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Mast Cell Biology at Molecular Level: a Comprehensive Review

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Abstract

Mast cells (MCs) are portions of the innate and adaptive immune system derived from bone marrow (BM) progenitors that are rich in cytoplasmic granules. MC maturation, phenotype, and function are determined by their microenvironment. MCs accumulate at inflammatory sites associated with atopy, wound healing, and malignancies. They interact with the external environment and are predominantly located in close proximity of blood vessels and sensory nerves. MCs are key initiators and modulators of allergic, anaphylactic, and other inflammatory reactions, by induction of vasodilation, promoting of vascular permeability, recruitment of inflammatory cells, facilitation of adaptive immune responses, and modulation of angiogenesis, and fibrosis. They express a wide range of receptors, e.g., for IgE (FcεRI), IgG (FcγR), stem cell factor (SCF) (KIT receptor or CD117), complement (including C5aR), and cytokines, that upon activation trigger various signaling pathways. The final consequence of such ligand receptor–based activation of MCs is the release of a broad array of mediators which are classified in three categories. While some mediators are preformed and remain stored in granules such as heparin, histamine, and enzymes mainly chymase and tryptase, others are de novo synthesized only after activation including LTB4, LTD4, PDG2, and PAF, and the cytokines IL-10, IL-8, IL-5, IL-3, IL-1, GM-CSF, TGF-β, VEGF, and TNF-α. Depending on the stimulus, MCs calibrate their pattern of mediator release, modulate the amplification of allergic inflammation, and are involved in the resolution of the immune responses. Here, we review recent findings and reports that help to understand the MC biology, pathology, and physiology of diseases with MC involvement.

Keywords FcεR1 · IgE · KIT receptor · Mast cell · Mediators · Stem cell factor

Abbreviations

BM	Bone marrow
CM	Cutaneous mastocytosis
DAMPs	Damage-associated molecular patterns
HCMCs	Human cultured mast cells
JAK	Janus kinase
LAT	Linker for activator of T cells
LT	Leukotriene
MC	Mast cell
MCp	Mast cell progenitor
NGF	Nerve growth factor
PAMPs	Pathogen-associated molecular patterns
PAR2	Protease-activated receptor2
PG	Prostaglandin
RER	Rough endoplasmic reticulum
SCF	Stem cell factor
SG	Secretory granules
SM	Systemic mastocytosis
SM-AHNMD	SM with associated clonal hematological non–mast cell lineage disease
Syk	Spleen tyrosine kinase
VEGF	Vascular endothelial growth factor

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Introduction

Paul Ehrlich was the first who used the term “Mastzellen” when he observed the granular cells in slides obtained from

connective tissues and stained with aniline dyes. The German word "Mast" (from the original Greek word μαστός = breast) mirrors the nourishing and "suckling" functions of MCs [1]. Using commercial dyes such as dahlia, toluidine blue (the stain of choice widely recommended for MC identification staining MC heparin), methylene blue (thiazine dye staining the anionic residues packed in the MC granules), and neutral red (azine dye), Ehrlich noted metachromatically staining of mature MCs in the connective tissue of several organs [2–5]. Since their discovery, an extensive understanding of MC biology has been published, which is highlighted in (Fig. 1) [3, 6–26]. MCs are terminally differentiated, highly distributed through the body, and granular immune cells of BM hematopoietic origin which derive from CD34+/CD117+ progenitor cells. MC progenitors then systemically migrate to target tissues, primarily those with direct contact to environmental antigens including the skin and the mucosal surfaces of the eye, respiratory, and gastrointestinal tracts. MCs complete the final biologic stages of differentiation and maturation in target tissues in the presence of the local growth factors including IL-9, IL-10, IL-3, IL-4, IL-33, CXCL12, nerve growth factor (NGF), and TGF-β [27]. The process of MC development from their progenitors is strictly controlled by microenvironmental stimuli that lead to considerable subtype differences [28]. In humans, MCs are traditionally classified based on the chemical composition of produced serine proteases, tryptase and chymase. MCs containing only tryptase (MC_T) predominantly reside in the alveolar septa and the mucosa of the small intestine; MCs containing chymase (MC_C) commonly reside in synovial tissue; and MC containing tryptase and chymase (MC_{TC}) are generally found in the skin, submucosal layers of the small intestine, and tonsils. MCs of rodents are classified a slightly different according to their phenotypic properties in two main subsets that have been identified as connective tissue MCs (CTMCs) located in the skin and peritoneal cavity and the mucosal MCs (MMCs) residing in the Lamina propria layer of the intestine [28]. Murine MCs unlike those in human are IL-3 dependent, but SCF independent for growth and expansion [29]. In vivo BM-derived MCs (BMMCs) resemble gastrointestinal mucosa residing MCs (MMCs) when cocultured with IL-3, whereas connective tissue MCs (CTMCs) isolated from the peritoneal cavity are IL-3

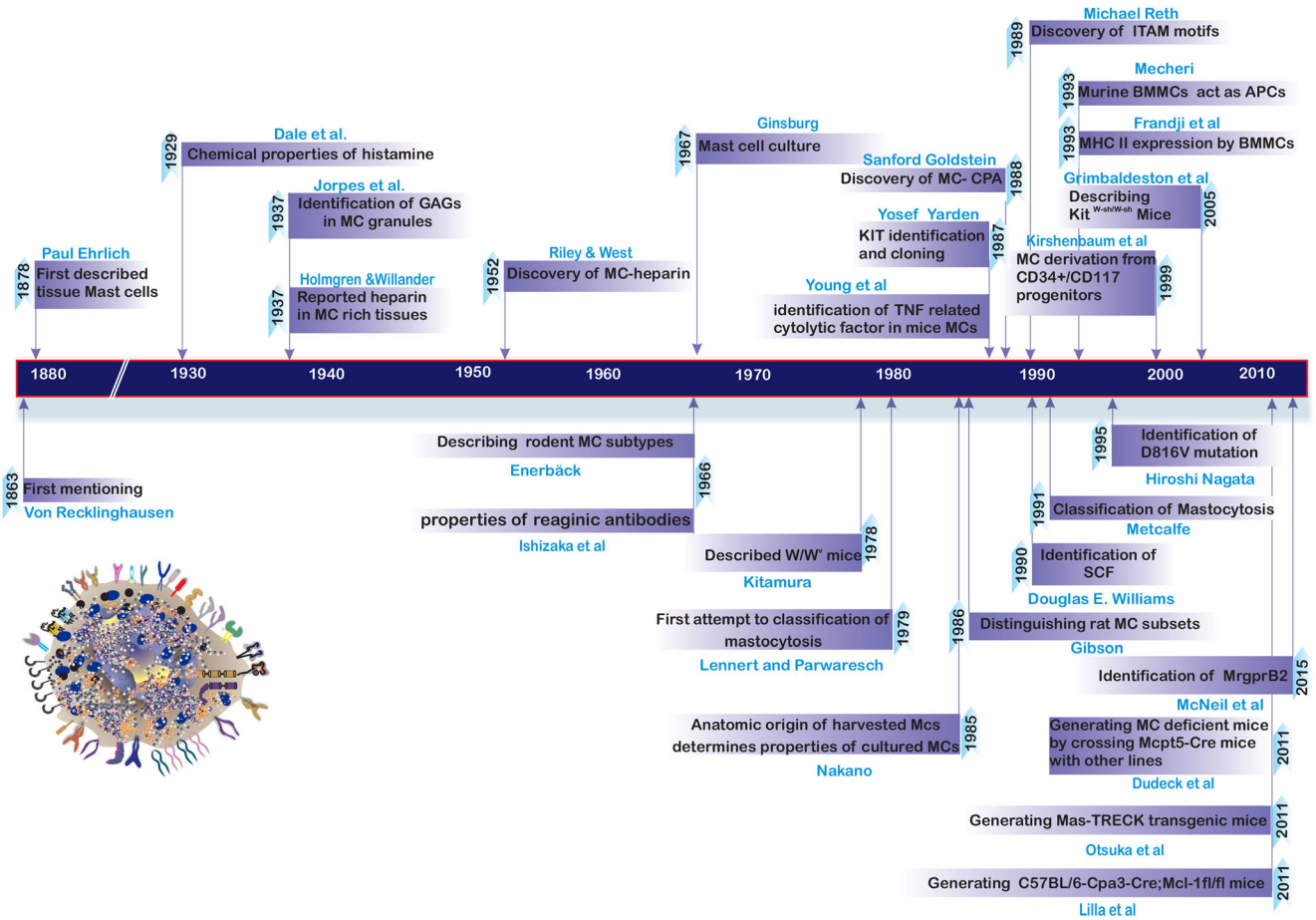


Fig. 1 Timeline highlighting the advances in mast cell biology. From the initial sighting of the MCs in 1863, there has been advances on the physical characteristics of identification staining techniques based on content while more functional changes have demonstrated the evolution of various subtypes with similar physical characteristics

and IL-4 dependent. Various immunologically activated resident cells including fibroblasts, T cells, and MCs produce IL-3 and IL-4 providing hematopoietic growth factors for other cell types [30]. Each MC contains approximately 1000 granules in the cytoplasm. The morphology of MCs appears to depend on the anatomical location with sizes ranging from 5 to 20 μm, varying from rounded-shaped to elongated forms, which are typical for perivascular MCs [31]. MCs can be activated via several pathways including aggregation of IgE bound to the FcεRI by polyvalent allergen, other ligand receptor interactions, including C3a-C3aR, C5a-C5aR (CD88), IgG-FcγRI, and NGF-TRKA, and opioid receptors [32].m

Mast Cell Subtypes

MC subtypes have been identified based on function, histochemical staining features, enzymatic content mainly proteases, and pattern of mediator release in response to selected secretagogues [28]. In rodents, MCs are classified as either CTMCs, which can be isolated from the skin, peritoneal cavity, and intestinal submucosa, or MMCs which are predominant in the mucosal layers [33]. CTMCs express a variety of proteases that include mMCP-4, mMCP-5, mMCP-6, mMCP-7, and CPA3, whereas MMCs express mMCP-1 and mMCP-2 [33]. MMCs can also be differentiated by their T cell–mediated expansion in response to certain parasites [28] (Table 1). The main subclasses of MCs in human classified according to protease content include "MC_T" that express tryptase only and the "MC_{TC}" that are known for their capability of expressing both tryptase and chymase [40] as well as MC-CPA [41] (Table 2).

