to be considered as a diagnostic marker.

Exosomes could be responsible for signs of the disease detected in other body fluids like the salivary secretion. Suppression of exosome biogenesis reduced the detection of a saliva based biomarker in an injected PDAC model [142]. An exciting new development is the ability to sort exosomes in the multichannel nanofluidic system from which exosomes can be isolated, and its RNA cargo can be profiled. Using machine learning algorithms, predictive panels could then identify samples from cancer-bearing individuals [141]. Exosomes are protected from monocytes and phagocytes by surface CD47. Evidence of novel direct usage of exosomes for therapeutic intervention in PDAC, using engineered exosomes called iExosomes from fibroblasts carrying short interfering RNA or short hairpin RNA specific to oncogenic KrasG12D has been reported [133]. We are also moving towards large-scale manufacturing of, and employment of, iExosomes using good manufacturing practice (GMP) standards with well-defined shelf life, biodistribution, toxicology profile, and efficacy in combination with chemotherapy [143]. All in all, in the face of this overwhelming evidence implicating involvement of exosomes in PDAC disease, use of exosomes and their unique cargo is crucial for breakthrough biomarker research as well as therapeutic intervention with increased efficacy.

Brain cancer The central nervous system (CNS) is peculiar in its microenvironment, and the blood-brain barrier (BBB)

restricts its interaction with the rest of the body. The presence of exosomes in body fluids (i.e., saliva, blood plasma, cerebrospinal fluid (CSF), urine) makes it particularly promising as a biomarker reservoir for both disease diagnosis and prognosis. Non-invasive biomarker analysis, especially from organs like the brain, is pragmatically meaningful in allowing the early detection of the tumor and to serve as a confirmatory result that is otherwise inconclusive.

Glioblastoma multiforme (GBM) is the most common type of brain cancer originating in the glia or glial precursor cells [144]. Graner et al. showed that exosomes released from D54MG and SMA560, cell line models of glioblastoma, contain specific members of the heat shock proteins (HSP27, 60, 70, and 90) [145]. In another study, mass spectrometry analysis on human glioblastoma astrocytoma-derived cell line, U373, revealed that the protein alpha-crystallin B chain (CRYAB) is present in significantly higher amounts in the exosomes. Further, when treated with pro-inflammatory cytokines, TNF-α, and IL-1β, the release of the protein is enhanced [146]. Nevertheless, conclusive evidence of these exosomal proteins in cancer progression is yet to be explored.

Quantitative high-resolution mass spectrometry of exosomes derived from GBM cell lines showed that there are significant differences in the expression of genes that are involved in cancer invasion. The authors also demonstrated that Cavitron Ultrasonic Surgical Aspirator (CUSA) washings were a novel source to isolate EVs from GBM. They identified upregulation of the same invasion-promoting proteins (annexin A1, actin-related protein 3, integrin-β1, insulin-like growth factor 2 receptor, and Alix) in these vesicles [146]. Co-culture experiments on neuroblastoma (NB) cells and monocytes established a connection between TAMs affecting the NB resistance to chemotherapy. In this study, researchers showed the exchange of miR-155 and miR-21 between NB cells and human monocytes revealing a new role for the exosomal miRNAs in exerting resistance to the anti-cancer drug Cisplatin through miR-21/TLR8-NF-κB/exosomal miR-155/TERF1 signaling pathways [147]. The first-ever proteomic characterization of NB exosomes was performed by Marimpietri et al. using human cell lines [148]. Among several tumor-promoting proteins identified fibronectin and clathrin were most prominently elevated. While fibronectin is essential for the migration of the NB cells, clathrin is involved in the formation of vesicles [148].

It is not surprising to assume that exosomes, which are long-distance cargo transporters, also mediates tumor metastasis. Accumulating evidences suggest that exosomes are indeed involved in metastasis of cancer mostly through miRNA delivery. MiR-112 predominantly secreted by breast cancer cells was shown to alter the glucose utilization by inhibiting pyruvate kinase. When tested, miR-122 containing exosomes successfully transferred the payload to lung fibroblasts, astrocytes, and neurons that are primary sites of breast cancer metastasis. Additionally, *in vivo* experiments showed that abrogation of miR-122 changes the glucose uptake and metastasis in distant niche organs [149]. Some of the other mechanisms exerted by exosomes during cancer metastasis include breaching of the BBB facilitating the movement of cells and cellular components freely in and out of the brain. Cancer derived exosomes when injected into the tail vein of severe combined immunodeficient (SCID) mice damaged the BBB and promoted cancer cell invasion. The molecular mechanisms of the breakdown of BBB is initiated by miR-181c that binds to the gene Pdpk1 (phosphoinositide-dependent kinase-1) leading to its degradation and disassembling actin filaments in endothelial cells [149]. Exosomes studies on other cancers (e.g., pancreatic and gastric) were shown to change the inflammatory responses in metastatic niches and promote cell adhesion with-in target sites [135]. The exosome mediated cross-talk between target sites and tumors is complex and yet to be understood completely. Recently Zhang et al. demonstrated an extraordinary signaling mode from target site to promote metastasis. MiR-19a containing exosomes from astrocytes specifically target breast tumor cells to suppress the expression of PTEN, a known tumor suppressor. The loss of PTEN expression upregulates CCL2 (cytokine chemokine ligand 2) necessary for recruitment of myeloid cells that support metastasis. *In vivo* experiments silencing astrocyte-specific PTEN-targeting miRNAs or blockade of astrocyte exosome secretion suppresses brain metastasis. These experiments reveal an adaptive metastatic growth of tumor cells that may have co-evolved with its microenvironment [150]. Our understanding of exosomes of the brain, particularly in cancer and its invasion to other organs is in its infancy. The field possesses undoubtedly a huge potential not only in the development of advanced therapeutics for brain cancer but also in expanding our knowledge about the fascinating organ, brain, and diseases that affect it.

5 Conclusion

In summary, we can conclude that exosomes are secreted by different cell types of diverse origin, and along with various active molecules, they carry ECM remodeling enzymes. In the tumorous condition, cancer-derived exosomes can alter the tumor microenvironment by promoting extracellular proteolysis via MMPs and ADAMTs, shedding cell surface receptors by overexpression of ADAMs, inducing ECM stiffening by LOXL mediated crosslinking of collagen fibers, and stimulating over secretion of glycosidases to cleave various sugar moieties in the ECM. These nano-sized vesicles play a deterministic role in the formation of a pre-metastatic niche by promoting angiogenesis, employing the stromal cells by corrupting their regular machinery and increasing the expression of EMT markers that promote cell migration and

metastasis. Recent reports on their interactions with the microbiome further deepen their connections in the tumor microenvironment. However, limited literature is available on how bacterial OMVs affect overall tumor microenvironment, but with the increasing relevance of the microbiome in cancer research, it will be interesting to explore how vesicles secreted from bacteria regulate the tumor microenvironment. As the majority of cancer cells secrete these tiny vesicles, their potential application in early detection of cancer is actively under consideration, especially since availability of vesicles in body fluids significantly cuts down downstream processing time, cost and manpower. With technological advancement in proteomic screening tools and accessibility of deep sequencing algorithms, new enzymes and proteases are being discovered in its cargo. Their implications in cancer is already an exciting area of research and will continue to be so in the foreseeable future.

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