

Mast Cells as Target in Cancer Therapy

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Abstract: A close interaction of cancer cells with their microenvironment is important for their growth and survival. In this respect, the involvement of inflammatory cells in the initiation, promotion and progression of cancer has pointed to new therapeutic opportunities in the treatment of cancer. The main immune cell types implicated in tumor-associated inflammation are macrophages, dendritic cells, lymphocytes, neutrophils, eosinophils and mast cells. Their precise role in intercellular communication, regulation of tumor inflammation, and to what respect this inflammation contributes to tumor development, are not completely understood. Mast cells are key effector cells in allergic diseases, but it has become apparent that they also contribute to other pathologies, including autoimmune diseases and cancer. Activated mast cells can release many pro-angiogenic and tumor growth stimulatory mediators. Increased numbers of mast cells are found in many tumors and it has been shown that the number of tumor infiltrating mast cells correlate with increased intratumoral microvessel density, enhanced tumor growth and tumor invasion, and poor clinical outcome. Therefore, modulating mast cell recruitment, viability, activity, or mediator release patterns at malignant sites can be of importance to control tumor growth. In this review, we will focus on the contribution of mast cells to tumor development and growth and the possibilities to interfere in mast cell activation and proliferation in the therapy of cancer.

Key Words: Tumor cell, cancer, mast cell, inflammation, c-kit, microenvironment, angiogenesis, stem cell factor.

1. MAST CELLS

Mast cells are generated from hematopoietic progenitor cells and are released from the bone marrow as immature cells. Mature mast cells cannot be recovered from the blood stream. Instead, the immature mast cells distribute throughout the body and mature in the tissues in which they will ultimately reside during their lifespan [1, 2]. Although mast cells are located in virtually every vascularized tissue, most mast cells are positioned close to blood vessels and nerves and at anatomical sites that are in direct contact with the environment, like the skin, airways and gastrointestinal tract [3, 4]. Since maturation takes place in different body parts under different microenvironmental conditions, immature mast cells evolve into phenotypically distinct mature populations. This results in a profound heterogeneity of mast cells throughout the body [1] which becomes apparent by differences in protease and glycosaminoglycan contents of granules, as well as differences in lipid-mediator production [5]. In addition, mast cells can proliferate and show extensive phenotypic plasticity after appropriate stimulation with a variety of factors, acting through autocrine, paracrine and/or systemic mechanisms [1, 6]. Stem cell factor (SCF) is the major survival and developmental factor for mast cells. Together with interleukin-3 (IL-3) and T helper type 2- associated cytokines like IL-4 and IL-9, this is the most important factor that influences proliferation and phenotypical aspects of mast cells. Moreover, a wide array of other cytokines, growth factors and chemokines can affect mast cells [6, 7].

Mast cells are most commonly known as the main effector cells in allergic, IgE-mediated immune reactions. In sensitized hosts, crosslinking of cognate antigen to IgE molecules that are bound to their high affinity receptor (FcεRI) activates mast cells to release their mediators, resulting in an inflammatory response [2, 8]. This process, however, can also be beneficial to the host, since this mechanism is well known to be involved in resistance to parasites [2, 9, 10]. In addition, mast cells can be activated by many other immunological and non-immunological signals, such as IgG, immunoglobulin free light chains, complement factors, bacteria, viruses, cytokines, inflammatory mediators, toll like receptors, and by T cells [5, 6, 11-13]. Depending on the type and strength of the activating stimuli, mast cells can release distinct patterns of a large array of mediators [3]. Three main classes of mediators can be distinguished [3, 5, 14]:

- pre-formed, granule-associated mediators (e.g. histamine, tryptase and heparin), and
- *de novo* synthesized lipid mediators (e.g. LTC₄, LTB₄ and PGD₂) and
- a variety of cytokines and chemokines

Mediator release can be accomplished by complete degranulation or by so-called piecemeal degranulation, leading to a less selective or more selective release of mediators, respectively [12, 14]. In this way, mast cells can initiate or maintain an appropriate and effective immune response, dependent on the activating signals. Mast cells not only function as effector cells, they can also act as regulatory cells. Mast cell mediators can exert proinflammatory, anti-inflammatory and/or immunoregulatory effects by influencing development, survival, proliferation, migration, maturation or function of other immune cells, like dendritic cells, B

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cells, T cells, macrophages, neutrophils and eosinophils [6, 7, 15-20]. Because of these immunomodulatory functions, mast cells are believed to be involved in both innate and adaptive immune responses and, thus, protect the body against harmful antigens and pathogens. Moreover, mast cells can also exert immunosuppressive effects [21-23] and induce tolerance mediated by regulatory T cells [24].

