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Stem cell factor-dependent mast cell proliferation, maturation and activity can be regulated by inhibitory receptors

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Abstract

Mast cells play an important role in many physiological and pathological processes. That is why, the factors and the mechanisms regulating mast cell development, maturation, proliferation, and activity within tissues are of special importance. More and more data indicate that mast cells express inhibitory receptors. Furthermore, there are findings that inhibitory receptors can modulate IgE-dependent mast cell activity, thereby influencing the intensity of allergic processes. Bearing in mind that c-kit (CD117)-specific stem cell factor (SCF) not only affects mast cell activity but also strongly promotes mast cell development and proliferation, it is extremely interesting whether inhibitory receptors modulate SCF-mediated mast cell response. Nowadays, certain data suggest that some inhibitory receptors, such as FcγRIIB, CD72 molecule, paired immunoglobulin-like receptor B (PIR-B), CD300a molecule, and gp49B1 glycoprotein, can affect CD117-dependent mast cell activity and proliferation.

Key words: *mast cells, inhibitory receptors, mast cell development, stem cell factor.*

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Introduction

More and more data indicate that many different regulatory mechanisms are needed to direct and control immune responses. Nowadays, it seems that the most important in the control of immune processes is balance between immune activation and inhibition. Notably, counterbalance between positive and negative signals prevents from inappropriate activation of the immune system and participates in immune response termination. Some information suggests that the loss of inhibitory signals may result in autoreactivity and, in consequence, may lead to autoimmune diseases. The disturbance in interplay of activation and inhibition results in the immune system hyperactivity and development of unchecked inflammatory responses as well.

During the 1980s more and more data suggested that cellular proliferation, differentiation and activity are regulated through the use of different cell surface molecules and receptors. Moreover, it was hinted that cell biology is controlled *via* equilibration between activating signals and suppressive signals. In 1998, Lanier unambiguously documented that NK cell-mediated cytotoxicity and cytokine expression are regulated by opposing signals from receptors that activate and inhibit effector functions [1]. Furthermore, Lanier suggested that NK cell inhibitory receptors are members of a larger set of molecules and formulated the term "inhibitory receptor superfamily" [2]. Nowadays, it is unquestionable that different inhibitory receptors play crucial role in the regulation of cellular biology. Whilst most of the data on inhibitory receptors have emerged from studies on NK cell function, B and T cell receptor signaling, it is well documented that these receptors influence the activity of macrophages, dendritic cells, neutrophils and eosinophils as well [3, 4].

A members of inhibitory receptor superfamily can be determined by a consensus amino acid sequence, named the immunoreceptor tyrosine-based inhibitory motif (ITIM), located in the intracytoplasmic domain of these molecules. The ITIM motif was originally identified in the cytoplasmic domain of FcγRIIB receptor, within the 13-amino acid sequence AENTITYSLLKHP. The classic ITIM sequence is composed of 6 amino acids (I/V/LxYxxL/V), where × represents any amino acid. Inhibitory receptors can express either one or several ITIM domains [3-5]. Engage-

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ment of inhibitory receptors with their ligands resulted in ITIM motif phosphorylation usually by Src-family kinases. It provides a docking site for the recruitment of cytoplasmic phosphatases having a Src homology 2 (SH2) domain such as SH2-containing phosphatase-1 (SHP-1) and/or SH2-containing phosphatase-2 (SHP-2) and/or SH2 domain-bearing inositol 5-phosphatase-1 (SHIP-1). These enzymes most likely dephosphorylate tyrosine residues that provides docking sites for signaling kinases connected with activating receptor pathways [3-5]. It seems that in order to achieve the inhibitory effect ITIM-bearing molecules must co-aggregate with activating receptors, however, in certain situations such co-ligation of two receptors is not required [4-6].

There are two different groups of inhibitory receptors, i.e. immunoglobulin-like superfamily receptors and C-type lectin inhibitory receptors. The immunoglobulin-like inhibitory receptors are characterized by the presence of one or more immunoglobulin-like domains in extracellular portion. The C-type lectin inhibitory receptors are calcium-dependent carbohydrate-binding proteins. These calcium-dependent molecules bind carbohydrates through a specific domain named CDR (carbohydrate-recognition domain) [3, 4].

