Immunology Letters 209 (2019) 28–35

Contents lists available at ScienceDirect

Immunology Letters

journal homepage: www.elsevier.com/locate/immlet

Mast cells: A double-edged sword in cancer

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ARTICLE INFO

Keywords:
Mast cell (MC)
Cancer
Pro-tumorigenic role
Anti-tumorigenic role

ABSTRACT

Mast cells (MCs), a type of innate immune cells, are derived from myeloid stem cells, sometimes known as mastocytes or labrocytes, and contain many granules rich in histamine and heparin. The mentioned cells are able to release various mediators such as cytokines, leukotrienes, and a large number of proteases into the environment. Many studies and experiments have established the infiltration of MCs into the tumor site. However, the findings are highly controversial to determine whether these immune cells contribute to the growth and development of the tumor or cause anti-tumor immune responses. Various studies have revealed that MCs have a pro-tumorigenic or anti-tumorigenic role depending on the type of cancer, the degree of tumor progression, and the location of these immune cells in the tumor bulk. Although these types of immune cells cause angiogenesis and tumor progression in some cancers, they have a significant anti-tumor role in some other types of cancers. In general, although a number of studies have specified the protective role of MCs in cancers, the increased number of MCs in the blood and microenvironment of tumors, as well as the increased level of angiogenesis and tumor progression, has been indicated in another array of studies. The function of MCs against or in favor of the cancers still requires further investigations to more accurately and specifically determine the role of MCs in the cancers. The function of MCs in tumors and their various roles in case of exposure to the cancer cells have been addressed in the present review. The concluding section of the present study recommends a number of methods for modification of MCs in cancer immunotherapy.

1. Introduction

Mast cells (MCs) are granulated innate immune cells, originate from hematopoietic precursors, are characterized by their ability to release inflammatory mediators, are long-lived and heterogeneous cellular population, and function as both positive and negative regulators of immune responses [1–4]. Mast cells in human tumors were first described by Paul Ehrlich in 1878 [5]. The interaction between the cancer cells and their microenvironment can lead to tumor progression or suppression [6–8]. The tumor microenvironment is composed of stromal cells as well as different types of immune cells such as neutrophils, macrophages, mast cells, myeloid-derived suppressor cells, dendritic cells, natural killer cells, and T and B lymphocytes recognized as the arms of the immune system [9]. Nevertheless, lymphocytes and tumor-associated macrophages (TAMs) are the major cellular populations infiltrated into the well-established tumors [10]. The available evidence indicates that mast cells are commonly present in various tumors and can be attributed to tumor rejection or tumor promotion. Tumor-infiltrating MCs are derived from both sentinel and recruited progenitor cells [11]. Mast cells play various roles in the regulation of inflammatory processes, tissue regeneration, and host defense. Most of these activities can be attributed to their function as sentinel cells and recruitment of the effector cells of the innate and adaptive immune system [12]. MCs can directly affect the promotion and invasion of tumor cells. Moreover, they can indirectly lead to tumor progression by organizing the tumor microenvironment and modulating the immune responses [13,14]. It has been revealed that MCs have various effects on the immune system and immune cells such as mobilization of T cells

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https://doi.org/10.1016/j.imlet.2019.03.011
Received 16 March 2019; Accepted 20 March 2019
Available online 21 March 2019

and antigen-presenting dendritic cells. Mast cells can affect the regulation of T cells (Treg) and alter or reverse the suppressive properties of T cells. The significant property of MCs in controlling the inherent immunity enables them to regulate the host responses to cancer and positively affect the fate of patients with cancer. MCs have a central role in controlling the innate immunity, which enables them to regulate the host responses to cancer and consequently affects the outcomes of the disease and the fate of patients with cancer [15–20].

1.1. Biology of mast cells

MCs are granulated tissue-resident cells, derived from hematopoietic precursors in bone marrow, and classified as both the innate and adaptive arms of the immune system [21–24]. It has been estimated that mast cells have been appeared more than 500 million years ago prior to the evolution of adaptive immunity and are present in all classes of vertebrates [25,26]. Human MCs have been developed from $CD34^+/CD117^+$ pluripotent progenitor cells [21,27].