Together, these data establish that the mast cell has an important function in orchestrating many immune responses. These immune responses are not always beneficial to the host, underlined by the critical involvement of mast cells in allergic disorders. However, in recent years, it has also become apparent that mast cells contribute to other pathologies, such as autoimmune diseases [25, 26] including rheumatoid arthritis [27-30] and multiple sclerosis [31-34] and cardiovascular diseases [35-37].

2. CANCER AND INFLAMMATION; CRITICAL ROLE FOR MAST CELLS?

The transformation of normal cells into malignant cells by genetic and epigenetic changes has generally been considered to result from activation of oncogenes that enhance unlimited cell proliferation, promote escape from apoptosis, stimulate angiogenesis, and increase invasion of surrounding tissues. During the last years, it is becoming apparent that the tumor microenvironment is a critical determinant of malignant transformation and tumor proliferation [38]. The tumor microenvironment mainly consists of tumor cells, stromal fibroblasts, epithelial cells, cells forming blood and lymphatic vessels, inflammatory cells and extracellular matrix components.

The observation that tumors contain inflammatory cells has already been recognized back in 1863 by Virchow. This could either mean that the inflammatory cells are active in fighting the malignant cells, stimulate tumor progression or a mix of both processes. The immune system may have a protective role in tumor development, known as cancer immunosurveillance. This process seems especially effective in virus-induced cancers, where a compromised immune system sparks a sharp increase in cancer incidence (e.g. Kaposi sarcoma in HIV-patients). In general, however, immunosurveillance likely eliminates a portion of early-stage transformed cells, whereas clinically advanced tumors probably avoid immunosurveillance by inducing immune tolerance [39, 40]. Recently, the involvement of inflammation in the initiation, promotion and progression of cancer has received more attention [38, 41-45].

The main immune cell types implicated in tumor-associated inflammation are macrophages, dendritic cells, lymphocytes, neutrophils, eosinophils and mast cells. Their precise role, communication, and regulation of tumor inflammation and how this inflammation contributes to tumor development are not completely understood. In this review, we will focus on the contribution of mast cells to tumor proliferation and possible strategies to interfere with mast cell activation.

2.1. Mast Cell and Tumor Development

The mast cell appears to be an attractive target in tumor therapy. In humans, increased levels of mast cells are found

in many tumors. Moreover, it has been shown that the number of tumor infiltrating mast cells correlates with increased intratumoral microvessel density, enhanced tumor growth and tumor invasion, and poor clinical outcome (Table 1). The observed correlations indicate an association between mast cells and tumor growth. This clinical observation, together with *in vitro* data and data from rodent tumor models, suggests an important role for mast cells in the development and progression of cancer [46-49]. An *in vitro* study using the human mast cell line LAD2, for example, showed that mast cells regulated migration of cervical cancer cells by the release of histamine and cannabinoids, suggesting that mast cells could contribute to cervical cancer cell invasion and spreading [50]. In addition, this study showed that factors secreted by cervical tumor cells stimulated LAD2 cell degranulation, demonstrating a cross-talk between tumor cells and mast cells (Fig. 1). Besides these *in vitro* data, there are a few studies using rodent tumor models in which a more clear-cut involvement is demonstrated of mast cells in tumor development. In 1988, it was already shown that mast cell-deficient mice exhibited a decreased rate of tumor angiogenesis compared to their wild-type littermates. In addition, development of spontaneous lung metastases was less frequent in mast cell-deficient mice. Reconstitution of the mast cell population largely restored the wild type phenotype [51]. This role of mast cells in angiogenesis is supported by studies in a HPV16 transgenic mouse model of squamous epithelial carcinoma [52]. Mast cell infiltration was found in hyperplasias, dysplasias, and invasive fronts of carcinomas together with the activation of metalloproteinase-9 (MMP-9). This coincides with the angiogenic switch in premalignant lesions. Degranulation of mast cells, releasing chymase and tryptase, was observed in close proximity to capillaries and epithelial basement membranes. The authors showed that tryptase is mitogenic for dermal fibroblasts that proliferate in reactive neoplastic stroma, and that chymase can activate MMP-9, which leads to extracellular matrix (ECM) remodeling. More important, mast cell deficiency resulted in a severe attenuation of early neoplasia, probably due to an impaired vascular response. Recently, a study by Soucek *et al.* [53] further supported the essential role of mast cells in tumor angiogenesis and growth. These authors used a transgenic Myc-induced pancreatic islet tumor model, in which they can reversibly switch Myc-expression. The Myc oncoprotein, a pleiotropic transcription factor that is overexpressed in many human cancers, rapidly induced the expression of several chemokines. This resulted in the predominant recruitment of mast cells within the first 24 hours. Macrophages and neutrophils were only found after one week of sustained Myc activity, occurring after onset of tumor angiogenesis. Subsequently, they demonstrated that mast cells were essential for tumor growth, since blocking mast cell degranulation using cromolyn, completely blocked Myc-induced islet expansion. In mast cell-deficient mice (*W-Sash*), the exact same phenotype as in wild-type mice treated with cromolyn was observed. Furthermore, the observed tumor growth inhibition appeared due to a deficit in the maintenance of tumor angiogenesis. In this model, functional mast cells seem required to maintain established tumors.