Mast cell characteristics

Mast cells are multifunctional long-lived secretory cells widely distributed throughout the vascularized tissues and serosal cavities. These cells have the potential to secrete a wide spectrum of biologically active mediators, cytokines, and chemokines [7, 8]. Mast cell mediators can be divided into preformed, granule-associated substances and *de novo* synthesized compounds. Preformed mediators are stored in secretory granules and on activation they are released into the tissues within minutes. Granule-associated mediators include histamine, neutral proteases, metalloproteinases (MMPs), proteoglycans, as well as some preformed cytokines, such as interleukin (IL)-3, IL-4, IL-6, IL-10, tumor necrosis factor (TNF) and chemokine CXCL8. Newly generated mediators comprise arachidonic acid metabolites, such as leukotrienes (LTs), prostaglandins (PGs), platelet activating factor (PAF), and *de novo* synthesized cytokines, including various ILs, TNF, interferons (IFNs), a lot of growth factors, such as stem cell factor (SCF), nerve growth factor (NGF) and granulocyte-macrophage colony stimulating factor (GM-CSF), as well as different chemokines. Moreover, there are some data that mast cells can synthesize corticotrophin-releasing factor (CRH) and its structurally related urocortin [9], endothelin-1 (ET-1) [10], amphiregulin [11], as well as granzyme B [12]. Mast cells are the source of some antimicrobial peptides such as human cathelicidin LL-37 or murine cathelicidin-related CRAMP and β-defensin-4 as well [13].

It should be underlined that mast cell mediators can exert diverse effects. Some mediators, cytokines and chemokines promote the development of inflammation, while some of the mast cell products exhibit anti-inflammatory and/or immunosuppressive properties. Mast cell mediators strongly influence the development, maturation, migration, survival, and function of immune cells. What is more, several mast cell products affect B lymphocyte development and function, and some mast cell derived cytokines/chemokines influence the polarization of T cell subsets. Certain mediators have angiogenic properties or take part in the turnover of extracellular matrix (ECM) proteins and in remodeling of structural elements of tissues [7, 14-16].

Mast cells express numerous different surface receptors, and thereby a lot of various factors can activate these cells to mediator release. Mast cells constitutively express the high affinity receptor for IgE (FcεRI) [17] as well as other receptors for Fc portion of immunoglobulins [18]. Indisputably, mast cells have different receptors specific for cytokines and chemokines [19], for several neuropeptides and hormones, and for certain complement system activation products [20]. What is more, mast cells have also been found to express H1, H2, and H4 histamine receptors [21, 22], cysteinyl (cys)LT1 and cysLT2 receptors [23], and protease activated receptor 2 (PAR2) [24] as well. It is well documented that these cells have Toll-like receptors (TLRs) [25], molecules specific for pathogen associated molecular patterns (PAMPs).

Considering that mast cells have the potential to secrete diverse biologically active substances in response to activation with a variety of stimuli, it seems obvious that these cells play an important role in many physiological and pathological processes. Undoubtedly, mast cells exert a vital role in maintaining homeostasis by participating in tissue remodeling and repair, stimulation of angiogenesis, and by vascular permeability regulation [7, 14, 15, 26]. These cells take part in innate and acquired immunity [27, 28]. Mast cells are also known to participate in the inflammatory processes [15, 26, 29]. What is more, these cells play a role in host defense against bacteria and viruses, and are important sentinels of the immune system in defense against parasites [30-32]. Mast cells are also implicated in diverse pathophysiological processes, such as allergic diseases, various autoimmune diseases, and other chronic inflammatory diseases [14, 29, 33, 34].

Mast cells are derived from CD13+CD34+CD117+ multipotent hematopoietic stem cells in bone marrow. Mast cell progenitors exit the bone marrow, enter into the blood and circulate in small numbers as mononuclear agranular cells. Subsequently, developing mast cells migrate to peripheral tissues where they terminate their maturation and differentiation under the influence of local micromilieu. It should be underlined that although mature mast cells are highly differentiated, they retain an extensive proliferation potential [35, 36]. Maturation and differentiation of mast cells are regulated by various humoral factors. It is well doc-

umented that mast cell proliferation is promoted by some cytokines, including IL-3, IL-4, IL-9, IL-10, and IL-13. Maturation of these cells is also affected, either positively or negatively, by IL-5, IL-6, IL-12, TNF, NGF, transforming growth factor (TGF)-β, and IFN-γ [37]. Some data indicate that mast cell development is also influenced by PGE_2 [38]. However, the most important factor for mast cell proliferation and maturation is SCF. This cytokine is constitutively produced by fibroblasts, keratinocytes, epithelial cells, endothelial cells, and marrow stromal cells and acts *via* the tyrosine kinase receptor c-kit (CD117) [39]. It should be stressed that CD117 is expressed on mast cells at all stages of their differentiation.