The development of mast cells requires the activation of the KIT (CD117), which is dependent on stem cell factor (SCF)-induced Kit dimerization and autophosphorylation [28,29]. Stem cell factor (SCF), known as the kit ligand, is produced by the MCs and structural cells in the tissues and in addition to the development of MCs plays a crucial role in the survival, migration, and function of mast cells [22,30]. Furthermore, a number of cytokines such as interleukin IL-3, IL-4, IL-9, IL-10, IL-33, and TGF-β have been observed to influence the growth and survival of MCs [31,32]. In addition to the expression of the Kit receptor (CD117), MCs express various receptors such as cytokine and chemokine receptors [33], Toll-like receptors (TLRs) [34], and vascular endothelial growth factor receptors [35]. Additionally, MCs express a very high-affinity IgE receptor (FcεRI), which induces the release of pro-inflammatory and immunomodulatory mediators by binding to its ligand [36,37]. MCs are present in the majority of tissues, all mucosal tissues such as skin and lung mucosa, digestive tract and located in close proximity to fibroblasts, epithelial cells, surrounding blood vessels, lymphatic vessels, and nerves [23]. MCs play an important role in inflammatory and immediate allergic reactions. MCs have a unique feature that is related to their granules and contain many storage and secretary granules such as histamine, serotonin, chemotactic factors, cytokines, and proteases including tryptases, chymases, and carboxypeptidase A3. All of these mediators act on the vasculature, smooth muscles, connective tissues, mucous glands, and inflammatory cells [24,38]. In MCs like other cells such as neutrophils, cytotoxic T cells, macrophages, and endothelial cells, serglycin proteoglycan has an important role in the assembly of mast cell granules by forming complexes with various granule proteases and bioactive amines, thereby causing retention of key inflammatory mediators inside the storage granules and secretory vesicles [39,40] (Fig. 1).

1.2. The notion of mast cell plasticity

Majority of the significant features of MCs such as proliferation, survival, storage capacity, and/or discharge of multiple and different products as well as the size and nature of their specific responses (secretion of mediators) to distinct activating signals are regulated by a number of environmental and genetic factors [41–43]. The unique and diverse characteristics of MCs depend on the host genetic background and/or local or systemic levels of factors that affect various aspects of mast cell biology. “Plasticity” in MCs can lead to the development of distinct phenotypic variations among mast cell populations in different anatomical regions or in different animal species [44,45]. In spite of various perspectives in this regard, it is now well-established that MC progenitors can give rise to two main subsets of mature MCs based on tissue distribution and differential composition in proteases and proteoglycans. Moreover, MC maturation depends on the exposure to a mixture of cytokines, which are provided by structural cells in local tissue microenvironments such as SCF [31].

Functional plasticity of MCs has been reported in the literature. The mentioned property leads to secretion of a number of factors, which exert pro-inflammatory, anti-inflammatory, or immunosuppressive actions following their activation [46].

1.3. Mast cells as a source of pro-angiogenic factors

The available evidence has well demonstrated that MCs are present in the microenvironment of several solid [27,47–54] and hematologic human tumors [50,51,53,54]. During the growth of malignant tissues, angiogenesis, which is the formation of new blood vessels, is a critical process to provide essential nutrients and oxygen to the malignant tissues [55]. Moreover, the formation of new lymphatic vessels, called *lymphangiogenesis*, is very important in the development of metastasis [56]. It has been shown that by producing chemotactic molecules, tumor cells recruit the MCs and macrophages to enter the tumor microenvironment that can be an important source of pro-angiogenic factors [57]. MCs not only produce different pro-angiogenic molecules such as VEGF-A, VEGF-B, FGF-2 [39,47], heparin [58], histamine [59], and stem cell factor (SCF) [60,61] but also produce lymphangiogenic molecules like VEGF-C and –D [27]. MCs express CD117, which binds to its ligand stem cell factor (SCF; kit ligand), stimulates the activation of the Kit signaling pathway, and drives the maturation, migration, and survival of MCs (56-59). MCs are derived from hematopoietic precursors inside the bone marrow and complete their differentiation and maturation within vascularized tissues [22,47,49,62]. During the growth and development of a tumor, the surrounding environment of the tumor through SCF chemotaxis causes the penetration and maturation of the MCs, which produce angiogenesis mediators, proteases, and growth factors promoting tumor growth and development [63]. Over MCs infiltration into an expanding tumor, an “angiogenic switch” is triggered; so that MCs directly increase angiogenesis to develop the tumor during the early stages of tumor growth, while tumor cells control the rate of tumor growth and angiogenesis at later stages as the growth becomes mast cell-independent [64,65]. By producing proteases such as tryptase in the tumor medium, MCs activate latent matrix metalloproteinases (MMPs) that degrade the extracellular matrix (ECM), increase the vascular tube formation, and subsequently release the trapped angiogenic factors leading to promotion of angiogenesis and metastasis [66] (Figs. 1 and 2).