Human MCs express γ-tryptase (also known as hTMT) which is a transmembrane tryptase exposed at the cell surface after the cell degranulates the cytoplasmic granules [41]. MC heterogeneity mirrors the experience that they gain in each specific tissue. In addition to the classical tryptases and chymases, resident MCs of various organs express peculiar factors, and release mediators responsible for their tissue-specific functions. For instance, skin MCs have low TLR expression but release carboxypeptidase, while intestinal MCs express α2β7, α2β1, and P2X7, have high TLR expression (in small intestine), and release cysteinyl leukotrienes [46]. Based on the fact that MC heterogeneity is the result of differences in tissue specificity, gene expression programs controlled by microenvironmental factors and stimuli that provoke their activation and/or degranulation, it is suggested to revise the historical classification of these cells according to their protease content [46] toward a classification that better reflects their functional state.

Phylogeny and Lineage Development

The egress of hematopoietic cells into the circulation in an identifiable mature state had secluded the origin of MCs as a mystery for decades. However, owing to advancement in the multicolor flow cytometry technique, and the availability of MC-specific antibodies such as mAb AA4 and mAb BGD6, characterization of the MC progenitors in terms of surface

Table 1 Comparing various characteristics of rodent MC subsets

Characteristic	(Connective tissue–type MCs) CTMCs	(Mucosal-type MCs) MMC	Ref
Size	Larger (10–20 μm)	Smaller (5–10 μm)	[34]
Formaldehyde fixation	Resistant	Sensitive	[35]
Staining	Safranin	Alcian Blue	[36]
Granule neutral protease	Chymase (RMCP I), tryptase, proteinase 5, carboxypeptidase A	Chymase (RMCP II)	[35]
Granule proteoglycan content	Heparin proteoglycan	Chondroitin sulfate E proteoglycan	[36]
T cell dependence	T cell independent	T cell–dependent in vivo	[35]
Heparin content	High	Low	[34]
Histamine content	High	Low	[36]
Fixators used in staining	Most of fixators including formalin	Only Carnoy's fixator or a mixture of formaldehyde and acetic acid	[34]
Cytokine needed to proliferation	IL-3 independent, IL-3 and IL-4 only synergistically support their proliferation	IL-3-dependent in vitro	[36, 37]
Compound 48/80-mediated activation	Yes	No	[38]
Polymyxin-mediated activation	Yes	No	[38]
Activated by substance P	Yes	No	[39]
Distribution in gastrointestinal tract	Widely distributed in submucosa, serosa, and mesentery	Restricted to the lamina propria	[34]

Table 2 Comparing various characteristics of human MC subsets

Characteristic	MC_T	MC_{TC}	Ref
Distribution	Predominant subtype in small intestinal mucosa (98%) and alveoli (93%)	Predominant subtype in the skin (88%) and small intestinal submucosa (87%)	[42]
Granule neutral protease	Tryptase	Tryptase, chymase, carboxypeptidase, cathepsin G	[43]
Granule ultrastructure	Cylindrical scrolls	Crystals (lattices/gratings)	[44]
T cell dependence	Yes	No	[35]
Sensitive to compound 48/80	No	Yes	[35]
Analogous to rodent MCs	MMC	CTMC	[45]
Sensitive to substance P	No	Yes	[35]
Inhibited by sodium cromoglycate	Yes	No	[35]

markers development and homing became possible [47–49]. Kitamura and coworkers provided the first evidence that MCs derive from progenitors of BM origin, using the beige mouse model (C57BL-Bgj/Bgj). Three-month-old wild-type mice were irradiated and adoptively transferred with BM cells of either beige or wild-type mice. Tissue samples obtained from the caecum and dorsal skin of recipient mice showed that most of the MCs in the caecum were of donor origin, whereas the majority of skin residing MCs were of host origin, indicating that the adoptively transferred BM cells differentiate finally to tissue MCs [50]. Gurish and coworkers demonstrated that MCps in mice are of BM origin by eliminating them with sublethal doses of γ-radiation and reconstitution with syngeneic BM. Since β7 integrin is critical for the trafficking of MCps to the small intestine, they benefited from anti-α4β7 integrin, anti-α4 integrin, anti-β7 integrin, and anti–MAdCAM-1 mAbs to block the recovery of MCps in the small intestine as late as 4 days after BM reconstitution. Applying the strategy of inhibition, they concluded that MCps must arise first in the BM, circulate in the vascular system, and then translocate into the intestine [51]. A "mast cell/basophil-like" (MCBL) cell with cytoplasmic histamine and heparin content was reported in the hemolymph (a fluid equivalent to blood in invertebrate creatures) of *Styela plicata*, a solitary ascidian that abounds in shallow, protected environments in tropical and warm-temperate oceans best known for possessing a unique allorecognition system [52, 53]), which appeared around 500 million years ago. Later, according to mouse model studies, it was suggested that both MCs and basophils originate from a granulocyte/monocyte progenitor (GMP) cell, which lineage specification is dependent to timed expression of the transcription factors GATA2 and C/EBPα. However, it has also been reported that MCs develop from common myeloid progenitors (CMPs), which are characterized by a lineage phenotype as (LIN) − KIT+ stem cell antigen 1 (SCA1) low FLT3− [54]. In the early 1990s, MCs were known to derive from BM CD34+/FcεRI− progenitors which transiently circulate in the bloodstream as morphologically undifferentiated cells composed of a subset of circulating CD34+/CD117+/Ly−/CD14−/CD17− cells [55]. Most recently, Dahlin et al. reported a human Lin−/CD34hi/CD117int/hi/FcεRI+ CD13−/+/integrin β7−/+ cell subset that gives rise to tryptase-positive granulated MCs expressing both CD117 and FcεRI at a frequency above 70% [56]. Chen et al. reported a cell population, identified as Lin − KIT+Sca-1 − Ly6c − FcεRIα−CD27 − β7 + T1/ST2+, as MCps in adult mouse BM [57]. Their results were consistent with results of Jamur et al. which benefited from applying AA4 and mAb BGD6 mAbs to purify the MCps from mouse BM [49]. In a mouse model investigation based on studying the MCp and mature MCs from peritoneal lavage by flow cytometry, Dahlin et al. reported that once the committed MCps leave the BM, they could be found in circulation as Lin− c-KIThi T1/ST2+ integrin b7hi CD16/32hi cells. After having entered the peripheral tissues, MCps are identified with a CD45+ Lin− CD34+ integrin β7hi FcεRIαlo profile [47]. The experiment strongly suggests that MCps are the progeny of multipotential progenitors (MPPs) other than common myeloid progenitors (CMPs) or granulocyte/macrophage progenitors. Furthermore, development of MCs from MPPs does not depend on cell division [58].

Further Mast Cell Surface Receptors and Mediators

A wide range of surface and cytoplasmic receptors make MCs capable of responding to various stimuli. Some of them are quite unusual and yet to be fully investigated. In this regard, the MC population is significantly higher in skin with direct exposure to light when compared with skin which is protected from sun exposure. Moreover ultra violet radiation may induce the MC activation. However, it is still not clear whether attraction of MCs to sun exposed skin or activation by ultraviolet follow a receptor signaling pathway and if so which receptor(s) is involved [59, 60]. Activation of MC expressed

chemokine receptors results in chemotaxis and induction of other stimulatory responses. For instance, the activation of CXCR3 and CCR2 promotes the migration of human cord blood MCs (hCBMCs) and induces the signaling events and partial degranulation even without the presence of antigens [61]. Histamine, which is the major mediator of MCs, delivers its biological effects through four receptors (H1–4). The H1 receptors (expressed by endothelial cells, bronchial, smooth muscle, and some neurons) and H2 receptors (expressed by vascular smooth muscle and gastric parietal cells) are associated with pathologic reactions including the wheal and flare reaction in skin, bronchoconstriction, drop in blood pressure, and gastrointestinal hyperactivity. H3 receptors are expressed primarily by the CNS, whereas H4 receptors are histamine receptors expressed on the surface of granulocytes including basophils, MCs, and eosinophils and participate in the process of chemotaxis [62]. The pattern of MCs trafficking depends on their ability to recognize appropriate chemotactic stimuli. Numerous chemoattractants are capable of inducing chemotaxis in MC models [63]. The main chemokine and their corresponding receptors are summarized in Fig. 2. MCs not only store ATP as an autocrine/paracrine factor in their secretory granules but also express P2X receptors, which sense extracellular ATP [64]. MCs may also express inhibitory G protein–coupled receptors including the β2-adrenergic receptor (β2AR), A2B receptor (the receptor for adenosine), and EP2 (PGE2 receptor) [65] Fig. 2. It should be considered that tissue resident MCs may differ in terms of expressing complement receptors. In this regard, unlike skin MCs, lung MCs do not express the C5a receptor (CD88) [66]. Some recently discovered MC receptors may have therapeutic importance, for instance, sialic acid–binding Ig-like lectins (Siglec) that preferentially bind to α2,8-disialyl and branched α2,6-sialyl carbohydrate structures [67]. Considering that Siglec-8 is expressed selectively on the surface of human eosinophils, MCs, and basophils, it may be a promising molecular target for immunomodulation of diseases [68]. Targeting Siglec-8 may be promising in the treatment of MC-related diseases, including allergic asthma, chronic rhinosinusitis, chronic urticaria, and mastocytosis [69]. Another clinically important receptor is the G protein–coupled MRGPRX2 receptor which is the human analogue of the mouse Mrgprb2. It may be involved in anaphylactoid non-IgE–mediated adverse drug reactions, e.g., to neuromuscular blocking agents used during anesthesia or chinolone antibiotics such as ciprofloxacine [17]. Most recently, MC expression of Mrgpr family has gained attention in dermatology. Meixiong et al., using Mrgprb2$^{-/-}$ mice model, reported that Mrgprb2 deficiency attenuates itch in allergic contact dermatitis (ACD) and that the activation of the receptor is IgE/FcεRI independent and results in non-histaminergic itching. They concluded that targeting Mrgprb2 signaling pathway may have promising therapeutic application [70]. Moreover, Green et al.