These studies put forward a critical role for mast cells in tumor angiogenesis. Angiogenesis is crucial for macroscopic

Table 1. Increased Mast Cell Numbers in Human Cancers and Positive Correlations between Tumor-Associated Mast Cell Numbers and Various Clinicopathologic Features

Increased Mast Cell Number	
Basal cell carcinoma [151-153]	Endometrial carcinoma [154]
Melanoma [155-158]	Laryngeal squamous cell carcinoma [159]
Pancreatic ductal adenocarcinoma [160]	Renal cell carcinoma [161]
Oral squamous cell carcinoma [162, 163]	Gastric cancer [164]
Lung cancer [165-167]	Multiple myeloma [168]
Breast carcinoma [169]	B-cell non Hodgkin's lymphoma [170]
Correlation between Mast Cell Number and Increased Microvessel Density/Angiogenesis	
Melanoma [157, 171, 172]	Gastric cancer [164]
Pancreatic ductal adenocarcinoma [160]	Multiple myeloma [168]
Oral squamous cell carcinoma [162]	B-cell non Hodgkin's lymphoma [170]
Lung cancer [165-167, 173, 174]	Colorectal carcinoma [175]
Endometrial carcinoma [154]	Uterine cervix carcinoma [176]
Renal cell carcinoma [161]	Esophageal squamous cell carcinoma [177]
Correlation between Mast Cell Number and Increased Invasive Ability/Metastasis	
Melanoma [172]	Gastric cancer [164]
Pancreatic ductal adenocarcinoma [160]	Colorectal carcinoma [175, 178]
Lung cancer [174]	Esophageal squamous cell carcinoma [177]
Correlation between Mast Cell Number and Tumor Stage/Poor Prognosis	
Melanoma [157, 171]	Uterine cervix carcinoma [176]
Lung cancer [166, 174]	Esophageal squamous cell carcinoma [177]
Endometrial carcinoma [154]	Prostate cancer [179]
Gastric cancer [164]	Hodgkin's lymphoma [180]
Colorectal carcinoma [175, 178]	

expansion of human tumors and essential for metastasis [54, 55]. This role for mast cells is not surprising given the capacity of these cells to produce and release a large array of potent angiogenic cytokines and proteases. As reviewed by Ribatti *et al.*, mediators like VEGF, FGF-2, TGF- β , TNF- α , IL-8, NGF, tryptase, chymase, heparin, and histamine can be involved in mast cell-induced angiogenesis [56]. Moreover, MMP-2 and MMP-9 can be synthesized and secreted by mast cells [57, 58], or activated by mast cell mediators [52, 59, 60]. This causes ECM remodeling, which releases angiogenic factors that are sequestered in the ECM (such as VEGF, FGF and TNF- α) that further intensify tumor-associated angiogenesis [44] and may facilitate invasion [61].

Next to the involvement in angiogenesis and the breakdown of surrounding stroma, mast cells also appear to be involved in promotion of tumor cell proliferation, and inhibition of the immune response against neoplastic cells. The mitogenic effect of the mast cell mediators FGF-2 and IL-8

is shown on melanoma cells [62, 63]. IL-6 enhances cancer cell proliferation in multiple myeloma [64, 65] and the same accounts for tryptase in a colon carcinoma cell line [66] and in a model for cheek pouch carcinoma [67]. Moreover, histamine and growth factors such as SCF, NGF, and PDGF can induce tumor cell proliferation [49]. The immunosuppressive effects of mast cells are supported by a recent finding that SCF-activated mast cells exacerbate tumor immunosuppression in mice by releasing adenosine and increasing regulatory T cells. This suppressed T cells and NK cells within the tumor [68].