It is well documented that activity, migration, and survival of mature mast cells within tissues are regulated by different humoral factors, including many cytokines [40-42]. Certainly among cytokines, SCF plays an important role in modulating tissue mast cell biology. It is well established that SCF promotes mast cell survival by suppressing apoptosis [43] and induces mast cell adhesion to connective tissue matrix [44]. This cytokine is also a potent mast cell chemoattractant [45] thereby influencing mast cell number within tissues. Some data prove that SCF can directly stimulate mast cells to degranulation and histamine release [46] as well as to synthesis and release of IL-6 [47]. What is more, the exposure of mast cells to SCF results in up-regulation of CCL2 mRNA expression, *de novo* expression of CCL3 mRNA, and release of CCL2 [48]. It was also noticed that the administration of SCF intradermally *in vivo*, at doses as low as 149 fM/site, induces activation of cutaneous mast cells and evokes mast cell-dependent acute inflammatory response [49]. It is also demonstrated that SCF can influence IgE-dependent mast cell activity. A brief preincubation of mast cells with SCF, at concentrations 10-100-fold lower than that required to promote cell proliferation, enhances histamine release as well as LTC_4 and PGD_2 synthesis by mast cells in response to IgE-dependent stimulation [46, 50]. This cytokine in synergy with antigen causes significant increase of mast cell degranulation and cytokine production [51]. On the contrary, prolonged exposure of mast cells to SCF resulted in marked attenuation of FcεRI-mediated degranulation as well as IL-6, TNF, IL-13 and CCL2 production [52]. In mice, chronic treatment with SCF causes diminution of the severity of IgE-dependent anaphylactic reactions [53]. These data suggest that SCF can play an important role in mast cells effector function regulation, especially in allergic processes.

Mast cell inhibitory receptors

Over the past several years, it has become clear that mast cells express a number of surface inhibitory receptors that can influence mast cell development and activity within tissues [54-56]. Among immunoglobulin-like superfamily of inhibitory receptors mast cells express FcγRIIB, paired immunoglobulin-like receptor B (PIR-B), molecule CD300a, glycoprotein gp49B1, molecule CD200R, molecule CD305, molecule CD172a, platelet endothelial cell adhesion molecule (PECAM-1), molecule allergin-1, and members of the sialic acid-binding immunoglobulin-like lectin family (Siglecs). Out of C-type lectin inhibitory receptors mast cells express mast cell function-associated antigen (MAFA) and molecule CD72. Basic information about mast cell inhibitory receptors is summarized in Table 1.

There are data that certain inhibitory receptors can modulate IgE-dependent mast cell activity thereby influencing the intensity of allergic processes. It was demonstrated that co-aggregation of FcγRIIB, CD300a, gp49B1, PIR-B or CD172a with FcεRI significantly reduces IgE-dependent mast cell activation [56, 57]. It was also stated that activation of inhibitory receptors, such as FcγRIIB, gp49B1, PECAM-1 or CD300a, *via* their specific ligand resulted in the decrease of mast cell anaphylactic response [57]. Moreover, there is extremely intriguing information that gp49B1 in cooperation with its natural ligand, that is integrin αvβ3, can play an essential role in the suppression of allergic response [58]. It was also suggested that cooperation between PIR-B and its natural ligand, i.e. MHC class I molecule, constitutively delivers negative signaling into mast cells and regulates cellular activation induced by IgE [59]. Bearing in mind the crucial role of SCF not only in the promotion and regulation of mast cell development, but also in the modulation of mature mast cell activity within tissues, especially in allergic processes, it is extremely interesting whether inhibitory receptors can influence SCF-mediated mast cell response.