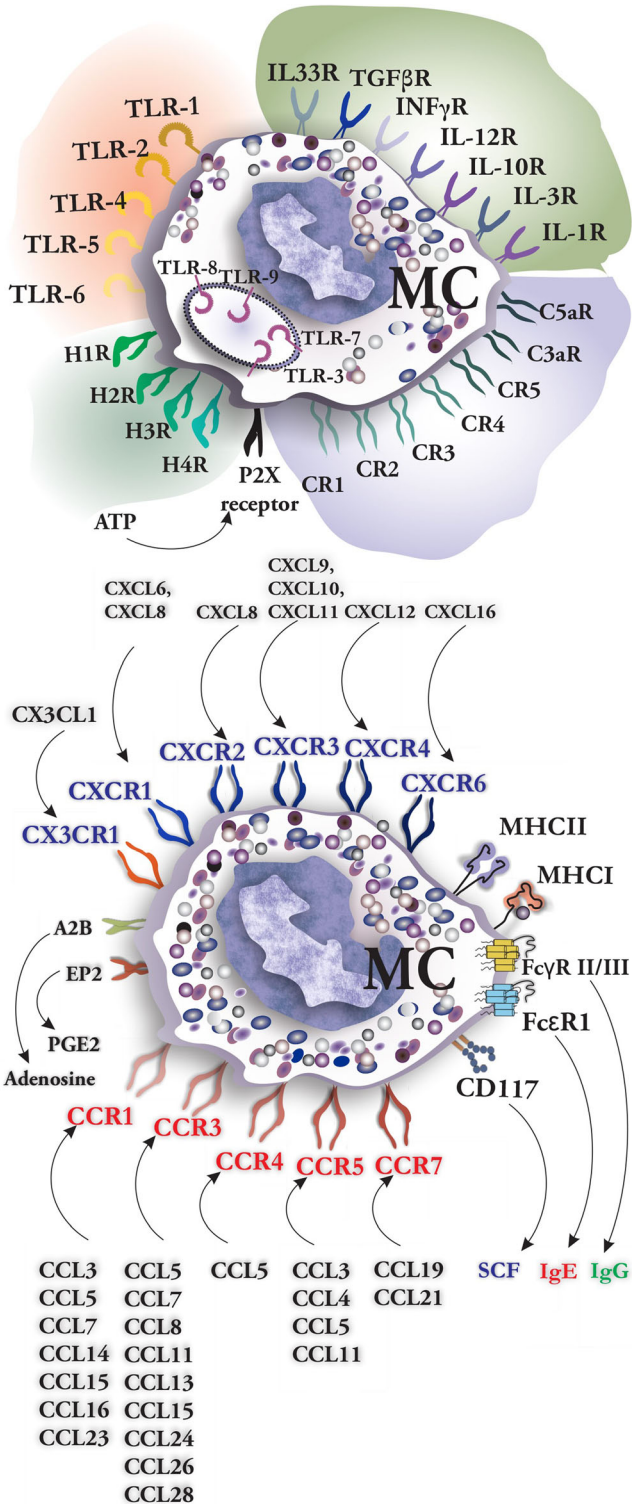
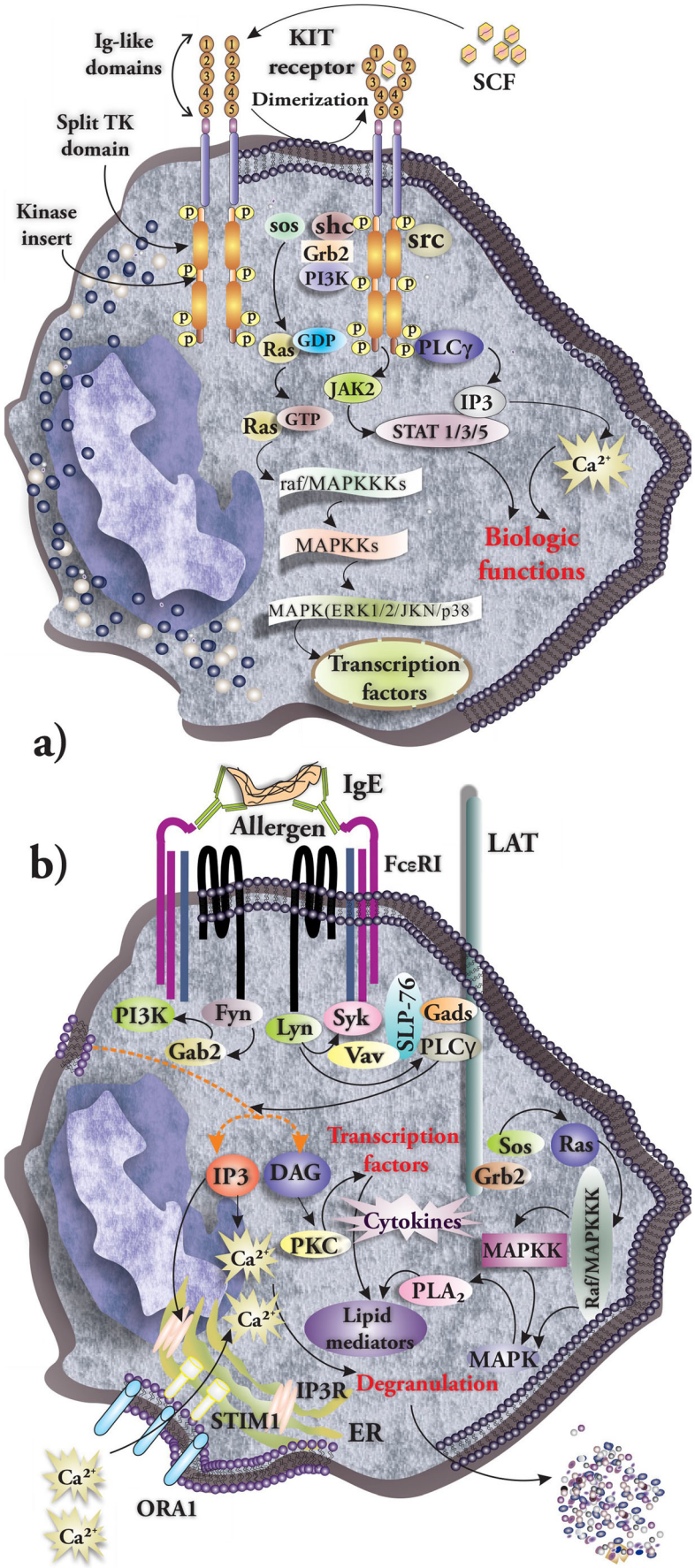


Fig. 2 Main MC surface receptors for cytokines, complement, and chemokines. The complete ligands for chemokine receptors are listed

investigated the involvement of Mrgprb2 in the process of pain by studying Mrgprb2$^{-/-}$ mice in two models of incision and injection of Complete Freund's Adjuvant (CFA) and found that Mrgprb2 deficiency could reduce the pain hypersensitivity. Interestingly, the P substance/Mrgprb2 receptor


Ig-like domains
KIT receptor
Dimerization
SCF
Split TK domain
Kinase insert
sos
shc
Grb2
PI3K
src
Ras
GDP
PLCγ
JAK2
IP3
Ras
GTP
STAT 1/3/5
Ca2+
raf/MAPKKKs
MAPKKs
Biologic functions
MAPK(ERK1/2/JKN/p38
Transcription factors
a)
b)
IgE
Allergen
FcεRI
LAT
PI3K
Fyn
Lyn
Syk
SLP-76
Gads
Gab2
Vav
PLCγ
Transcription factors
Sos
Ras
IP3
DAG
Grb2
Cytokines
Ca2+
PKC
MAPKK
Raf/MAPKKK
PLA2
Ca2+
Lipid mediators
MAPK
IP3R
Degranulation
STIM1
ER
Ca2+
ORA1
Ca2+

◀ **Fig. 3** **a** Schematic representation of the signaling events during KIT activation by SCF in MCs; **b** FcεRI-stimulated assembly of macromolecular signaling complexes

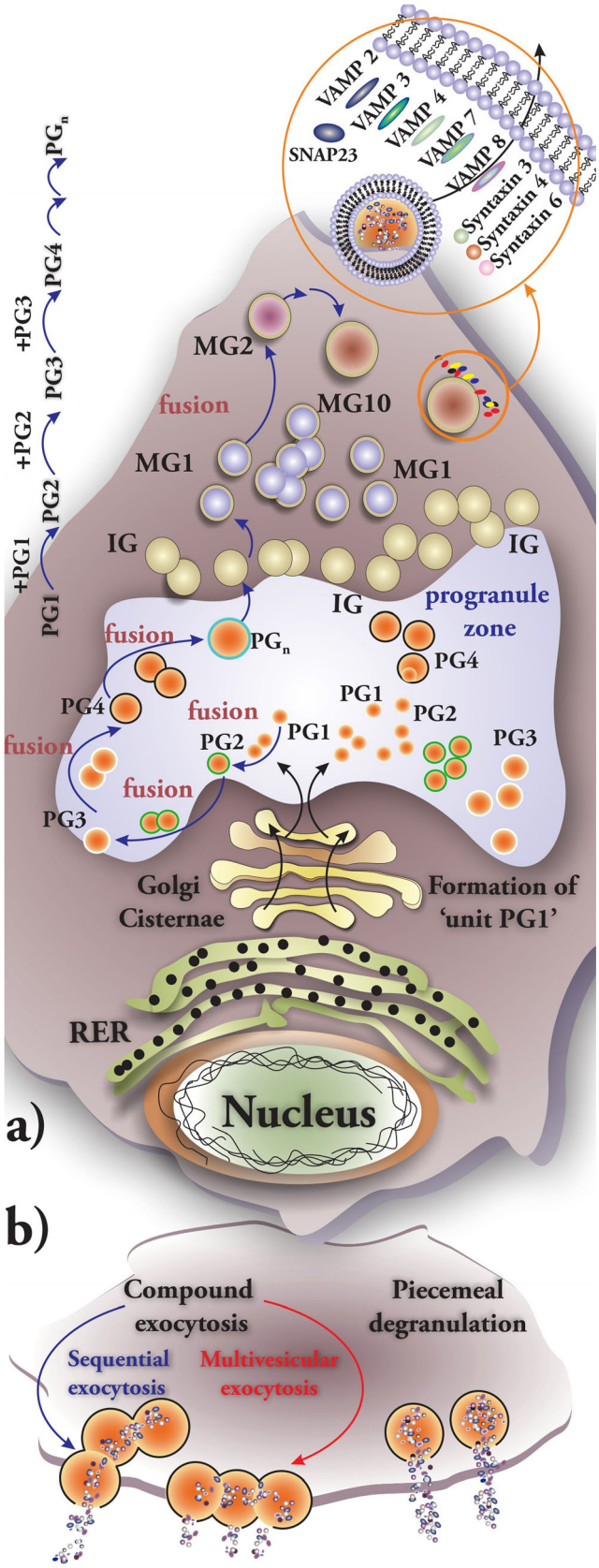
interaction plays a role in recruitment of innate immune cells to the site of inflammation [71].