Despite this substantial amount of evidence for the role of mast cells in different aspects of tumorigenesis and tumor proliferation, the exact mechanisms leading to the recruitment and activation of mast cells and other inflammatory cell types, are still undefined. Some factors are likely candidates for attracting mast cells to neoplastic lesions and for their activation. Of these, SCF is probably the most impor-

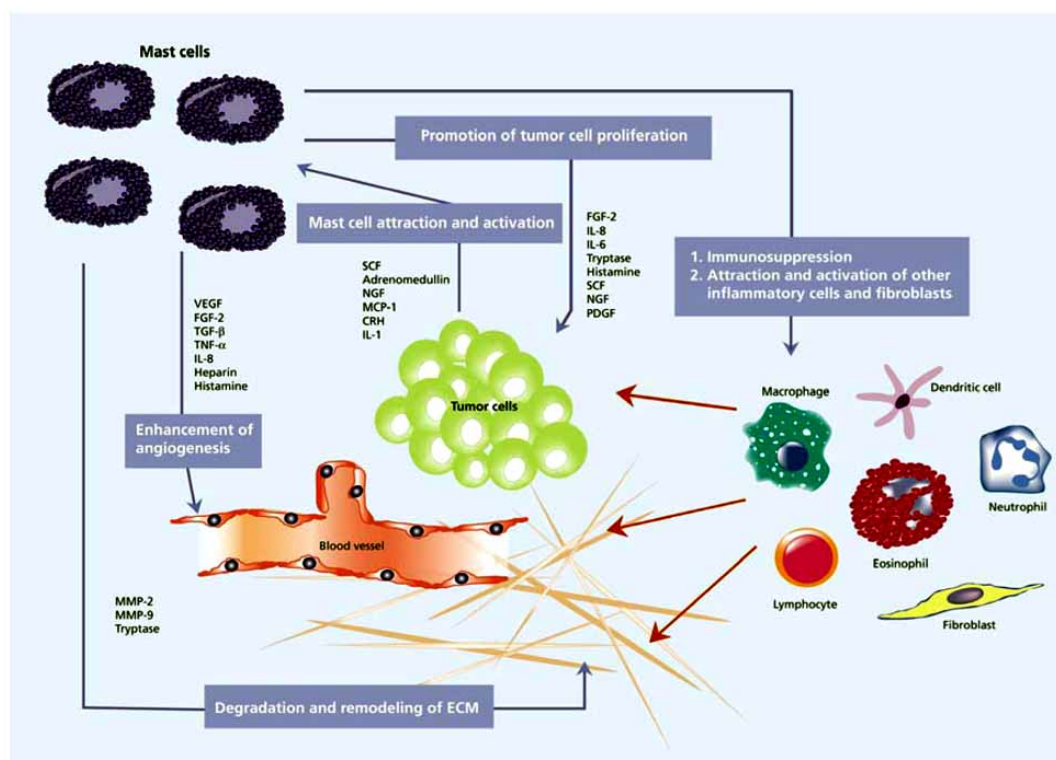


Fig. (1). Possible contribution of tumor-associated mast cells to tumor progression. During neoplastic progression, various cancer tissues release chemotactic factors which recruit mast cells to the tumor microenvironment. There, mast cells become activated to (selectively) secrete a plethora of mediators. This results in a pro-tumor microenvironment by the enhancement of angiogenesis, promotion of tumor cell proliferation, degradation and remodeling of the extracellular matrix (ECM), and immunosuppression. In addition, mast cells are possibly involved in the recruitment and activation of other inflammatory cells and fibroblasts, often found in tumor stroma. On their turn, these cells can further augment tumorigenesis by enhancing tumor cell proliferation, angiogenesis, and extracellular matrix remodeling.

tant. SCF is a powerful mast cell chemo-attractant and activator [69, 70]. Increased production of SCF is found in several human tumor cell lines [71]. When SCF-expression was boosted by transfection of tumor cells with SCF-encoding DNA, the number of infiltrating mast cells in the tumor increased and enhanced tumor vascularization compared to control tumors was observed. This was in contrast to tumor cells transfected with non-coding DNA, where tumors showed lower mast cell numbers, decreased vascular density, and diminished tumor growth [72]. Recently, Huang *et al.* also demonstrated SCF expression in human and murine tumor cell lines and corresponding tumor tissues. The authors showed the potential of SCF to recruit mast cells to (low SCF concentration), and activate mast cells (high SCF concentration) within tumor tissue [68]. These tumor-infiltrating mast cells were found to produce many inflammatory factors, to increase IL-17 expression in tumor cells, and to regulate immunosuppression. This suggests that mast cells do not only participate in remodeling the tumor microenvironment, but also critically regulate inflammation and immunosuppression.

The expression of adrenomedullin can be upregulated by hypoxia [73, 74]. This peptide is abundantly produced in a variety of cancers [75]. Adrenomedullin is chemotactic for human mast cells and it can induce histamine and β -

hexosaminidase release by mast cells, and stimulate expression of VEGF, MCP-1, and FGF-2 [76]. This might indicate that hypoxia serves as an initial signal leading to mast cell recruitment. Besides SCF and adrenomedullin, other mast cell chemoattractants like NGF, RANTES, MCP-1, VEGF, bFGF, PDGF and activators, including NGF, IL-1, and CRH have been identified [12, 77]. Putatively, these factors are involved in mast cell recruitment and/or activation in cancer as well. For MCP-1 this is suggested by the study of Soucek *et al.*, in which Myc activation resulted in a high and rapid induction of MCP-1 expression [53].