Regulation of SCF-mediated mast cell proliferation and maturation *via* inhibitory receptors

As far as immunoglobulin-like inhibitory receptors are concerned, the best investigated and described is FcγRIIB. This receptor belongs to a large family of molecules characterized by their ability to bind IgG constant (Fc) region, however the affinity of FcγRIIB for IgG is low. Almost all cell populations involved in immunological processes, including B lymphocytes, T lymphocytes, macrophages, monocytes, neutrophils, dendritic cells, platelets, natural killer cells, and basophils, express this receptor. Expression of FcγRIIB molecule is well documented also on mast cells, but mainly on cultured cell lines such as rat cell line RBL-2H3, murine mast cells derived from bone marrow (BMMCs), mast cells cultured from umbilical cord blood (CBMCs), and HMC-1 cells [56]. Currently, more and more data indicate that FcγRIIB can modulate mast cell activity in anaphylactic reactions. It has been proven in *in vitro* experiments that co-aggregation of FcγRIIB with FcεRI resulted in significant inhibition of IgE-mediated mast cell degranulation and preformed mediator release as well as *de novo* cytokine synthesis. The influence of FcγRIIB on

Table 1. Mast cell inhibitory receptors [55, 56]

Receptor	Physiological ligand	Receptor structure	Expression
		Immunoglobulin-like receptors	
FcγRIIB	IgG	2 Ig-like domains 1 ITIM motif	BMMCs, CBMCs, HMC-1, RBL-2H3
PIR-B	MHC I	6 Ig-like domains 4 ITIM motifs	BMMCs, progenitor fetal spleen-derived MCs
CD300	phosphatidylserine	1 Ig-like domain 4 ITIM motifs	BMMCs, CBMCs, HMC-1, human lung MCs
gp49B1	integrin αvβ3	2 Ig-like domains 2 ITIM motifs	BMMCs, RBL-2H3, murine peritoneal MCs
CD200R	CD200	2 Ig-like domains lack of ITIM motif	BMMCs, CBMCs, human and murine cutaneous MCs
Siglecs	various	variable number of Ig-like domains and ITIM motifs	CBMCs, HMC-1, LAD, PBMCs, RBL-2H3
CD305	collagen type XVII	1 Ig-like domain 2 ITIM motifs	HMC-1
CD172a	CD47	3 Ig-like domains 4 ITIM motifs	CBMCs, HMC-1, human lung, gastrointestinal tract and cutaneous MCs, BMMCs isolated from patients with systemic mastocytosis
allergin-1	unknown	1 or 2 Ig-like domains 1 ITIM motif	BMMCs, RBL-2H3
PECAM-1	integrin αvβ3	6 Ig-like domains 2 ITIM motifs	BMMCs, RBL-2H3, murine peritoneal MCs
		C-type lectin receptors	
MAFA	unknown	1 ITIM motif	RBL-2H3
CD72	CD100	1 ITIM motif	HMC-1, LAD, PBMCs

FcεRI-dependent mast cell activation was thoroughly documented *in vivo* as well [57].

The effect of FcγRIIB on SCF-dependent mast cell proliferation and differentiation was studied by Malbec *et al.* [60, 61]. It should be stressed that the experiments were performed on mast cells differentiated *in vitro* from murine bone marrow, i.e. BMMCs, which represent a key type of primary immature cells. It should be also remarked that to the study mast cell proliferation thymidine incorporation assay was used. The authors stated that BMMCs generated from FcγRIIB-deficient mice and BMMCs obtained from wild-type mice, when incubated for 24 h with SCF, incorporated comparable amount of thymidine. However, co-aggregation of CD117 with FcγRIIB, *via* anty-kit specific IgG antibodies which bind simultaneously to CD117 by their Fab portion and to FcγRIIB by their Fc portion, in BMMCs from wild-type mice resulted in inhibition of *c-kit*-mediated BMMC proliferation, as assessed by thymidine incorporation assay. The inhibition of mast cell proliferation correlates with a blockade of the G1-S transition, during the cell cycle. It was also documented that co-aggregation of CD117 with FcγRIIB resulted in tyrosyl-phosporylation of FcγRIIB, which selectively recruited phosphatase SHIP. These observations strongly indicated that FcγRIIB is a functional molecule which prevents excessive mast cell proliferative response and negatively regulates CD117-induced proliferation.