KIT and IgE Signaling

KIT (CD117) belongs to the tyrosine kinase activity superfamily [72, 73]. SCF (first introduced as steel factor and became to be known as KIT ligand later) is synthesized as a transmembrane protein from two alternatively spliced mRNAs which are enzymatically cleaved to soluble or membrane-bound forms [74]. Dimerization of KIT induces activation of the inherent catalytic activity associated with the split tyrosine kinase domain contained within the cytosolic COOH-terminal region [75]. SCF binding to KIT facilitates the formation of a homodimeric state of c-KIT through placing between the Ig-like domain 4/5 of a couple of adjacent monomeric KIT receptors. This leads to trans-phosphorylation in the regions "juxtamembrane," "kinase insert," "kinase domain," and, finally, "COOH-terminal tail." To trigger the signaling cascade, phosphorylated residues serve as docking sites for surrounding signaling molecules including Src kinases, PI3K, Shc, and phospholipase Cγ (PLCγ). The triggered signalings of GTP exchanger molecule SOS, PI3K, PLCγ, and JAK2 result in activation of Ras-Raf-Map kinase (MAPK) cascade that consequently leads to an increase of the Ca^{2+} concentration and activation of a number of transcription factors required for the biological function of MCs (Fig.3a). MC activation in type I allergy is mainly triggered by FcεRI when crosslinking of FcεRI allergen–bound IgE occurs [76]. According to the FcεRI structure, the α chain serves as a binding site to IgE. The receptor in addition of α chain has a tetraspanning β chain and two γ chains linked by disulfide bonds. The β subunit effectively boosts the signals induced by IgE/allergen interactions. Additionally, two γ subunits have a role in initiation and conducting of FcεRI downstream signaling [77]. Upon antigen binding, the FcεRI forms dimers. This activation initiates cytoplasmic signaling by rendering "immunoreceptor tyrosine-based activation motifs" (ITAMs) phosphorylated in the cytoplasmic ends of the β and γ subunits by engaging the Src-family protein tyrosine kinase Lyn. Syk is bound to ITAMs in the γ units through which it adopts to a spatial conformation susceptible to become phosphorylated by Lyn. Syk promotes the phosphorylation of several targets including TRAPs, LAT, and NTAL. TRAPs after having become phosphorylated act as plasma membrane docking points for binding of cytoplasmic SH2 domain containing molecules mainly Grb2 and "phospholipase Cγ" (PLCγ). The latter molecule after anchoring and becoming activated catalyzes the "phosphatidylinositol 4,5-biphosphate" (PIP2) hydrolysis to form "diacylglycerol" (DAG) and inositol 1,4,5, −triphosphate (IP3) which are mainly known as the second messengers. IP3 binds to its receptors on the "endoplasmic reticulum" (ER) that promotes Ca^{2+} efflux from the ER. IP3 activates the IP3-receptor on the ER to release Ca^{2+}. The calcium sensor stromal interaction molecule 1 (STIM1) then interacts with the ORAI1 membrane protein opening the CRAC channels allowing the increase in intracellular calcium. The final result of calcium influx is increasing of the free cytoplasmic Ca^{2+} concentration, which is necessary to trigger further signaling events [78–80] (Fig. 3b).

Biogenesis and Degranulation of MC Granules

Following the production of proteins to be secreted into MC cytoplasmic granules, these products are directed to the secretory pathway of the "rough endoplasmic reticulum" (RER). During the passage through the Golgi apparatus, posttranslational modifications occur on the proteins and they reach the "trans-Golgi network" (TGN) [81]. In the following step, a regulated fusion of unit granules is initiated (also called small fusogenic granules) and these granules bud from the trans-Golgi region [82]. Their fusion results in formation of progranules in a defined region by the outermost cisternae of Golgi, RER, and results in mature granules in the cytoplasm. Having left the zone as immature granules (type III granules), the progranules mature via fusing with surrendering immature or mature granules. During "condensation" the volume of the granules is reduced, the contents of the granules become organized, and various sizes of mature granules are generated. Type III granules are capable of fusing with endosomes or lysosomes (type I granules) to form type II granules (secretory lysosomes) [82, 83]. The preformed "secretory granules" (SG) act as degradative and secretory compartments and due to their lysosomal properties contain lysosomal enzymes, present lysosomal membrane proteins, therefore, they possess a low acidic pH, and are regulated by synaptotagmins [84](Fig. 4a). During exocytosis, SGs through a mechanism called compound exocytosis form channels by fusing with each other. The process can proceed either in a multivesicular or sequential pathway. Sequential exocytosis involves the initial fusion of vesicles with the plasma membrane. Next, the vesicles will fuse with the first vesicle. In contrast, multivesicular exocytosis involves vesicles fusing together prior to having interacted with the cell membrane [85]. Additionally, "piecemeal" degranulation is another mechanism of exocytosis through which MCs degranulate. This mechanism is characterized by gradual loss of contents of cytoplasmic granules without distinguishable granule fusion [85]. According to the strength of the degranulating signal, the potency and capacity of exocytosis can be significantly boosted by compound secretion, and



◀ **Fig. 4** **a** The classical model of secretory granule formation starts within endoplasmic reticulum and Golgi to form progranules. The fusion of progranules results in immature granules which then fuse and, finally, give rise to mature granules which are exocytosed using a molecular mechanism mediated by a variety of proteins including SNARE proteins. **b** Main mechanisms of exocytosis that are being used through MC degranulation are piecemeal and compound exocytosis

further SGs homotypic fusion results in a rapid discharge of SGs located distally, which bypasses the need for their transport to the membrane [84](Fig. 4b). The appropriate fusion of vesicles to the membrane depends on the presence of specific set of highly conserved proteins called "Soluble N-ethylmaleimide-sensitive factor attachment protein receptors" (SNAREs) [85, 86]. Multiple SNARE proteins including VAMP 8, 7, 4, 3, and 2; SNAP23; and syntaxins 6, 4, and 3 are engaged during MC exocytosis [84]. For instance, VAMP-8 deletion results in inhibition of cathepsin D and serotonin release; however, the release of histamine or TNF-α is not influenced by VAMP-8 deletion [87]. Other complexes involved in exocytosis are Rab GTPases that regulate exocytosis; for instance, Rab27a, when accompanied with its effector molecule Munc13–4, increases FcεRI-induced capacity of MC degranulation [32]. Membrane, retrieve upon exocytosis, is a crucial step required for maintaining its integrity by a series of regulated endocytosis. Thus, endocytosis is considered as an essential step in avoiding complete exhaustion of the vesicle system and for maintaining normal MC morphology. Three forms of exocytosis-coupled forms of endocytosis are known in MC biology: slow endocytosis mediated by clathrin (invagination and internalization of the surface membrane coated with clathrin, and then removing of the clathrin), kiss-and-run endocytosis (a proposed mechanism through which vesicles do not fully collapse into the membrane but they recycle just after closure of a fusion pore), and bulk endocytosis [88].

Mast Cell Mediators

MC mediators are traditionally classified as pre-stored and de novo synthesized. The latter are arachidonic acid metabolites produced and released rapidly and cytokines produced and secreted less quickly. (Table 3) The class of mediators stored in granules includes important biologic mediators among them serotonin, histamine, heparin, TNF-α, and enzymes such as tryptase and chymase. De novo synthesized mediators are produced following MC stimulation such as lipid mediators including LTs, PAF, and PGs. Another class of MC cytoplasmic content being released includes cytokines, chemokines, and growth factors such as IL-10, IL-3, IL-8, IL-1, IL-4, IL-5, GM-CSF, TGF-β, VEGF, TNF-α, CCL2, CCL5, fibroblast growth factor (FGF), and platelet-derived growth factors (PDGF). Their release occurs over a period of hours rather than minutes, except for the preformed cytokines including TNF-α due to the possibility of storing and

Table 3 Mast cell mediators and their main features and function

Mediator	Main features and functions
	Pre-stored mediators
Bioactive monoamines	Histamine and serotonin are 1,4/1,3-diamines produced by amino-acid decarboxylases [89] Involved in vasodilation, angiogenesis, mitogenesis, pain [90] The key biogenic amine released upon engaging IgE-FCεRI signaling pathway in
Histamine	Human MC (3–8 pg/cell) Measuring the concentration of plasma histamine remains problematic due to its short half-life (10–30 min) [91]
Serotonin	Involved in vasoconstriction, pain [90] Unlike humans, it is found in high concentrations in rodent MCs Acting as neurotransmitter Possibly involved in MC-neuron interactions [92]
Dopamine	Not found in human MCs Acting as neurotransmitter Potential role in MC-mediated signaling to nerve endings [92]
MC-specific proteases	Appear as fully enzymatically active biological compounds both in the presence or absence of anionic GAGs [33] Have capacity to electrostatically binding with high affinity to heparin [33] Contribute to maintain the barrier function of intestinal, clearance of helminths, and may support blood pressure upon occurrence the anaphylaxis through generation of angiotensin II [93]
Chymases	Have chymotrypsin-like specificities and belong to the serine protease class [41] Generate mature forms of IL-33 by acting on full-length IL-$33_{1–270}$ to activate ILC2s and eosinophils in vivo [94]
Tryptases	Major protein component found in the stored SGs in human MCs [95] Catalyze β-protryptase to active β-tryptase2 [95] The main tryptases in humans include βI−, βII−, and βIII and the enzymatically inactive α-tryptase [92] Soluble β-tryptases stimulate nerves by activating PAR2 affect airway smooth muscle and fibroblasts by acting as mitogens Recruit neutrophils and eosinophils and degranulate MCs [96] Found as an activated form inside of MC granules [97] Promote fibroblast collagen synthesis [98] Have trypsin-like cleavage specificities and belong to the serine protease class [41] Have clinically diagnostic importance (as minor diagnostic criterion) in diagnosis of systemic mastocytosis when > 20 ng/ml [91]
Carboxypeptidase A3	Contributes to the generation/degradation of angiotensin II, degradation of apolipoprotein B, and metabolism of leukotrienes [99] Synthesized as a proenzyme with a 94-amino-acid activation peptide [99] Specificity for cleaving proteins/peptides from C-terminal end [41] Zinc-dependent metalloprotease [41] with exopeptidase activity [99]
	De novo synthesized mediators
LTC4	promoting migration eosinophil, bronchoconstriction, and vascular permeability [100]
PGD2	Promotes vasodilatation, permeability, migration of inflammatory cells, and production of cytokines [100] Involved in bronchonstriction, pain [90] Acting as chemoattractant factor for human airway smooth muscle (HASM) by interacting with the CRTH2/DP2 receptor and may promote ASM migration toward the subepithelial BM [101]
PAF	Activation of platelets, induction of bronchoconstriction, bronchial hyperresponsiveness, and chemotaxis of MC, increases vascular permeability, and accumulation of inflammatory cells [102]
PGE2	Seems to have profound immunosuppressive abilities [100]
Cytokine and growth factors	Main features and functions
TSLP	Also secreted from DCs and basophils; activates Th2 cells, MC, DCs, eosinophils, and basophils [100]
IL-3	Provokes IL-4, IL-13, histamine, and LTC4 release from basophils [100]
IL-4	Increases collagen production, stimulates synthesis of the extracellular matrix proteins including types I and III collagen and fibronectin in fibroblast culture [103] IL-4 supports the surface expression of FcεRI on MCs and basophils [104] Stimulates class switch of B cells to IgE production together with IL-5 and IL-13
IL-31	Also secreted from Th2 cells; involved in the T cells, MC, and eosinophils interaction with epithelial cells to release chemokines and other cytokines [100]
L-33	IL-33 promotes IgE/Ag-, SCF, C5a-, monomeric IgE- and NGF-mediated cytokine production in HMC-1 cell line and human MCs [105]