1.4. The role of mast cells in anti-tumor immunity

In addition to the role of MCs in tumor angiogenesis, it has been indicated that these cells also have the ability to affect the anti-tumor immunity. In order to provide an effective anti-tumor immunity, it is required to employ and activate various types of immune cells like dendritic cells (DCs), natural killer (NK) cells, cytotoxic T (CD8 +) cells, and T-helper (CD4 +) cells at tumor sites and simultaneously inhibit immune suppressive cells including T-regulatory cells (Tregs), myeloid-derived suppressor cells (MDSCs), and alternatively activated (M2) macrophages [67–69]. However, the researchers suggested that MCs suppress immune responses in solid tumor sites by producing and releasing mediators and interacting with regulatory T cells and MDSCs [70].

1.5. Mast cell as an immune suppressor

Various functions of MCs, especially their “double-edged sword” role in promoting or inhibiting tumor progression, have been acknowledged in the literature [27]. Inducing a strong anti-tumor immune response requires overcoming the suppressed environment of the immune system in solid tumors. MCs are capable of secretion and production of several active biological agents involved in the modulation of tumor growth. The human MCs are able to secrete several

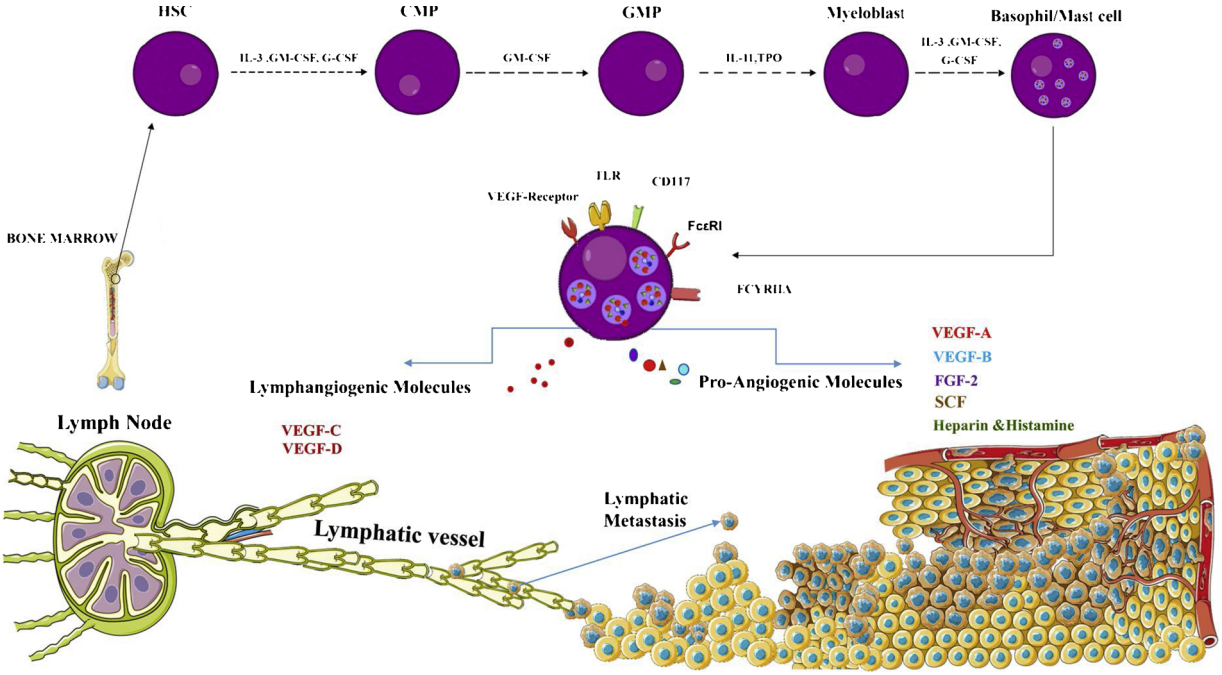

Fig. 1. Maturation of MCs and its role in the progression of cancer.
The Kit signaling pathway is necessary for the maturation, migration, and survival of mast cells (MCs). During the maturation of MCs, hematopoietic stem cells (HSCs) will convert to the common myeloid progenitor (CMP) and then will convert to the granulocyte macrophage progenitor (GMP) and then will convert to myeloblast. Mature MCs will be formed at the end of the stage. MCs produce many pro-angiogenic factors like vascular endothelial growth factor (VEGF) A, VEGF-B, fibroblast growth factor-2, histamine, heparin, and stem cell factor which promotes angiogenesis. Moreover, MCs can produce lymphangiogenic molecules such as vascular endothelial growth factor-C and -D, which contribute to lymphomagenesis. All the mentioned factors are presented in Fig.1 (see the text for additional details). Fig. 1. was provided by Servier Medical Art (http://smart.servier.com/).