So far we have discussed mediators that promote tumorigenesis and tumor growth. Nevertheless, mast cells also have the ability to synthesize and release mediators which can be harmful to the tumor. A tumor suppressive action has been described for TGF- β [78], IL-10 [79], and IL-4 [80], whereas a direct cytotoxic effect has been shown for TNF- α [81]. As summarized by Galinsky *et al.*, mast cell heparin can also reduce tumor growth [46]. Other mast cell mediators that have been described to inhibit cancer are IL-1, IL-6, IFN- α , and arachidonic acid products [49]. These findings underline the seemingly opposite roles of mast cells in cancer. They are further supported by clinical observations that show a positive correlation between mast cell number and prognosis in several tumor types, especially in breast cancer [82-84],

colorectal cancer [85, 86], and non-small cell lung cancer (NSCLC) [87, 88]. Theoharides *et al.* proposed that this dual role of mast cells can be explained by the selective release of mediators, regulated by distinct signals [49]. Thus, depending on specific microenvironmental conditions, mast cells might be exposed to signals that either promote or inhibit tumorigenesis. In turn, the tumor microenvironment possibly influences the ultimate response by different mediators, since some mediators can exert both pro- and anti-tumor effects (Fig. 1).

Modulating mast cell recruitment, viability, activity, or mediator releasing patterns at malignant sites can be of importance to control tumor growth. In the following paragraphs, we will discuss important pathways that are active in mast cells that could be targets for pharmaceutical intervention.

3. MAST CELLS AS POSSIBLE TARGET FOR CANCER THERAPY

The signaling pathways that regulate mast cell degranulation have been studied extensively, especially in allergy research. As discussed above, mast cells generate and release several kinds of mediators. In the next sections, we will discuss some approaches to inhibit activation and proliferation of mast cells or to neutralize its released mediators.

3.1. Mast Cell Stabilizers

Mast cell activation has two distinct phases, the first consisting of release of preformed mediators occurring within minutes and the second consisting of release of newly synthesized molecules at 3-12 hours later. Cromolyn, the archetypic mast cell stabilizer, appears to be effective against both reactions. Currently there are over 20 compounds identified that inhibit mast cell activation, but may also have additional features. Olopatadine demonstrates mast cell stabilizing activity, but also acts as an anti-histaminic [89]. Ketotifen is a mast cell stabilizer used to treat asthma which can also help to prevent fibrosis [90]. Iodoxamide tromethamine is a mast cell stabilizer that inhibits *in vivo* type I immediate hypersensitivity reactions and inflammation [89].

Treatment of breast carcinoma with cimetidine, a H₂ receptor antagonist, showed that it may influence histamine activity or mast cell activation [91]. JNJ 7777120 is a new H₄ receptor antagonist and the H₄ receptor has been identified on human mast cells. H₄ receptor activation induces calcium mobilization in mast cells but does not affect IgE crosslinking-induced degranulation [92]. Drugs as azelastine and episastine have been examined to inhibit IgE-mediated phosphorylation of FcεRIγ protein [93]. Many other compounds such as syk kinase inhibitors [94, 95], MAP kinase inhibitors, ion channel antagonists [96, 97] and sphingosine kinase inhibitors [98] could be used to block mast cell activation, but in most cases also activation of other cells may be influenced.

3.2. Protease Inhibitors

Tryptase is considered to be a pro-inflammatory mediator and increased tryptase levels reflect ongoing mast degranulation. Increased concentrations of tryptase in biological fluids can be found in several disorders, including systemic ana-

phylaxis, and other hypersensitivity and autoimmune disorders [99, 100]. In addition, as discussed above, mast cells act at sites of new vessel formation in part by secreting tryptase which then functions as a potent angiogenic factor [101, 102]. Mast cell tryptase can be targeted by various tryptase inhibitors and notable compounds include guanidino dipeptide, guanidino dimers, delta inhibitors, benzamidine dimers etc, most of them have a preclinical application [100].

3.3. IgE and Anti-IgE in the Treatment of Cancer

Treatment with anti-IgE (Omaluzimab; XolairTM) reduces the free IgE concentrations in the circulation. Interaction of IgE with its high affinity receptor FcεRI without the need of receptor crosslinking by antigen has been shown to increase the survival of mast cells. Therefore, in theory, anti-IgE treatment may reduce the number of mast cells in inflammatory conditions. However, it was shown in a recent study that treatment of patients with anti-IgE (XolairTM) reduces the number of basophils in the circulation, but not mast cells in the skin [103]. This lack of effect may be due to the long half life of skin mast cells. Thus far, anti-IgE treatment has not been applied in cancer patients.