Table 3 (continued)

Mediator	Main features and functions Pre-stored mediators
IL-5	Dominant MC released cytokine involved in survival, trafficking, migration, differentiation, maturation, development, and biological function of eosinophils [100]
Nerve growth factor	Released upon FCεRI-crosslinking Mediates the interactions between MCs and peripheral nerve endings [92]
Stem cell factor	Present in the cytoplasm Not released upon IgE receptor crosslinking
TNF-α	Preformed cytokine stored in granules [2] Membrane-bound form optimizes the migration of tissue DCs to the draining LNs Soluble form participates in DC recruitment to sites of inflammation [106] Induces DC migration; increases DC longevity [106]
TGF-β1	Profibrotic multifunctional growth factor Stimulates fibroblast proliferation and matrix formation [107]
TGF-β2	Involves in marked collagen deposition [107]
Proteoglycans	Main features and functions
Chondroitin sulfate	Cartilage synthesis, anti-inflammatory
Heparin	Involved in angiogenesis; nerve growth factor stabilization
Hyaluronic acid	Connective tissue, stabilize NGF [90]

releasing it from cytoplasmic granules [108, 109]. Secretory granules contain many secretory compounds, mainly heparin/chondroitin sulfate proteoglycans with negative charge [33]. Heparin side chains of serglycin, which possess negatively charges, are required for appropriate storage of MC-restricted proteases as they possess positive charges. Additionally, serglycin has a role in regulation of the enzymatic activities of proteases [110]. Tryptases, chymases, and CPA3 are considered as MC-specific proteases but MC granules also possess MC non-specific proteases mainly cathepsin G, MMP9, active caspase3, ADAMTS5, granzyme B, and renin [92]. Among the lipid mediators of MCs, eicosanoids that are synthesized from a common precursor molecule, namely arachidonic acid (AA), play a prominent role [111].

Mast Cell–Deficient Mouse Models for Investigating Mast Cell Biology In Vivo

The proto-oncogene c-KIT is mapped to the dominant "white spotting locus" (W) on mouse chromosome 5. When mutations occur at the "murine-dominant white spotting locus" (W), they may influence biologic functions of variety of cells including the hematopoiesis, proliferation, and migration of primordial germ cells and melanoblasts during the process of embryogenesis. Many independent semidominant mutations have been identified at the W locus. Occurrence of the different alleles is associated with various degree of severity and effect on the different cell lineages [112]. The severity of the phenotypic traits influenced by mutations is in an inverse correlation with the activity of tyrosine kinase receptor [113]. So far, mice with a specific lack of all populations of MCs have not been described yet; instead, mice deficient for KIT have been widely used to analyze the functions of MCs in vivo [114]. According to previously published data, two types of MC-deficient mice have been most frequently used for such studies, namely WBB6F1-Kit^{W}/$Kit^{W\text{-}v}$ and C57BL/6-$Kit^{W\text{-}sh}$/$Kit^{W\text{-}sh}$ mice. The main specifications are listed in (Table 4). The fertility accounts as an advantage for the $Kit^{W\text{-}sh}$/$Kit^{W\text{-}sh}$ mice when researchers wished to produce MC–deficient mice with multiple genetic abnormalities. Additionally, more complex and expensive breeding strategies are required when sterile Kit^{W}/$Kit^{W\text{-}v}$ mice are included in investigations [115]. Differences in biological responses in such mice and wild-type (WT) mice could be due to the presence of any of abnormalities, and not necessarily associated with MC-related deficiencies [117]. In recent years, novel Kit-independent MC-deficient mouse models have been developed and started to be used by many research labs (Table 4). Such models clearly benefit from the lack of Kit-mediated off-target effects, which have to be overcome in the Kit-dependent models by selective MC reconstitution strategies. On the other hand, these mice challenge the investigation of MC biology since their response differ from Kit-dependent mice in various disease models. Nevertheless, these new models open the scene for better mechanistic studies to further explore MC biology in vivo [121, 122].

MC Involvement in Type I Hypersensitivity

MCs were primarily known as the main effector cells in type-I allergic reactions and diseases, e.g., allergic rhinoconjunctivitis, urticaria, and anaphylaxis [123, 124]. The first pathogenic

Table 4 Main differences between two common types of MC-deficient mice

	Mutant mice with MC deficiency related to c-kit abnormalities		Mutant mice with MC deficiency unrelated to c-kit abnormalities		
	WBB6F1-Kit^{W}/$Kit^{W\text{-}v}$	C57BL/6-$Kit^{W\text{-}sh}$/$Kit^{W\text{-}sh}$	Mcpt5-Cre;R-DTA	$Cpa3^{Cre/+}$, Cre-Master	Cpa3-Cre; Mcl-$1^{fl/fl}$
Genetic characterization/disorder	$Kit^{W\text{-}v}$ reduces the kinase activity of the receptor	$Kit^{W\text{-}sh}$ is an inversion mutation affecting the transcriptional regulatory elements upstream of the c-kit transcription start site on mouse chromosome 5 [114]	Crossed MC protease (Mcpt)5-Cre transgenic mice with R-$DTA^{fl/fl}$ mice		Crossed MC protease Cpa3-Cre transgenic mice with Mcl-1 floxed mice
Cell deficiency rather than MCs	Lack of melanocytes, germ cells, interstitial cells of Cajal [115]	Reduced melanocytes		Reduced basophils	Marked deficiency in basophils (58–78%)
Sterility	Sterile [116]	Fertile	Fertile	Fertile	Fertile
Hematologic abnormalities	Macrocytic anemia have reduced numbers of neutrophils and basophils [117]	Increased numbers of neutrophils and basophils			Reduction in bone marrow, blood and spleen basophils. Exhibit markedly reduced MC–dependent tissue swelling and leukocyte recruitment in IgE-dependent PCA [26]
Coat color	White [116]	Heterozygotes are black with a broad white sash/belt in the lumbar region while homozygous W^{sh} mutant mice are black-eyed whites with small black patches [118]	Black	Black	Black
Other	Have < 1% the wild-type levels of skin MCs	Enlarged spleens and mild cardiomegaly [117] Reduced muscular fitness	Lack of MCs in peritoneal, abdominal, back skin, and ear skin [114]	Profound depletion of MCs, deleting 28 nucleotides of the first exon of Cpa3, that encodes for the MC-associated protease CPA3 [119] Refractory to IgE-mediated anaphylaxis [120]	Known as “Hello Kitty” mice, marked kit-independent constitutive reduction in numbers of MCs [114]

DTA diphtheria toxin alpha chain, *Cre-Master* Cre-mediated mast cell eradication