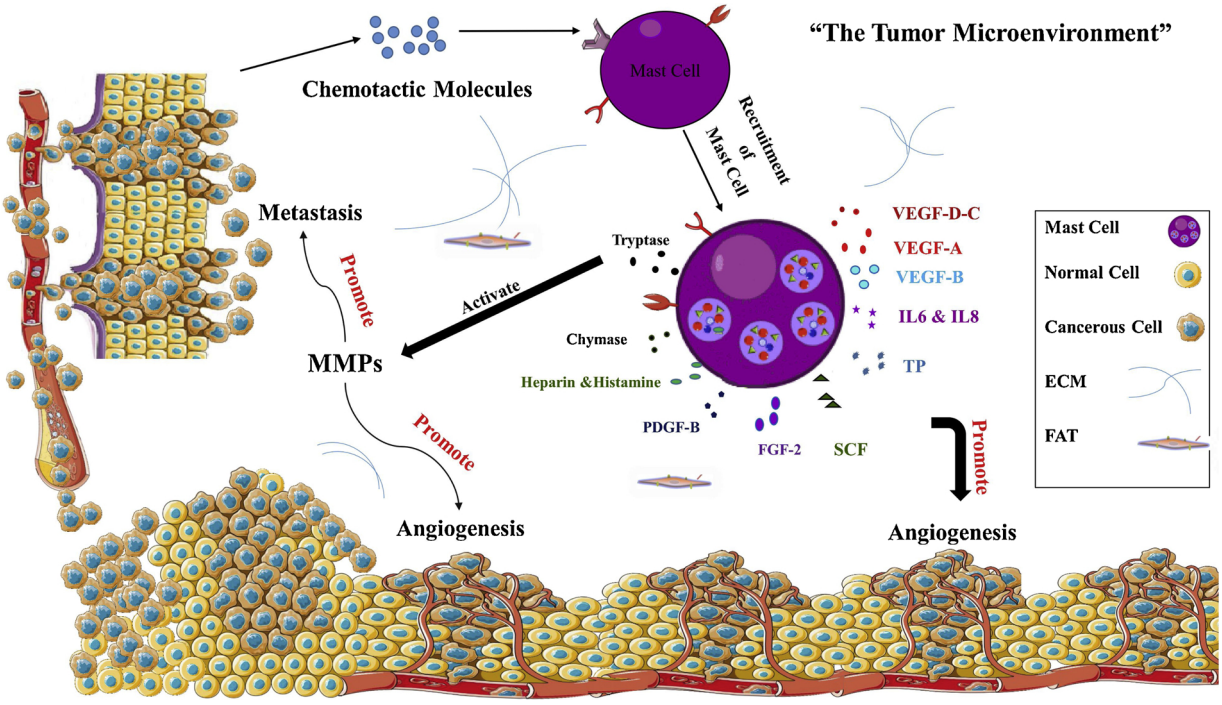

Fig. 2. The role of MCs in angiogenesis and metastasis.
Angiogenesis is important for tumor growth and progress. As tumor cells intend to stimulate irregular angiogenesis to promote tumor progression, they produce chemotactic options such as CXCL12 for CXCR4, which are a receptor on the surface of the mast cells (MCs) and recruit MCs into the tumor microenvironment. Then, MCs are recruited into the tumor site, stimulate angiogenesis by releasing several pro-angiogenic factors like enzymes, cytokines, and other factors stored in the cytoplasm and their granules. These factors include platelet-derived growth factor-β (PDGF-β), vascular endothelial growth factor (VEGF), interleukin (IL)-6, IL-8, fibroblast growth factor-2 (FGF-2), thymidine phosphorylase (TP), heparin, histamine, and stem cell factors (SCF) that induce angiogenesis in the milieu of tumors. It is of great significance to mention that tryptase and chymase that are released by MCs and induce proteases have an imperative role in tumor angiogenesis by activating the matrix metalloproteinase (MMP). Fig. 2 was provided by Servier Medical Art (http://smart.servier.com/).

immune suppressive cytokines such as IL-10 and TGF-β1, which can contribute to local immune deficiency. Latent TGF-β-binding protein (LTBP) and TGF-β are present in the endothelial basement membrane. During the inflammatory processes and degranulation of MCs, chymase and leukocyte elastase are released, which can act on matrix-associated latent TGF-β complexes and lead to the release of latent TGF-β from the subendothelial extracellular matrix [71]. In addition, the histamine secreted from MCs can mediate the immune suppression by inhibiting both T_H1 and T_H2 responses through the activation of H2 receptors [72]. Furthermore, MCs have a strong effect on the functional capacity and development of effective tumor immunity via interactions with immune suppressor cells like MDSCs and regulatory T cells. A complex interrelationship between MCs, MDSCs, and Tregs has been revealed in a murine model of liver cancer. MCs also employ the MDSCs to induce the production of IL-17, which in turn helps to the mobilization of Treg cells and boosts their suppressive function. Moreover, MCs can recruitment of MDSCs in the tumor site too [73].