On the other hand, specific IgE could be used to specifically target tumor cells and to activate tumoricidal effector cells such as eosinophils, mast cells and macrophages (for review see [104]).

3.4. Stem Cell Factor (SCF) and c-Kit Mediated Signaling Pathway

Mast cell degranulation can be influenced by stem cell factor (SCF) and its cognate receptor c-Kit. Therefore, pharmaceuticals interfering with SCF/kit or their downstream signals may alter mediator release (patterns) by mast cells.

3.4.1. SCF

SCF, also known as c-Kit ligand, is a glycoprotein which is the major survival and developmental factor for mast cells as described above. SCF can be expressed in two active isoforms [105]. One isoform is a 248 amino acids long protein, known as sSCF248. It is membrane bound in the full length form, but it contains a specific proteolytic cleavage site at Ala165 (Val-Ala-Ala-Ser, aa 163-166), which generates a soluble form of 164 amino acids length. The second isoform is 220 amino acids long and is membrane-bound (mSCF220). mSCF220 lacks the proteolytic cleavage site and remains a transmembrane protein that consists of a 157 amino acid extracellular domain, a 27 amino acid transmembrane domain and a 36 amino acid cytoplasmic tail (reviewed in [106]). The ratios of the two isoforms vary considerably in different cells and tissues. *In vitro* experiments provide evidence for differential functions of mSCF and sSCF. For example, the phenotype of Sl/Sl mice which produce only sSCF due to a deletion of the transmembrane and cytoplasmic domain, provides strong evidence for an essential role of mSCF and a less important role of sSCF, as these mice are mast-cell deficient due to lack of the correct microenvironmental signals for mast cell development [107].

SCF is vital for mast cell survival, degranulation and release of inflammatory-cytokines. The presence of SCF

amplifies the antigen-stimulation signal leading to pro-inflammatory/pro-angiogenic mediator release from mast cells. This is the result of the interaction of SCF with c-Kit to activate calcium mobilization, which is an important step in the degranulation. SCF, by itself, can also stimulate mast cell degranulation irrespective of antigen stimulation [108].

At the molecular level, SCF is generated in a variety of cell types in response to diverse intracellular signals. For example, IL-18 enhances SCF-production in B16 murine melanoma cells through pathways involving ROI and activation of p38 MAP kinase [109]. SCF production is also increased by IL-1 β , TNF- α or phorbol 12-myristate 13-acetate (PMA) in vascular endothelial cells [110] and lung fibroblasts [111].

As discussed above, SCF is expressed by several human and murine tumor cell lines and corresponding tumor tissues [68], indicating that tumor cells may stimulate mast cell degranulation and that SCF inhibition in tumors may be beneficial. In a clinical setting, SCF is primarily known for its ability to stimulate unwanted histamine production in allergic reactions. The treatment is generally aimed at inhibiting these symptoms and usually consists of prophylactic antihistamines, an H2-receptor antagonist and β -adrenoreceptor stimulant inhaler [112]. Glucocorticoids interfere with the SCF pathway, as the drugs can downregulate SCF production as demonstrated in lung fibroblasts, thereby reducing levels of the protein [111]. Alternatively, SCF could be targeted directly. There are two methods to control the level of SCF in a direct manner. One is the use of neutralizing antibodies to reduce the availability of SCF and bring the concentration to human physiological levels, which averages 3.3 ng/mL [113]. This approach has been claimed as a therapeutic strategy to treat asthma and acute myeloid leukemia [114]. The second approach is the use of antisense oligonucleotides to down-regulate SCF expression [112, 115].

3.4.2. c-Kit

C-Kit is the receptor for SCF and is a member of the tyrosine kinase growth factor receptor family which is expressed on a variety of hematopoietic cells, including mast cells [116]. SCF-dependent activation of c-Kit leads to activation of a number of downstream signaling pathways (Fig. 2). These downstream pathways are critical for mast cell function and mast cell number. Blocking c-Kit or downstream pathways have been investigated as strategies for blocking c-Kit-mediated responses.

C-Kit has a large extracellular domain with five immunoglobulin-like domains, a single transmembrane span, and a long cytoplasmic tail containing a kinase domain which is split into two domains by an insertion region [106]. In addition, the intracellular domain has multiple tyrosine residues which are targets for phosphorylation. SCF binds with high affinity to c-Kit which induces dimerization of c-Kit and the initiation of its tyrosine kinase activity. This leads to phosphorylation of 9 tyrosines in the cytoplasmic tail [108]. Associating Src kinases such as Lyn and Fyn may also contribute to the phosphorylation [117]. The importance of c-Kit in mast cell function is exemplified by mutations that alter the functionality of c-Kit. For example, when c-Kit is inappropriately activated such as by the substitution of valine for

aspartic acid 816 (D816V) in the kinase domain, mastocytosis can occur [116].