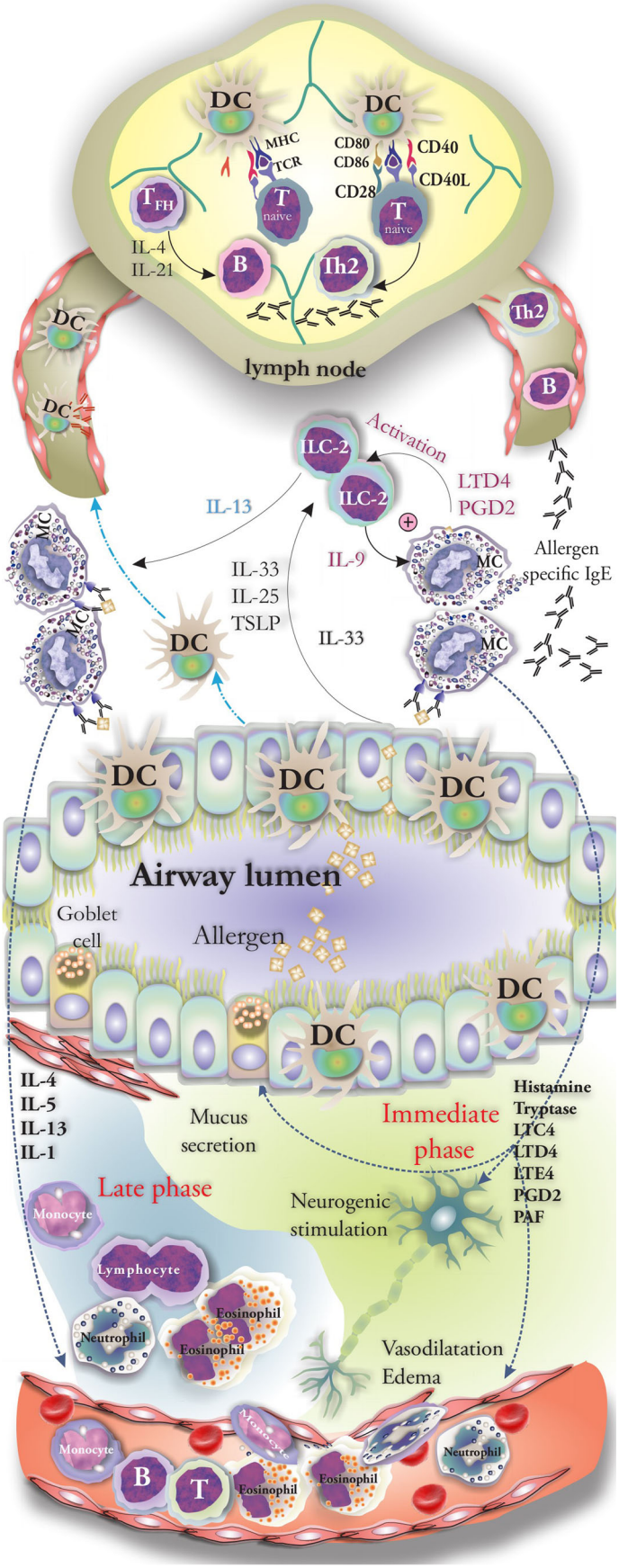
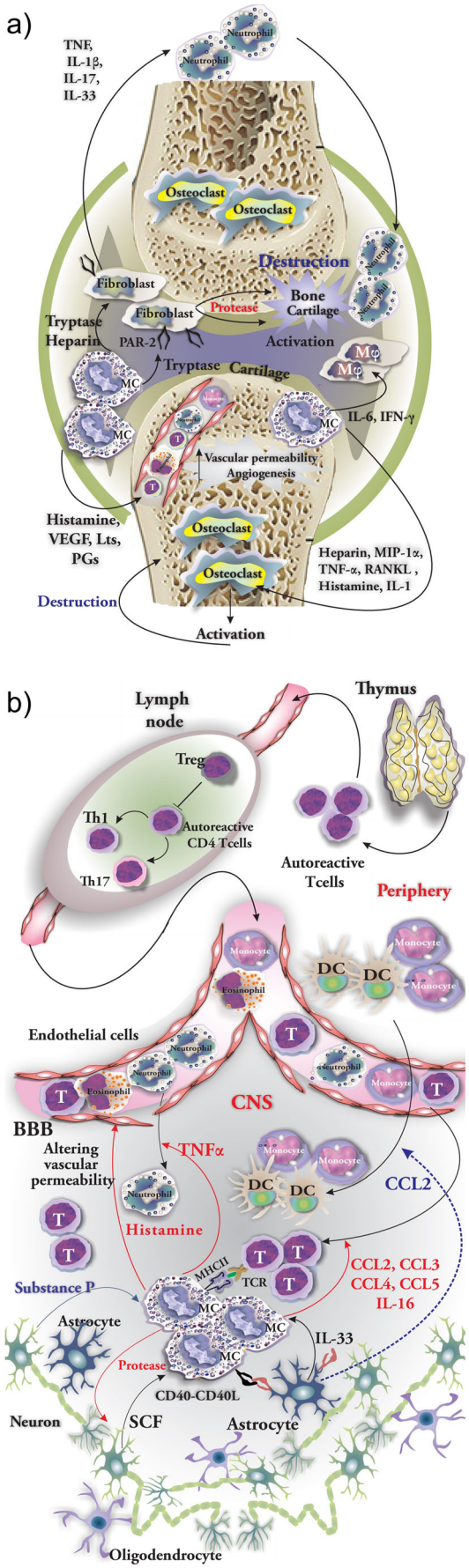


Fig. 5 DCs act as APCs by allergen uptake and a migrating to regional lymph nodes, afterwards. This is mediated by ILC-2, which release IL-13 onto the activated, naïve lymphocyte, which favors the differentiation to Th2 cells. IgE class switching of B cells occurs in lymph nodes and allergen–specific IgE is produced. The IgE is released into the serum, loaded onto the FcεRI receptor, and the MC becomes sensitized. Further exposure to allergen results in rapid, IgE-dependent activation of MCs, degranulation, and release of different classes of mediators involved in orchestration of the cellular and molecular events during immediate and late phases



◀ **Fig. 6** **a** MCs participate in recruitment of inflammatory cells into the joints that exacerbate the inflammation process. MC mediator–dependent activation of fibroblasts and osteoclasts results in destruction of cartilage and bones. **b** Regulatory T (TReg) cells control and monitor autoreactive T cells that escaped deletion in the thymus during establishment of self-tolerance. In multiple sclerosis, they become activated in the periphery as aggressive effector cells and Th1 and Th17 infiltrate the central nervous system (CNS). Neurons induce the release of histamine from MCs by secreting substance P. Histamine can alter the vascular permeability of BBB, thus facilitating the infiltration of inflammatory cells into CNS. CD40-CD40L interaction between astrocytes and MCs results in astrocyte release of CCL2 (green pathway), which can attract DCs and monocytes to the site of autoimmunity. MC-derived IL-1β induces the release of GM-CSF from T cells which attracts monocytes into CNS. Neutrophils are recruited by MC-derived TNF-α

process in the development of IgE-dependent type I allergy is sensitization, which is mediated by allergen uptake by professional antigen presenting cells (APCs, e.g., DCs in mucosa or skin). Immature DCs take up the allergen, mature, and then find their way to regional lymph nodes to present these antigens to naïve T cells which is a necessary step for the differentiation of CD4+ T cells into Th2 cells [125]. Th2 lymphocytes secrete IL-4, which is essential to induce the isotype switching from IgM to IgE class antibodies in B lymphocytes. Once produced by plasma cells, IgE molecules are released into the bloodstream and bind to FcεRI receptors of both tissue resident MCs and circulating basophils. Subsequent allergen binding and crosslinking of IgE molecules already bound to the FcεRI on the surface of the MC trigger MC degranulation and the release of pro-inflammatory cytokines responsible for the clinical manifestations of type-I allergic diseases [126, 127]. During the immediate period 0- to 60-min post exposure to the eliciting allergen, MCs become activated through IgE-dependent signaling and the release of preformed mediators, including histamine and tryptase, platelet-activating factor (PAF), and the newly synthesized LTC4, LTD4, LTE4, and PGD2 occurs. The biologic consequence of mediator release in immediate phase of type I hypersensitivity includes local vasodilatation, edema formation, local neurogenic stimulation, and mucus secretion in the early phase [128]. In late phase, a release of IL-1, IL-13, IL-4, and IL-5, as MC inflammatory cytokines, paves the way for activation of local cells and recruitment of inflammatory cells including granulocytic leukocytes (neutrophils, basophils, eosinophils) and agranular leukocytes (monocytes, lymphocytes) to the site of inflammation [129] (Fig. 5).

Beyond an Anaphylaxis-Triggering Cell

Rheumatoid Arthritis

In rheumatoid arthritis (RA), synovial joints are the primary targets of synthesized autoantibodies that are responsible for triggering the auto immune response. MC accumulation and

localiziation observed in RA occur in response to local release of several MC-derived mediators. Tryptase when complexing with heparin promotes the inflammatory responses. For instance, it induces the release of neutrophil chemotactic factors mainly IL-1β, IL-17, IL-33, and TNF-α by synovial fibroblasts. IL-33, in turn, promotes the expression of additional inflammatory cytokines and chemokines through acting directly on MCs. Additionally, tryptase/PAR2 interaction activates synovial fibroblasts and enhances their capacity to produce proteases capable of degrading the structure of cartilage and bone [130]. MC-derived mediators including histamine, VEGF, LTs, and PGs have a role in increasing of vascular permeability and angiogenesis. Additionally, mediators such as heparin, MIP-1α, TNF-α, IL-1, histamine, and RANKL are capable of inducing differentiation and activation of osteoclasts that is associated with bone destruction in RA [131, 132]. IL-6 and IFN-γ are able to activate macrophages [131]. (Fig. 6a).

Multiple Sclerosis

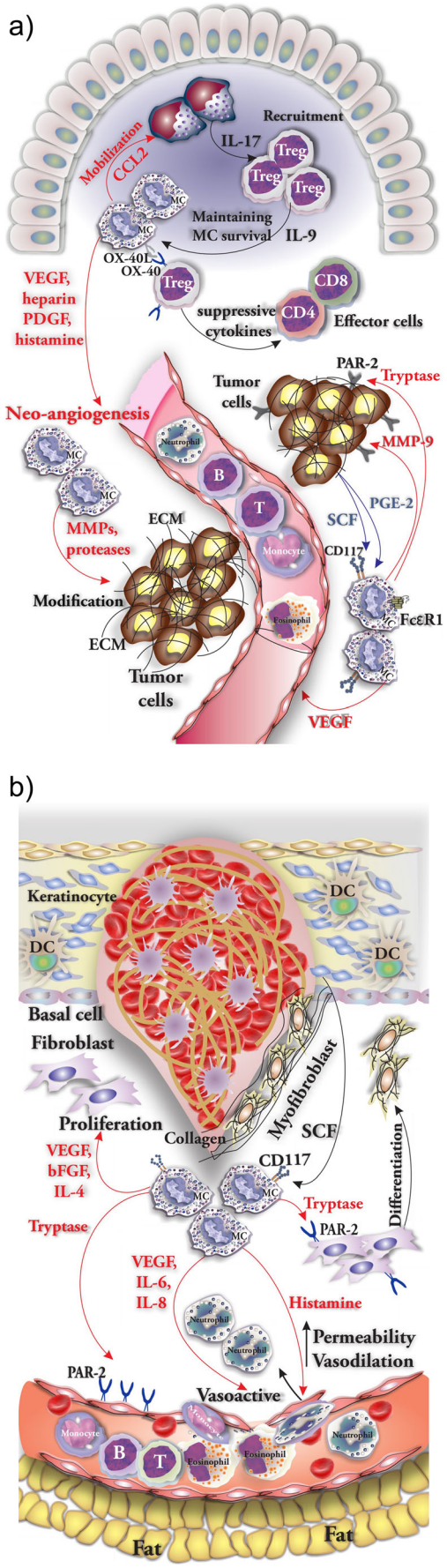
In MS, autoreactive T cells become activated in the periphery as aggressive effector cells that infiltrate the CNS. MCs interact with astrocytes (through CD40-CD40L interaction), neurons (through releasing proteases), and T cells for recruiting immune cells and damaging myelinated neurons. Peptidergic neurons modulate MC activity by secreting neuromediators: mainly substance P, which effectively induces histamine release from brain MCs [133]. Histamine released by MCs facilitates the penetration of autoreactive T cells into the CNS through CNS surrounding blood brain barrier (BBB) by alteration of vascular permeability [133]. MCs are capable to recruit inflammatory cells such as neutrophils by secreting TNF-α. Moreover, MC proteases have myelinolytic capacity; in return, some myelin proteins released from damaged myelin sheaths are potent to stimulate MC degranulation [133]. MC chemokines, among these mainly CCL2, CCL3, CCL4, CCL5, and IL-16, enhance T cell recruitment to the site of inflammation [134]. Additionally, MCs acting as APCs activate T cells through presentation of myelin antigens to T cells [135, 136]. In this regard, MCs express a large number of costimulatory molecules, including 4-1BB, CD40L, OX40L, CD80, CD86, and CD153, to activate T cells [137] (Fig. 6b).