Various studies have shown that MCs can regulate MDSCs through the release of histamine, which regulates myeloid cell differentiation. It has been shown that histamine-deficient mice indicated a decrease in myeloid cell differentiation and decrease the accumulation of immature CD11b + Gr1 + myeloid cells. Moreover, injection of exogenous histamine to histamine-deficient mice induced the maturation of immature CD11b + Gr1 + and inhibited their ability to increase the tumor growth rate in vivo [74]. Furthermore, a number of transplantation studies suggested that there is an important relationship between MCs and Tregs in allograft tolerance [75]. On the other hand, the regulatory T cells can modulate the activity of MCs through an OX40 / OX40L-dependent pattern, which prevents their degranulation and enhances their secretion of IL-6 via TGF-β1 [76–78]. In addition, it is worth mentioning that the release of histamine from MCs can inhibit the repression function of regulatory T by H1 receptor [79]. MCs are able to deviate the differentiation of the regulatory T cells into the TH17 inflammatory cell phenotype through both IL-6-dependent and independent mechanisms [73]. Although T_H17 cells can contribute to tumor-promoting chronic inflammation, they have potent anti-tumor effects in some cases [80]. Therefore, MC activation, as an adjunct to tumor immunotherapy, may reduce the function of Treg cells in tumor sites and increase the effectiveness of anti-tumor immunity.

1.6. The role of MCs in immune cell recruitment

Activation of MCs is associated with the release of a wide range of inflammatory mediators. It has been shown that MCs cause selective recruitment of immune effector cells to tissue sites by enhancement of adhesion interactions, vascular permeability, and direct chemoattractant actions. By activating TLR2, MCs secreted CCL3, which caused recruitment of NK cells and T cells in a CCL3-dependent manner in vitro [81]. Moreover, the available evidence reveals that CCL3, CCL5, and CXCL10 derived from MCs can play a key role in the infiltration of T cells into tumor sites. In addition, other mediators released from MCs can also be associated with the infiltration of the effector cells into the microenvironment of the tumor. For example, the leukotriene B4 (LTB_4) released from the activated MCs can affect the migration of T CD8 + cells [82]. The role and significance of human MCs have been well recognized in the literature by specifying them as regulators in the recruitment of immune effector cells. For example, upon the interaction between MCs and activated T cells, human MCs induced the migration of neutrophils via CXCL8 [83], which is also a strong and selective inducer of NK cells following viral infections and activation of human MCs [84].

