Regulation of the pleiotropic effects of tissue-resident mast cells

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Mast cells (MCs), which are best known for their detrimental role in patients with allergic diseases, act in a diverse array of physiologic and pathologic functions made possible by the plurality of MC types. Their various developmental avenues and distinct sensitivity to (micro-) environmental conditions convey extensive heterogeneity, resulting in diverse functions. We briefly summarize this heterogeneity, elaborate on molecular determinants that allow MCs to communicate with their environment to fulfill their tasks, discuss the protease repertoire stored in secretory lysosomes, and consider different aspects of MC signaling. Furthermore, we describe key MC governance mechanisms (ie, the high-affinity receptor for IgE [FcεRI]), the stem cell factor receptor KIT, the IL-4 system, and both Ca^{2+}- and phosphatase-dependent mechanisms. Finally, we focus on distinct physiologic functions, such as chemotaxis, phagocytosis, host defense, and the regulation of MC functions at the mucosal barriers of the lung, gastrointestinal tract, and skin. A deeper knowledge of the pleiotropic functions of MC mediators, as well as the molecular processes of MC regulation and communication, should enable us to promote beneficial MC traits in physiology and suppress detrimental MC functions in patients with disease. (J Allergy Clin Immunol 2019;144:S31-45.)

Key words: *FcεRI, stem cell factor, IL-4, calcium signaling, phosphatases, chemotaxis, tryptase, chymase, integrins, Toll-like receptors, ion channels*

Abbreviations used

BM:	Bone marrow
CPA3:	Carboxypeptidase A3
CRAC:	Ca^{2+} release–activated Ca^{2+}
CTMC:	Connective tissue mast cell
DUSP:	Dual-specificity phosphatase
ERK:	Extracellular signal-regulated kinase
GPCR:	G protein–coupled receptor
HSC:	Hematopoietic stem cell
IP_3:	Inositol-1,4,5-trisphosphate
MAPK:	Mitogen-activated protein kinase
MC:	Mast cell
MC_C:	Mast cell expressing only chymase
MCp:	Mast cell precursor
MC_T:	Mast cell expressing only tryptase
MC_{TC}:	Mast cell expressing tryptase and chymase
MMC:	Mucosal mast cell
mMCP:	Mouse mast cell protease
MyD88:	Myeloid differentiation response gene–88
PEP:	PEST domain–enriched tyrosine phosphatase
PLC:	Phospholipase C
PMC:	Peritoneal mast cell
SCF:	Stem cell factor
SOCE:	Store-operated Ca^{2+} entry
S1P:	Sphingosine-1-phosphate
TLR:	Toll-like receptor
TRIF:	TIR domain-containing adapter inducing IFN-β
TRP:	Transient receptor potential
TULA-2:	T-cell ubiquitin ligand 2

HETEROGENEITY OF MAST CELLS

The term mast cell (MC) describes a highly heterogeneous cell population. Numerous MC subtypes have now been characterized in both human subjects and animals based on differences in cell morphology, histochemical properties, protease content in granules, piecemeal or anaphylactic types of degranulation, receptor expression, and function.[1,2] A certain subtype plasticity has been recognized depending on the tissue environment, and *in vitro* MCs change their phenotype depending on culture conditions.[3-5]

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In addition to intraspecies heterogeneity, interspecies heterogeneity has been discovered.[6] This is of relevance because a large part of the scientific literature on MCs is based on animal work, in particular mouse studies. Data on human MCs are scarce because they are difficult to collect from tissue sources. Therefore many laboratories use genetically transformed human MC lines instead of primary MCs from tissue or immature MCs derived from bone marrow (BM) or peripheral blood that are partially maturated under particular culture conditions. Although it is well known that such MCs differ functionally from primary tissue MCs, they have nonetheless provided useful insights into the regulation and function of human MCs.

MC subtypes in human subjects

Human MCs can be characterized according to the types of proteases they contain, such as mast cells expressing tryptase and chymase (MC_{TC}s), mast cells expressing only tryptase (MC_Ts), and the rare mast cells expressing only chymase (MC_Cs). MC_{TC}s are located at nonmucosal sites (in the skin, the submucosa, adjacent to blood vessels, and in the peritoneum in mice), whereas MC_Ts are primarily found at mucosal sites (nose, lung, and intestine).

Further division of these subtypes into site-specific populations has been proposed to reflect the microenvironment of the anatomic compartments where they are localized, such as "lung MC_T" to reflect prevalence in the bronchi, bronchioles, and alveolar parenchyma and "MC_{TC}" to denote abundance in pulmonary vessels and the pleura. Within each MC_{TC} and MC_T population, there are also distinct localization-specific expression patterns of receptors, enzymes, and growth factors that can be used for further characterization. For instance, bronchial MC_Ts consistently express more histidine decarboxylase than alveolar MC_Ts, whereas for both MC_{TC}s and MC_Ts, the high-affinity receptor for IgE (FcεRI) is highly expressed in conducting airways but virtually absent in alveolar parenchyma.[7] It is not only the tissue site but also the disease status that influences MC heterogeneity. In patients with poorly controlled, severe, T_H2-associated asthma, an altered subtype that could play a role in the pathophysiology of this disease[8] has been described to express tryptase, chymase, and/or carboxypeptidase A3 (CPA3). Genetic analyses have revealed even more heterogeneity among MCs from different sites within one tissue, although the clinical implications are yet unclear.[9]