The multiplication of cells, their survival and death are governed by complex mechanisms of cell cycle control. Without any doubt the most important regulators of the cell division cycle are cyclins. These proteins regulate the cell cycle by binding and activating cyclin-dependent kinases (Cdks). Phosphorylation of specific proteins by cyclin-Cdk complexes activates different processes that conduct the cell cycle in a timely manner [62]. It was demonstrated that CD117 aggregation in BMMCs caused significant increase in intracellular levels of cyclins D2, D3, and A, while co-ligation of CD117 with FcγRIIB resulted in no change of cyclin levels. Inhibition of cyclin levels following co-aggregation of *c-kit* with FcγRIIB correlated with suppression of mast cell proliferation [63].

Aside from FcγRIIB mast cell growth and proliferation can be modulated *via* CD72 molecule, C-type inhibitory receptor. This molecule is predominantly expressed on

B-lineage cells and can affect some activities of B cells [64]. CD72 is also expressed on T cells, NK cells, dendritic cells, and macrophages [64, 65]. This molecule was found to be expressed on peripheral blood-derived mast cells (PBMCs), and mast cell lines HMC and LAD, as well. It has been indicated that co-aggregation of CD72 molecule with FcεRI does not affect IgE-mediated mast cell degranulation and preformed mediator release [66]. On the contrary, there are convincing data that this inhibitory receptor can strongly influence mast cell growth and proliferation. Kataoka *et al.* [66] documented that concurrent action of CD117 ligand, i.e. SCF, and CD72 ligand, i.e. CD100 protein or CD72 agonistic antibodies (BU40), resulted in a marked reduction in the ratio of mast cells in the G2/M + S phases of cell cycle, indicating cell growth arrest. Moreover, CD100 protein as well as CD72 agonistic antibodies significantly diminished the proliferation of human mast cells (PBMC, HMC and LAD) as determined by bromodeoxyuridine (thymidine analogue) incorporation into DNA. What is more, mast cells treated with SCF in the presence of BU40 antibodies or CD100 protein showed a substantial increase in tyrosine phosphorylation of CD72, which was linked to a marked enhancement of the SHP-1 association with CD72. These events correlated with SFKs and ERK1/2 but not PI3K/AKT and Stat3 dephosphorylation, the crucial signaling molecules which participate in the CD117-dependent pathway.

It seems to be of great importance to understand the mechanisms underlying mast cell migration into and within tissues. There are many factors that regulate migration of mast cell progenitors from the blood into tissues and the migration of mature mast cells within tissues leading to the rapid local accumulation that occurs in diverse pathological conditions [42]. It is well documented that SCF is one of the most important mast cell chemoattractant [45]. Thus, it is extremely interesting that the ligation of CD72 significantly reduced SCF-mediated mast cell chemotaxis [66].

There are data indicating that FcεRI-dependent mast cell activation is strongly modulated by PIR-B molecule [57]. Sparse data suggest that mast cell proliferation can be also affected by this inhibitory receptor. Chen *et al.* [67] stated that coordinated ligation of PIR-B and c-kit led to suppression of SCF-induced proliferative response of mast cells.

Molecule CD300a is expressed on NK cells, T cell subsets, granulocytes, monocytes, and dendritic cells [55, 56]. The expression of this molecule is well documented on BMMCs, CBMCs, and HMC, as well [56]. It is established that CD300a modulates mast cell activity in anaphylactic reaction [57]. Bachelet *et al.* [68] indicated that CD300a can also affect mast cell maturation and survival. Bispecific antibodies linking CD117 with CD300a significantly inhibited CBMC transition into fully mature mast cells by 50%, as evaluated by flow cytometry analysis of tryptase. Additionally, when cultured with Kit-CD300a bispecific antibodies, in the presence of SCF, human mature mast cell survival dramatically decreased.

Inhibitory receptors can affect SCF-mediated mast cell activation

Taking into account that SCF can directly stimulate mast cells to mediator and cytokine/chemokine release it seems to be important whether inhibitory receptors affect CD117-dependent activation. Currently, there are some data that SCF-mediated mast cell stimulation is controlled by gp49B1 glycoprotein, CD300a, and CD72 molecules.