In viral infections following the activation of MCs, it has been indicated that MCs induced the recruitment of CD56 + T cells including invariant NKT cells and cytotoxic T cells through CCR3 and CCR5 ligands. Moreover, MCs are the main source of CXCL10, CCL5, and CCL4. Therefore, it seems that MCs have an important role in recruitment the immune cells into the tumor site by providing a chemokine environment [78].

1.7. The role of the tumor and its environment in the activation of mast cells

For the first time in 1891, Westphal proposed the pro-tumorigenic role of MCs, as a result of which the number of MCs were increased in the tumors [15,18,85,86]. It has been shown that tumor-associated mast cells (TAMCs) are present in the microenvironment of several human solid [15,47–49,52,85,87–90] and hematologic tumors [4,50,51,91,92]. For example, there is a high number of MCs in the context of different tumors such as thyroid, colorectal, pancreas, prostate, melanoma, and breast cancers (90–95). MCs with the expression of CCR2, CXCR2, and CXCR3 and binding to their respective ligands produced by human tumors, i.e. CCL2, CXCL1, and CXCL10, can play a critical role in TAMC localization [15,49]. Various studies have shown that tumor microenvironment is rich in soluble mediators including SCF, monocyte chemoattractant protein-1 (MCP-1), vascular endothelial growth factor (VEGF), angiopoietin 1 (Ang1), IL-8, CCL2, CXCL1, CXCL10, and osteopontin (OP), all of which in addition to the activation of MCs result in recruitment of MCs and stimulation of MCs development [17,49,93–95]. In fact, upon the activation of MCs by tumors, they release a wide spectrum of growth factors, angiogenic factors, and pro-inflammatory molecules, which are responsible for TC aggressive phenotypes [15]. Moreover, MCs express HIF-1, which in turn activate the MCs under hypoxic conditions [96,97]. Furthermore, the expression of adenosine and PGE2 increases in the hypoxic microenvironment of tumor [98,99]. Adenosine activates MCs to release pro-inflammatory cytokines through A2b and A3 receptors [100]. PGE2 can increase the production of mediators such as IL-6 [101], vascular endothelial growth factor (VEGF) [6], and CCL2 in MCs [102]. A number of studies have shown that a high number of MCs activating neuropeptides in the tumor environment can increase tumor growth [103]. Hence, recruitment of MCs to tumor cells is of great value in various cancers.

1.8. The role of mast cells in tumor growth

The increase and accumulation of MCs in tumors were described by Ehrlich [104]. However, the role of MCs in the progression or prevention of tumors is still a challenging issue [105]. Some pieces of evidence propose that MCs can promote tumorigenesis and tumor progression as a number of clinical data sets as well as experimental tumor models indicate that MCs seem to have functions favoring role against the tumor [104]. Therefore, depending on the milieu, MCs can be the main source of pro-tumorigenic (e.g., angiogenic and lymphangiogenic factors) and anti-tumorigenic (e.g., TNF-α and IL-9) molecules [105]. MCs have a variety of important mediators in their granules, some of which can cause tumor growth. In all the studied species, it has been revealed that granules of MCs contain a mixture of histamine (also serotonin in rodents), proteins, cytokines, and growth factors embedded in a glycosaminoglycan of the human meshwork [106]. Histamine can induce tumor cell growth and proliferation and suppress the immune system through H1 and H2 receptors, respectively [107]. It has been reported that histamine H1- and H2-receptors are present in human carcinomas [108]. Tryptase is the most abundant mediator stored in the MC granules [109] and is a highly specific marker of this cell type [110]. The evidence reveals that tryptase causes tumor growth in some cancers [19,20,111]. In some specific types of cancers, the location of MCs is very important in the prognosis of cancers and specification of whether MCs would lead to tumor growth. For example, it has been observed that MC density in the intratumoral border region, as compared with the peritumoral or the intratumoral central region, is associated with a worse prognosis in the pancreatic canal adenocarcinoma [112]. However, high intratumoral MC density is associated with good prognosis in prostate cancer [113]. Moreover, a number of studies have revealed