Dimerization of c-Kit by SCF and subsequent autophosphorylation of tyrosines in the cytoplasmic domain of c-Kit initiates the activation of different critical signaling molecules. The phosphorylated tyrosines within the cytoplasmic tail of c-Kit serve as docking sites for Src homology 2 (SH2) domains of associating signaling proteins, including: 1) cytoplasmic adaptor molecules such as Grb2 and SHC; 2) Src kinases such as Lyn and Fyn; 3) signaling enzymes such as phospho-inositide 3-kinase (PI3K), and phospholipase C γ (PLC γ). The activation of PI3K, in addition to the activation of the Ras/Raf/MAPK and the JAKs/STATs pathway, leads to the activation of a variety of transcriptional/survival factors (reviewed in [106, 118-122]). These latter signals are important, amongst others, for cytokine production, mast cell migration and survival (Fig. 2). A recent study showed the importance of functional c-Kit for the development of neurofibroma in neurofibromatosis type 1-deficient mice. Moreover, pharmacologic inhibition of c-Kit activity with imatinib mesylate therapy resulted in a dramatic reduction in the tumor volume in a patient with plexiform neurofibroma [123].

3.4.3. Inhibition

Various tyrosine kinase inhibitors block c-Kit activity [120]. The most widely recognized compound blocking c-Kit catalytic activity is imatinib mesylate (also known as STI 571/Gleevec/Glivec). Imatinib mesylate blocks c-Kit signaling within mast cells and mastocytoma cells, preventing cell proliferation and survival [124]. Besides, imatinib also inhibits Bcr-Abl and PDGF receptor tyrosine kinases, and is currently used for the treatment of patients with chronic myeloid leukemia (CML) [125], and gastrointestinal stromal tumors (GISTs) [126]. Nilotinib (AMN107) is an orally available signal transduction inhibitor of c-Kit, Bcr-Abl, and PDGF receptor (PDGFR) tyrosine kinases. Nilotinib inhibits both wild-type Kit and Kit carrying mutations, except of the D816V mutation and could therefore inhibit activation and proliferation of mast cells [127]. PI3K appears to be major signaling protein in tumors and is immediately downstream of c-Kit in a signaling pathway also known as the "survival" kinase pathway [128, 129]. Downstream of c-Kit are signaling pathways involving PI3K and other important kinases called AKT and mTOR. Currently, there are drugs in clinical trials that inhibit the PI3K downstream pathway. However, blocking PI3K may induce side effects such as inhibition of insulin function and heart-failure [130, 131].

A number of other compounds that are primarily considered to be multiselective tyrosine kinase inhibitors could be used to inhibit mast cell proliferation and activation *via* c-Kit or other targets in the activation pathway:

1. Dasatinib is an orally bioavailable, synthetic small molecule-inhibitor of multiple tyrosine kinases, such as c-Kit, including the D816V mutated c-Kit, ABL, SRC, and PDGFR [132]. Dasatinib blocks proliferation of neoplastic mast cells *via* c-Kit [133]. IgE-mediated activation of basophils [134] is inhibited by dasatinib and a similar inhibitory effect on mast cells is expected.