Feldweg *et al.* [69] thoroughly documented the role of gp49B1 in regulation of SCF-dependent mast cell activity. They noticed that intradermal injection of SCF induced tissue swelling in *gp49B*$^{+/+}$ mice. In contrast, tissue swelling challenged with injection of SCF in *gp49B*$^{-/-}$ mice was significantly greater than that in *gp49B*$^{+/+}$ mice. Moreover, tissue swelling remained meaningly greater in *gp49B*$^{-/-}$ mice for 8 hours after injection and returned to baseline by 24 hours. In the tissues of *gp49B*$^{-/-}$ mice 1 hour after SCF injection edema was substantially greater, compared with the edema in *gp49B*$^{+/+}$ mice, as evaluated by histological analysis. In addition, one hour after SCF injection *gp49B*$^{-/-}$ mice had threefold more degranulating mast cells than *gp49B*$^{+/+}$ mice. Taken together, all these observations clearly indicated that *gp49B1*-deficient mast cells are more susceptible to SCF-induced activation *in situ*. The effects of receptor antagonists for mast cell granule-derived and lipid-derived mediators on SCF-induced tissue swelling were studied, as well. When *gp49B*$^{+/+}$ and *gp49B*$^{-/-}$ mice were pretreated with antagonists of the serotonin type 1, 2, and 7 receptors and antagonist of histamine type 1 receptors, SCF-induced tissue swelling was reduced up to 90% and 62%, respectively. Antagonist of the type 1 and 2 cysLT receptors reduced SCF-induced tissue swelling by 20% and 40% in *gp49B*$^{+/+}$ and *gp49B*$^{-/-}$ mice, respectively. When *gp49B*$^{-/-}$ mice were pretreated with all three inhibitors before SCF injection, tissue swelling was reduced by 95%. These findings indicate that *gp49B1* modulates the release of mast cell mediators in response to SCF stimulation *in vivo*.

There are also data that SCF-dependent mast cell activity can be regulated by CD300a and CD72 molecules. Bachelet *et al.* [68] determined that CD300a with CD117 co-aggregation *via* bispecific antibodies resulted in inhibition of SCF-induced mast cell activation, as stated by the measurement of tryptase activity. In addition, SCF-induced calcium influx was inhibited by CD117-CD300a co-aggregation as well. Furthermore, CD300a-CD117 co-ligation abrogated SCF-mediated HMC-1 degranulation and β-hexozaminidase release. Upon c-kit linking, CD300a underwent rapid phosphorylation and recruited SHIP-1 but not SHP-1. Additionally, CD300a regulated CD117 signaling *in vivo*, as well. Treatment with CD117-CD300a bispecific antibodies simultaneously with administration of SCF completely abrogated skin mast cell degranulation and, in consequence, caused the decrease in SCF-induced cutaneous reaction intensity. Kataoka *et al.* [66] documented that concurrent CD117 activation

by SCF and CD72 by CD100 or anti-CD72 antibodies significantly inhibited mast cell CCL2 synthesis as well as degranulation and β-hexosaminidase release.

Concluding remarks

Mast cells play an important role in diverse physiological processes, take part in mechanisms of both innate and adaptive defense, and participate in the course of many pathological processes. That is why, the factors and the mechanisms regulating mast cell development, maturation, survival, and activity within tissues are of special importance. Since the discovery of inhibitory receptors, growing evidence indicates that these molecules strongly affect cellular biology. Inhibitory receptors can influence mast cell activity, as well. It is very intriguing that some inhibitory molecules, *via* interaction with their natural ligands, modulate physiological mast cell activity. Keeping in mind the essential role of mast cells in allergic processes, extremely important are observations that some inhibitory receptors affect IgE-induced mast cell response. SCF, acting *via* c-kit receptor, can directly stimulate mast cells to degranulation and preformed mediator release as well as to synthesis *de novo* different cytokines and chemokines. Furthermore, without any doubt SCF is one of the key growth factor regulating mast cell development, maturation, proliferation, and survival in the physiological conditions. However, it is well known that the interaction between SCF and mutated c-kit receptor may cause enhanced mast cell proliferation and, in consequence, may lead to mastocytosis [70]. Additionally, it should be emphasized that mastocytosis is partially a result of the presence of "overactive" c-kit receptor. For this reason the mechanisms responsible for negative regulation of c-kit signaling should be recognized. Moreover, the knowledge about the influence of inhibitory receptors on SCF-mediated mast cell proliferation could provide the basics for developing new therapeutic approaches to mast cell proliferative disorders [71].

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