that intratumoral MCs inhibit tumor growth, while peritumoral MCs stimulate human prostate cancer [52]. IgE receptor FcεR1, a specific receptor of MCs, plays a very crucial role in the relationship between MCs and cancer. Moreover, the effect of IgE-mediated activation of MCs on tumor growth and development has been investigated in previous studies [114]. In the absence of antigens, monomeric IgE results in the production of VEGF-A from MCs as well as the increased growth of melanoma [115]. Furthermore, there is an increased expression of immunoglobulin free light chains (FLCs) in the stroma of various human cancers [116]. According to the available results, MCs cause tumor growth; however, further investigations are required to shed more light on the mechanism of MCs associated with tumor cells and other immune cells in tumor stroma (Fig. 2).

1.9. The role of mast cells in tumor angiogenesis

Angiogenesis is indispensable for the consecutive growth of the malignant tumors; however, during angiogenesis, capillaries produce irregular, sinuous, and fenestrated capillaries that lack pericytes, are unable to induce vasoconstriction, cause turbulent flow, and favor thrombosis and bleeding. The mentioned properties increase the spread of local tumor and formation of embolism [117]. It is worth noting that tumor angiogenesis is crucial for tumor growth, invasiveness, and metastatic spread [118]. CXCL12 produced by tumor and stromal cells is one of the important chemokines that is essential for attracting the MCs to tumor sites [119]. The studies have reported that tumor-associated MCs express CXCR4 [120] and CXCL12 and induce trans-endothelial migration of human MCs in vitro [121]. Hence, it is remarkable to mention that MCs can stimulate angiogenesis, and CXCL12 can enhance the secretion of a pro-angiogenic factor from MCs [121]. CXCL12 in collaboration with VEGF and CXCL8 may enhance angiogenesis through the recruitment of MCs to the edge of the solid tumors [122]. As previously mentioned, MCs can stimulate angiogenesis by releasing several angiogenic agents such as enzymes, cytokines, and other mediators stored in the cytoplasmic granules [3]. Pro-angiogenic factors that can be secreted from MCs include VEGF, platelet-derived growth factor-β (PDGF-β), fibroblast growth factor-2 (FGF-2), IL-6, IL-8, and thymidine phosphorylase (TP) [1,2,16,110,123–134]. Other factors released by MCs such as proteases, tryptase, and chymase have an imperative role in tumor angiogenesis [135]. Some studied have demonstrated that the function of all MC factors such as histamine, heparin, and other molecules favoring angiogenesis not only increases the endothelial cell migration, proliferation, and differentiation but also promotes the adhesion between tumor and endothelial cells [135]. However, on the other hand, MCs can inhibit the angiogenesis by secreting prostaglandin D2 (PGD2) [136]. It is worth mentioning that the overall role of MCs in tumor angiogenesis depends on the type of MCs activating stimuli and the subsequent mediator released by MCs cells under a particular condition [78].

1.10. Various functions of mast cells according to their microenvironment and tumor stages

Various studies have shown that the stage of tumor development and location of MCs in the tumor can help improve tumor immunity or increase inflammatory changes that result in the intensification of local angiogenesis [137]. Although it is well known that different types of solid cancers and hematologic malignancies are accompaniedby an increase in MC density, MC count is associated with tumor stage, prognosis, and invasiveness [15,85,138,139]. One of the most common features in the advanced stages of the tumor is MC degranulation. Hence, it can be concluded that a significant decrease in the number of MCs in the advanced stages of the tumor is due to the destruction of MCs leading to tumor growth [140]. In fact, the role of MCs in different tumors is different and still a controversial issue [105]. For example, MCs can contribute to tumor progression in the early stages of prostate cancer by producing MMP-9, while they have effective roles in the prevention of tumor growth in later stages [85,141]. It has also been reported that MCs play an important role in the development of colon cancer in early stages by producing VEGF-B, as an angiogenic agent [93,142,143].