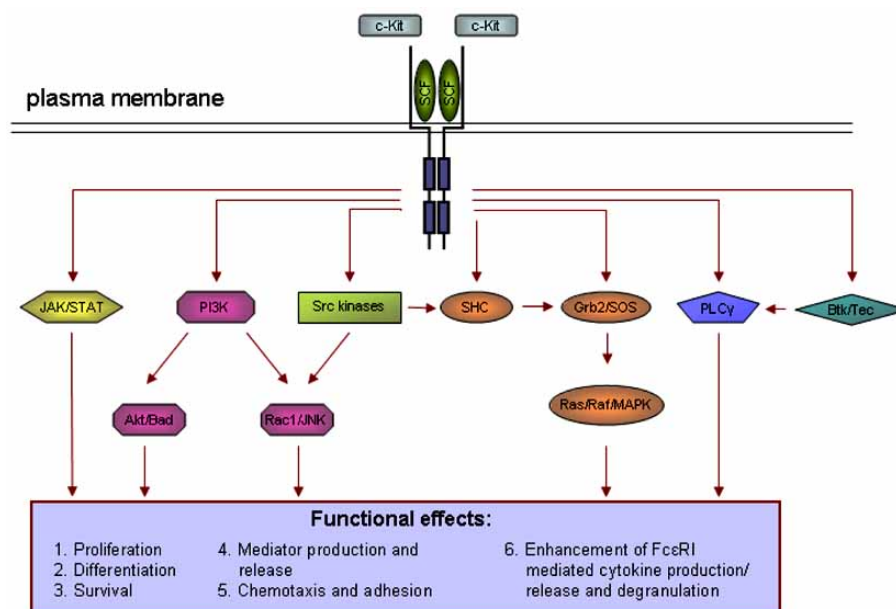


Fig. (2). Schematic representation of major signaling cascades activated in mast cells after SCF binding to the c-Kit receptor. Binding of SCF rapidly induces receptor dimerization and subsequent autophosphorylation of tyrosine residues within its cytoplasmic tail. This leads to the activation of several signal transduction pathways, including the JAK/STAT pathway, PI3K, Src kinases, the Ras-Raf-MAP kinase cascade, and PLCγ. Activation of these pathways results in multiple functional effects, like increased cell proliferation, differentiation and survival. For detailed information about these signaling cascades, see [106, 118, 119, 121, 122].

2. Midostaurin is a synthetic multikinase inhibitor with potential anti-angiogenic and antineoplastic activities. Midostaurin inhibits c-Kit, VEGFR2, PDGFR, and FMS-like tyrosine kinase 3 (FLT3), which may cause disruption of the cell cycle, inhibition of mast cell proliferation, and inhibition of angiogenesis [135, 136].
3. Hypothemycin is a resorrcyclic acid lactone antibiotic that was identified as active in a screen for inhibitors of T cell activation [137]. Hypothemycin is able to inhibit the phosphorylation of the classical MAP kinases ERK1/2. Hypothemycin also inhibits mast cell activation at the level of Btk and subsequent PLCγ1 activation and calcium mobilization [138, 139].
4. MLN518 is a substance being studied in the treatment of some types of cancer. It is a type of tyrosine kinase inhibitor also called tadutinib. MLN518 inhibits cell proliferation by inhibiting different classes of c-Kit mutants by specific targeting the phosphorylation of signal transducers and activators of transcription factor 3 (STAT3) [140].
5. PD180970 inhibits mast cell growth by blocking the Bcr-Abl kinase mediated STAT 5 signaling pathway. This compound is a potential therapeutic agent for chronic myelogenous leukemia [141].
6. Sunitinib is a multikinase inhibitor of VEGFR, PFGFR and FLT3. It has also been reported to inhibit c-Kit containing mutations in systemic mastocytosis and imatinib-resistant Kit mutations [142].
7. Enzastaurin is a type of serine threonine kinase inhibitor of protein kinase β (PKC β) which can be regulated by

calcium-mobilization in mast cells. This kinase has been involved in regulation of mast cell activation and cytokine release [143, 144]. Enzastaurin may prevent cell growth and mast cell degranulation.

8. Semaxinib is an antitumor compound that inhibits c-Kit, VEGFR-2, and FLT3 [145]. Semaxinib inhibits the function of c-Kit by targeting Akt, ERK1/2 and STAT3 downstream signaling pathways and could therefore affect mast cell activation and growth [146].
9. Miscellaneous: Sorafenib is an oral tyrosine kinase inhibitor that inhibits the tyrosine kinase activity of Raf kinase (Raf-1, wild-type B-Raf, and B-Raf V600E), VEGFR, and PDGFR [147]. Pazopanib (GW786034) is another oral, multitargeted kinase inhibitor with specificity for c-Kit, VEGFR, and PDGFR. Both inhibitors are used as drugs in the treatment of renal cancer and are expected to also have inhibitory activity in mast cell activation [148].

4. CONCLUDING REMARKS

As discussed in this review, mast cells can either be beneficial or detrimental to tumor development, which may depend on the stage of tumor development during which mast cells infiltrate, the communication with other cell types, or on the tumor microenvironment. The tumor promoting effects of mast cells are mainly mediated by secretion of pro-angiogenic factors and by tissue remodeling, enhancement of tumor cell proliferation, and immunosuppression. However, many other inflammatory cells infiltrate into the tumor microenvironment. These cells, including tumor associated macrophages (TAMs), are also thought to have important

roles in tumorigenesis [44, 47, 149, 150]. Since mast cells are capable of affecting chemotaxis, proliferation, and activity of many of these cell types, they might be critical regulators within the tumor microenvironment of inflammation and consequently of tumor growth. Besides, we discussed many therapeutic strategies that are available to inhibit mast cell activation and chemotaxis, although most therapeutics will also affect other immune cells. Further research in preclinical tumor models is necessary to delineate the value of the mast cell as a therapeutic target cell in the treatment of cancer.

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