Cancer and Tumor Progression

The complex role of MCs in shaping tumor microenvironment and interactions with a variety of tumor resident cells such as infiltrating immune cells, and tumor cells and, as well as the extracellular matrix have been investigated [138]. MCs can be recruited to the tumor microenvironment by tumor-derived SCF. In cancer biology, mediators released from MCs are described to be involved in angiogenesis, the growth and survival of tumor cells, invasion, and metastasis [139]. In a tumor with MC-remodeled microenvironment, NF-κB and AP-1 have intensified activity. Additionally, suppression of T cells and natural killer (NK) cells is exacerbated in such a microenvironment [140]. Among the cytokines contributing to tumor inflammation, TNF-α, IL-6, VEGF, iNOS, Cox-2, and MMP-9 can be produced by MCs [140]. Histamine may have a modulatory role in the chronic inflammatory responses associated with developing neoplasms through having interaction with its four G protein–coupled receptors. Histamine by acting via H1R regulates T cell polarization, in favor of enhancing Th1 responses. Additionally, while acting via H2R, histamine inhibits both Th1 and Th2 responses. Moreover, MC-released histamine plays a role in MC/peripheral monocytes interactions through acting on monocyte expressed H2R. Histamine also promotes IL-10 production and reduces the secretion of IL-12, and polarizes the skewness of engaged naive CD4+ T cells toward a Th2 phenotype [139]. Tryptase activates latent MMPs that is associated with the ECM degradation, vascular tube formation, and release of angiogenic compounds [141]. MCs-Treg cells crosstalk through the OX40/OX40 ligand (OX40L) axis to inhibit histamine release in anaphylactic reactions. In the presence of IL-6, MCs can revert Treg cell suppressive activity triggering OX40 on their membrane and promote Treg cells into pro-inflammatory cells which produce IL-17 [139]. It should be considered that Tregs may have a different profile of released cytokines in different models of cancers, thus may act in favor of suppressing the anti-tumor responses or support pro-inflammatory responses. For example, adenomatous polyp resident Tregs shift their production of IL-10 to IL-17 [142]. The interaction between MCs and MDSCs with CD14 + CD19 + HLA-DR−/low phenotype is thought to shape an immunosuppressive microenvironment at least in patients suffering from colon cancer and melanoma. MDSC-derived IL-17 actively recruits IL-9 producing Treg cells that provide IL-9 for the survival of tumor resident MCs [143]. The SCF produced by tumor cells not only acts as a survival factor for MCs but even promotes the production of MCs MMP-9 by these cells. MMP-9 is capable of clipping the membrane-bound SCF expressed by tumor cell that consequently promotes bioavailability of SCF. Tryptase when secreted from activated MCs enhances the activity of tumor cell COX through interacting with the PAR-2 receptors. In return, COX mediates the production of PGE-2 and activates MCs to secrete VEGF that induces the tumor angiogenesis [144] (Fig. 7a).

Wound Healing

MCs also participate in overlapping phases of wound healing including inflammation, proliferation, and remodeling [145]. Injury is capable of triggering MC activation after which release of preformed or de novo synthesized mediators occurs [145]. MC-derived histamine induces capillary permeability



◀ **Fig. 7** **a** Tumor cells facilitate the infiltration of MCs into tumor and contribute to their survival by releasing SCF. OX40-OX40L interaction between Tregs and MCs results in releasing suppressive cytokines by Tregs that suppress CD4 and CD8 T cell activities. MCs contribute to neo-angiogenesis via secreting mediators and they also play a role by releasing proteases and MMPs to modify the ECM. The interaction among tumor-infiltrating MCs, MDSCs, and Tregs results in formation of a highly immunosuppressive microenvironment and evade of tumor cells from immune response. **b** MCs participate in all stages of wound healing by releasing mediators involved in immune cell recruitment, activation, and proliferation of fibroblasts and their differentiation into myofibroblasts, collagen synthesis, and neo-angiogenesis

and vasodilation that promote neutrophil influx to the site. MC released vascular endothelial growth factor (VEGF), and IL-6 and IL-8 also have vasoactive bioactivity [146]. Tryptase binding to PAR2 on endothelial cells causes vasodilatation that facilitates the infiltration of neutrophils and other inflammatory mediators into the injury site [147]. During the proliferative stage, keratinocytes attract MCs toward the epidermis by releasing SCF. Histamine and tryptase stimulate dermal fibroblasts to release growth factors including FGF-2 or FGF-7, respectively [103]. MCs are able to promote the fibroblast proliferation via releasing VEGF, IL-4, and basic fibroblast growth factor (bFGF) [148, 149]. Owing to chemotactic and mitogenic effects of tryptase on fibroblasts, MCs interact actively with them and participate in fibroblast biological functions mainly synthesis of collagen, contraction, and terminally differentiation into myofibroblasts [81]. MC mediators including IL-8, IL-4, NGF, FGF-2, PDGF, TGF-β, and VEGF participate in neo-angiogenesis, fibrinogenesis, or re-epithelization, the biological functions and processes required to proceed and finalize the wound repair [150, 151] (Fig. 7b).

MCs Crosstalk with Immune Cells

Interaction with the Innate Immune System

MCs have crosstalk with myeloid-derived suppressor cells (MDSCs) and support not only their mobilization and infiltration into the tumor but also promote their ability to produce IL-17. MDSCs, in turn, attract Tregs and stimulate them to produce IL-9, a survival factor for MCs [152]. MC-released histamine induces MDSC activation, proliferation, and IL-4 and IL-13 production through acting on MDSC surface–expressed H1R and H2R receptors. This enhanced cytokine production results in the skewing of immune responses toward Th2 which supports occurrence of allergic events [153]. MCs and DCs gather around environmental interfaces and MC-derived soluble promote DC activation, migration to lymph nodes, and facilitate the process of Th2 polarization. Recently, Carroll-Portillo et al. reported a direct intercellular crosstalk through an immunological synapse between MCs and DCs. A formation of synapses promotes the exchange of MC internalized–

specific antigen and transfer it to surrounding DCs to be processed and presented to T cells for the purpose of their activation [154]. MC-derived IL-10 reduces DC migration, maturation, and activation while it enhances DCs ability of reducing T cell proliferation and cytokine production by downregulation of co-stimulatory molecule expression by DCs [98]. MCs released TNF-α and IL-1 promote DC migration and maturation; furthermore, cytokines including IL-18 and IL-16, CCL5, and PGE2 facilitate DC migration [155]. MC-derived TNF-α and IL-6 are involved in monocyte and macrophage activation and the local recruitment of neutrophils [156]. MC-derived IL-10 is potent to suppress the cytokine production by monocytes [98]. Upon LPS stimulation through TLR4/MyD88 signaling pathway, MCs and macrophages release CXCL1 and CXCL2 capable of binding to CXCR2 receptor through which they recruit neutrophils to the site [157]. MC-released MCP-6, tryptase β2, and IL-5 are potent to recruit eosinophils [158]. A major role of MCs in innate immunity is to enhance the local recruitment of neutrophils by secreting TNF-α, which can either enhance host resistance or contribute to pathology [159]. Additionally, MC-derived mMCP-6 contributes to the recruitment of neutrophils to sites of bacterial infection [40]. MC interactions with ILCs include the production of PGD2 by MCs through which they promote the chemotaxis of ILC2s. Moreover, MCs upon becoming activated via IgE/FcεRI signaling or in response to extracellular ATP release IL-33 which induces the production of IL-13 by ILCs. The latter cytokine contributes to the restriction of helminth infection. MCs, after becoming activated by IL-9 from IL-33-elicited ILC2s, produce IL-2, which in return promotes the expansion of CD25+ ILC2 population [160] (Fig. 8).

Interaction with the Adaptive Immune System

MCs have surface expression of both MHC I and II molecules, and by having interaction with T cell–expressed TCRs, they induce antigen-specific clonal expansion of T cells [8]. Having direct interaction with CD4+ T cells via MHC II and OX40L and also releasing TNF-α, MCs augment their own activation, proliferation, and cytokine secretion (e.g., IL-22, IFN-γ) [8]. MCs promote the recruitment of CD8+ T cells by releasing CCL5 and LTB4 [8]. Tregs promote MCp recruitment to the lung during allergic inflammation, while Treg-derived IL-9 promotes recruitment of MCs into transplanted allografts, important for maintaining allograft tolerance [161]. Engagement of OX40L (expressed on MCs) and OX40 (expressed on Tregs) [152] is a mechanism through which Treg can suppress IgE-mediated MC degranulation [162]. Additionally, IL-10 and TGF-β secreted by Tregs have been shown to inhibit the FcεRI expression by MCs [163]. Moreover, MC-derived TGF-β contributes to generation of Tregs [106]. MCs augment IgE production of B cells by releasing IL-13 and IL-4 and expressing CD40L [98] (Fig. 8).

Mast Cells and Host Defense

Mast Cell Recognition of Microbial Infection

MCs express a broad range of cell surface receptors. These receptors are actively involved in the detection of harmful pathogenic microorganisms including viruses, parasites (mainly helminths), and bacteria. MCs respond to pathogens after detecting them by releasing mediators including TNF-α, LTs, and proteases as well as recruiting immune cells mainly neutrophils and DCs. MCs respond to microbial structures and products by recognizing PAMPs by the help of "pattern recognition receptors" (PRR). The main classes of PRRs are (1) "Toll-like receptors" (TLRs) which are expressed on plasma membrane or membrane of cytoplasmic endosomes and (2) the cytoplasmic "nucleotide-binding oligomerization domain" (NOD)-like receptor (NLRs) [62]. TLRs are defined as type-I transmembrane proteins possessing ectodomains containing leucine-rich repeats, which enable them to recognize the PAMPS and DAMPs. Over time, TLR1 to TLR9 conserved their structure in both mice and humans. However, in mice, TLR-10 is nonfunctional due to the presence of a retroviral insertion. TLR-11, TLR-12, and TLR-13 have not yet been determined in humans. TLR1, TLR-2, TLR-4, TLR-5, TLR-6, and TLR-10 are known to be widely expressed on the plasma membrane, while TLR3, TLR-7, TLR-8, TLR-9, TLR-11, TLR-12, and TLR-13 are expressed in the endosome [164]. TLRs are able to bind to diverse molecular structures, including lipids (TLR4: LPS via MD2; TLR2: lipoproteins), proteins (TLR5: flagellin; TLR2 and TLR4: HMGB1), and nucleic acids (TLR3: dsRNA; TLR7/8: ssRNA; and TLR9: unmethylated CpG motifs in bacterial, viral, and fungal DNA) [165]. Generally, the strength of signal generated by engaging TLRs is below the threshold needed for triggering calcium flux and granule exocytosis in MCs, except TLR2 [166]. TLR2 (through inducing the production of IL-6) and TLR4 signaling is significantly dominant in MC-mediated immune responses against bacteria. Interestingly, "lipopolysaccharide" (LPS)-TLR4 interaction has been shown to stimulate rodent MCs and promoting the cytokine production without occurrence of degranulation. In contrast to TLR-4, stimulation of MCs through TLR2 peptidoglycan interaction induces both degranulation and cytokine production [167]. MCs benefit largely from a wide range of proteins including immunoglobulins, complement components, and surfactant lipoproteins, which serve as opsonins to indirectly recognize and interact with bacteria [168].