1.11. Methods to change the function of mast cells in tumor immunotherapy

MCs contribute to the development of a number of diseases such as cancers. During tumor growth, some immune cells present in the microenvironment of the tumor correlate with the tumor. As discussed earlier, the activation of MCs leads to the production of factors that contribute to the growth, development, and angiogenesis of tumors. Moreover, the increased number of MCs in a large number of tumors is associated with poor prognosis, increased intravascular angiogenesis, and increased invasive clinical prognosis of tumors. Therefore, the regulation of MC activation, MC recruitment, MC status, and the amount and type of the released agents and mediators at the tumor site can be useful in management and control of tumor growth [144]. There are several therapeutic strategies to reduce tumor growth by targeting the MCs and their mediators [145].

It has been revealed that in pancreatic islet tumors induced by Myc, tumor growth can be impeded by inhibition of MC degranulation by cromolyn sodium [146] in the experimental pancreatic cancer, thyroid cancer, and cholangiocarcinoma [15,88,147]. However, it must be considered that MC degranulation and its association with tumors are still controversial issues [90]. One of the main causes of skin cancer is exposure to UV radiation from the sun that causes the basal cell carcinoma (BCC) and squamous cell carcinoma (SCC). It has been shown that UV radiation causes the skin mast cell migration by altering the CXCR4–CXCL12 axis [148] and pharmacological blockade of the CXCR4–CXCL12 pathway inhibited skin cancer caused by sunlight [105]. MC activity can also be suppressed with the application of MC-stabilizing agents or MC-targeting mediator agents such as the anti-TNF monoclonal antibody infliximab. The mentioned method has a major role in reducing the development of a colorectal tumor [149]. It is clear that stem cell factor (SCF) / c-kit is very essential for MC development. Research has shown that the use of c-kit tyrosine kinase inhibitor STI571 and a tyrosine kinase inhibitor imatinib mesylate that inhibits signaling through c-kit reduce the effect of MC on tumor growth [150]. Anti-tumor IgE may play a significant role in anti-tumor immunity. In one study, serum levels of IgE and sCD23 in patients with pancreatic cancer were significantly increased as compared with those of the control group. Moreover, it has been shown that IgE isolated from the serum of patients with pancreatic cancer can increase the ADCC of the pancreatic cells with peripheral blood mononuclear cells. The mentioned findings suggest that IgE may be a useful marker in patients with pancreatic cancer and may be relevant to the immune response to this disease, while direct treatments with IgE may lead to direct therapy [151].

It seems by employing therapeutic strategies to enhance the local mast cell degranulation, create an anti-tumor immune response, including increasing the recruitment of effector cells, the direct impact of granule-associated and de novo synthesized mediators on tumor cells and secondary effects on immune regulation. Although the function of histamine in the tumor microenvironment is complicated [152]. It has been shown that MCs consolidation with sodium cromoglicate in a xenograft model of thyroid cancer significantly reduced tumor growth [15]. In a study with a murine model of breast carcinoma, it was shown that stabilization of MCs with sodium cromoglycate or depletion of MCs with imatinib mesylate increases tumor growth, blood coagulation, and hypoxia in the tumor (157,158). Accordingly, spacious inhibition of the MC function may not be useful in all types of tumors. Therefore, extensive inhibition of MC function may not be beneficial for all tumor types [78].

2. Conclusion

Many immune cells are infiltrated into the tumor tissues, where the function of many of these cells is changed and lead to exhibition of dual behavior of these cells. One of these cells is MCs, which, act in favor of the immune system in some cancers and protect the body by their anti-tumorigenesis function. However, they act in favor of the tumor by their pro-tumorigenesis function in a significant number of cancers and provide a poor prognosis for the patient due to their production factors. Whether MCs are more likely to accompany the tumor or the immune system is still not thoroughly comprehended. In general, the role of MCs in this regard depends on the type of tumor, its level, its degree of progression, different anatomical position of MCs, and different methods of MC detection such as tryptase+, chymase+, toluidine blue, CD117+, and Giemsa. The present review study discussed how to change the performance of the MCs that are associated with tumors. Further research is required to better clarify the role of MCs in relation to tumors to offer better treatment and clinical services.

Conflict of interest

The authors declare that there is no conflict of interest.

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