Mast Cells and Defense Against Bacterial Infection

In addition to recognizing bacteria, MCs can recognize and respond to other dangers such as toxins. For instance, binding the Vibrio cholerae toxin-Ganglioside GM1 selectively

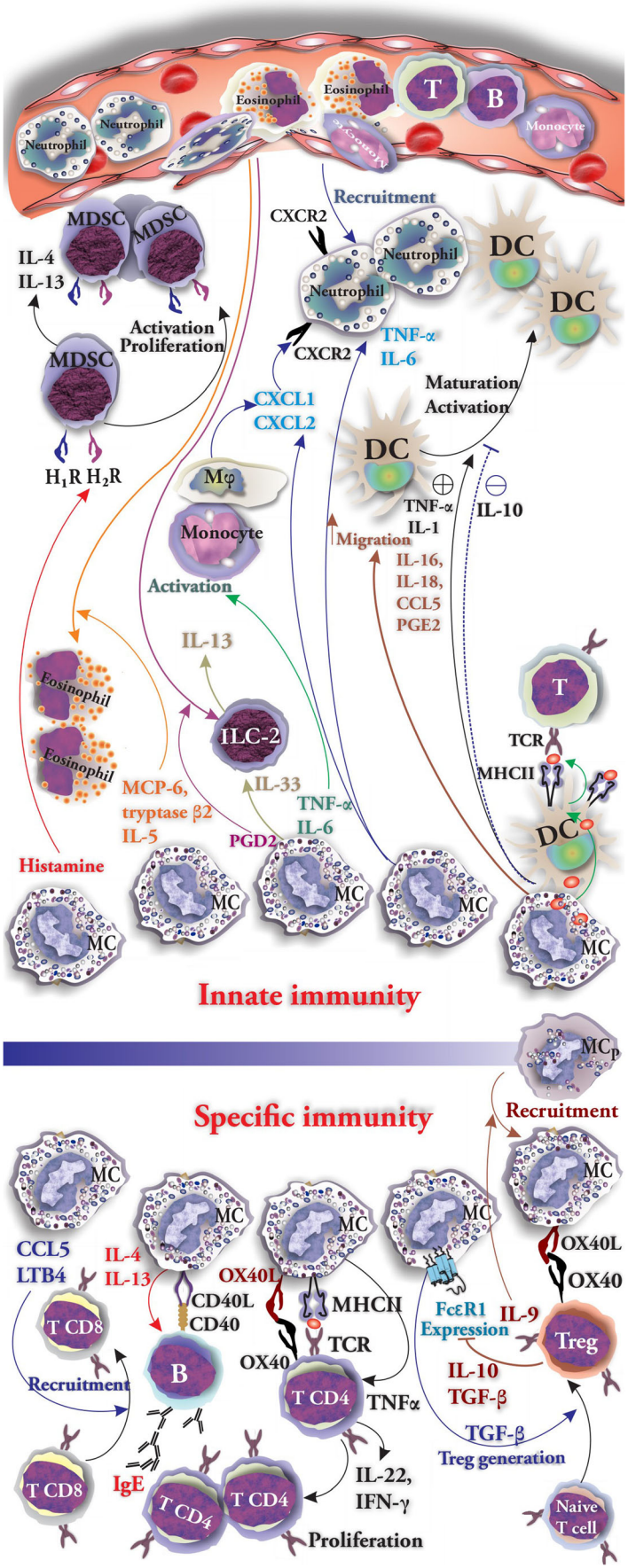


Fig. 8 MCs interact with cells of both the innate and adaptive immune system by releasing activating or suppressing mediators or engaging surface expressed receptors to have direct cell-to-cell interaction

promotes IL-6 production, while hampering the production of other mediators. Another example is *Clostridium difficile* toxin that induces MC degranulation after binding neurokinin-1 [168]. During bacterial infection, MCs are activated by engaging complement receptors (CRs), capable of being directly activated by bacterial products and expressed molecules including CD48 (bacterial expressed FimH receptor) [169]. Carlos et al. reported that MC activation results in acquiring resistance during infection with *Mycobacterium tuberculosis*. Their studied TLR2$^{-/-}$ mice showed increased mycobacterial load, deficient recruitment of myeloid cells, and pro-inflammatory cytokine production. Adoptive transfer of TLR2$^{+/+}$ MCs could effectively correct the susceptibility of TLR2-deficient mice to MTB infection [170]. MC-derived TNF-α is an effective neutrophil recruiting mediator to infection sites. Interestingly, MCs play an active role in antibacterial defense possessing bactericidal activity (e.g., by releasing cathelicidins or proteases). MC proteases have been reported to play a role in the control of gut infections. Mouse tryptase mMCP6 (but not the related protease mMCP7) attracts neutrophils when injected into the peritoneal cavity. Moreover, Mcpt6 $^{-/-}$ mice clear *Klebsiella pneumoniae* inefficiently and are more likely than +/+ mice to die following an injection of *K. pneumoniae* into the peritoneal cavity [93]. Following intranasal/intraperitoneal inoculation with *K. pneumoniae*, IL-6$^{-/-}$ mice are less likely to survive than wild-type controls. At the time of death, IL-6$^{-/-}$ mice were found to have higher bacterial load but not inflammatory cells in lungs and peritoneum [171]. Junkins et al. used MC-deficient Kit$^{W\text{-}sh}$/Kit$^{W\text{-}sh}$ mice model to investigate the MCs capability in microbial defense against *Pseudomonas aeruginosa*. They found MC-deficient mice with greatly increased bacterial dissemination, epithelial permeability, and neutrophil load when compared with WT control group after *P. aeruginosa* infection. In their study, MCs were shown to reduce *P. aeruginosa*–mediated epithelial cell apoptosis and TNF production by epithelial cells [172]. Investigation of MCs involvement in skin immune defense in lesions induced by *P. aeruginosa* in MC-deficient Kit^{W}/Kit$^{W\text{-}v}$ mice, normal Kit$^{+/+}$ mice, and MC-reconstituted Kit^{W}/Kit$^{W\text{-}v}$ mice suggested endothelin-1 as a possible mediator to induce activation of MCs to augment neutrophil recruitment to infection sites and therefore bacterial clearance [173].

Mast Cells and Defense Against Viral Infection and Toxins

In the context of viral infection, the TLR3-dependent activation of MCs by viruses hampers their capacity to attach to fibronectin and vitronectin. Additionally, TLR3 activation abrogates MC attachment–dependent potentiation of IgE-mediated responses. MCs produce type I IFNs in response to engaging endosomal TLR3 upon exposure to double-stranded RNA [169]. Moreover, exposure to gp120 envelope protein of HIV promotes IL-4 and IL-13 production by MCs [169]. It has been proposed that MCs in HIV/AIDS act as inducible reservoirs of infectious viral clones. Gp120 is capable of activating MCs and basophils, via IgE binding to FcεRI. Consequently, a Th2-dominated response is generated that may downregulate the protective anti-viral immune responses [174]. MCs produce IFN in response to viral infection when stimulated through TLR3 and can modulate T cell responses to viral infections [175]. MC-derived TNF-α and IL-6 are able to protect mice from HSV-induced mortality. This has been reported after intradermal injection with HSV-2 into MC-deficient Kit^{W}/Kit$^{W\text{-}v}$ mice [176]. Various microbes employ distinct mechanisms to suppress the role of MCs in host defense. For instance, the ES-62 protein, secreted by nematodes, is able to degrade PKC-α, an intermediate molecule in MC-activating cascade. M. Toxoplasma employs unknown factors to suppress MC degranulation by inhibition of signaling through tyrosine phosphorylation [177]. MCs may also play a protective role. In mouse models, MCs can protect from envenomation from bee [178] and scorpion stings, and snake bites [179]. For instance, MC-Carboxypeptidase 3 can degrade the snake venom toxin safarotoxin [109].

Conclusion

MCs, tissue-localized cells of hematopoietic origin, are best known for their harmful effects when eliciting immediate hypersensitivity reactions. However, in recent times, they have gained attention as major effector cells in numerous other pathological but also physiological situations. Owing to the expression of a variety of receptors and a wide spectrum of mediators, MCs play a role in many inflammatory diseases, tissue remodeling, and anti-tumor immune responses. Moreover, they continue to play a crucial role in antimicrobial defense and tissue repair mechanisms due to their anatomical distribution at sites that exhibit direct interaction with the surrounding environment. The current knowledge of MC biology is based on four techniques, namely (1) transgenic and mutant mice, (2) human and mouse MC lines, (3) MC targeting antibodies, and (4) pharmacological strategies to modulate MC activation or mediator effects. Current insights into the role of MCs in the pathophysiology of variety of MC-involved diseases are mostly gained through investigations on animal models and the extension of these roles to human diseases requires further cellular and molecular investigations. According to the complexity of immune responses orchestrated by MCs due to expression of variety of receptors some of which have recently determined, and the differences in degranulation profile of MCs subsets in response to different stimuli, it should be considered that implying the in vitro

laboratory results to clinically significant disorders needs further investigation to avoid any unwanted extrapolation.

Authors' Contributions Daniel Elieh Ali Komi, Stefan Wöhrl, and Leonard Bielory have been directly involved in the preparation of the manuscript. Daniel Elieh Ali Komi has designed and created the figures. Leonard Bielory and Stefan Wöhrl have reviewed, revised, and added inputs.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent No informed consent was required to prepare the manuscript.

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