MC subtypes in rodents

In mice and rats MCs are traditionally subtyped into connective tissue mast cells (CTMCs) and mucosal mast cells (MMCs) based on their histochemical properties, mediator content, and functional properties.[10] CTMCs can be stained with both Alcian blue and safranin, whereas MMCs can only be stained with Alcian blue. In terms of their mediator content, heparin proteoglycans predominate in CTMCs, whereas chondroitin sulfate predominates in MMCs. In their functional properties CTMCs typically contain rodent tryptases, chymases, and CPA3, whereas MMCs contain chymases only and thus differ fundamentally from their human counterparts in mucosal tissues that contain tryptase only. The subtyping of murine MCs into CTMCs and MMCs might be an oversimplification for the mouse intestine and peritoneum but not for the lung.[11]

REGULATION OF MC DEVELOPMENT

Development of MCs can be subdivided into 3 major steps: differentiation of hematopoietic stem cells (HSCs) to mast cell precursors (MCps) in the BM, distribution of MCps through blood and transendothelial migration into target tissues, and eventually phenotypic maturation in different tissues. Although there are still certain discrepancies concerning our understanding of MCp development in the BM, it is justified to suggest that committed MCps stem from bipotent progenitors endowed with the capacity to differentiate into both MCs and basophils, as has been studied in mice.[12]

Expression of the receptor tyrosine kinase KIT for MC development is mandatory. Likewise, expression of the KIT ligand stem cell factor (SCF) is obligatory for MC development *in vivo*. Mature MCs are usually characterized by their expression of KIT and FcεRI, as well as distinct metachromatic cytoplasmic granules. MCps do not necessarily express FcεRI and are typically not identifiable by means of metachromatic staining, indicating that commitment to the MC lineage occurs before FcεRI expression. Indeed, early committed MCps lack FcεRI expression but show KIT expression.[13] Hence MCps ready to leave the BM can be either FcεRI positive or FcεRI negative. Less is known about committed MCps in human subjects, although an immature human MCp population, similar to mouse MCps in terms of amount and developmental state, has recently been identified in human blood. These have been reported to be lineage-negative $CD34^{hi}KIT^{int/hi}Fc\varepsilon RI^{+}$ cells and to give rise only to granulated tryptase-positive $KIT^{+}Fc\varepsilon RI^{+}$ MCs.[14] Interestingly, the frequency of development of such MCs starting from a lineage-negative $CD34^{hi}KIT^{int/hi}Fc\varepsilon RI^{-}$ cell subset was reduced by more than a factor of 10, indicating the importance of FcεRI expression for MC commitment.

After leaving the BM, MCps are distributed through the blood to their target tissues. This requires productive interaction between surface molecules of MCps and endothelial cells for transendothelial migration. Homing of MCps to the small intestine requires expression of the α4β7 integrin on MCps[15] and mucosal vascular addressin cell adhesion molecule 1 and vascular cell adhesion molecule 1 as counterligands on intestinal endothelial cells for interaction.[15,16] Integrin activation requires chemokine receptor–mediated inside-out signaling by CXCR2 expressed on MCps.[16] Although β7 integrin–deficient mice showed impaired MCp homing to the intestine, homing to the lung was still possible, although reduced. By using a model of ovalbumin-induced allergic airway inflammation, pulmonary recruitment of MCps was shown to depend on both α4β7 and α4β1 integrins on the MCps and on vascular cell adhesion molecule 1 on the endothelial side.[17] The same transmigration mechanism was recently demonstrated in influenza A–infected mice.[18]

Homing of MCps to the small intestine occurs in a constitutive manner in naive mice,[15] although it can be amplified by inflammatory conditions. In contrast, in the lung the numbers of MCps that home constitutively is strongly exceeded by numbers recruited on inflammation in a T cell–dependent manner.[19] In addition to the intestine and the lung, the skin is an important

MC-containing tissue. However, less is known about MCps homing to the skin, although a promoting role for the fractalkine receptor CX3CR1 on MCps has been suggested.[20]

After migration to their respective tissues, MCps differentiate into 2 major subclasses of mature tissue MCs: MC_{TC}s and MC_Ts (see the section "Heterogeneity of mast cells"). Finally, maturation of MCs, both *in vitro* and in different tissues, is associated with downregulation of cell-surface adhesion molecules and chemokine receptors. As an example, primary peritoneal and pulmonary MCps from naive mice express considerably higher levels of β7 integrin than the respective mature MCs.[21] Moreover, analysis of MCps and mature MCs differentiated *in vitro* from human cord blood revealed expression of 4 different chemokine receptors (CXCR2, CCR3, CXCR4, and CCR5) on MCps, whereas only CCR3 was retained on mature MCs.[22] Generally, expression of plasma membrane proteins important for migration changes during MC maturation.

Very recently, with the aid of a new hematopoietic fate mapping model, murine MCs were demonstrated to have dual developmental origins arising through both primitive (yolk sac–derived) and definitive (HSC-derived) hematopoiesis.[23] MC maintenance in adult tissues was found to occur largely independent of the BM, probably through proliferation of tissue-resident MCps differentiated from HSCs during embryogenesis.[23] This intriguing study proves that much more remains to be discovered in MC development and migration to target tissues, and it would be exciting to learn about the respective processes in human subjects.

REGULATION AND FUNCTION OF MC PROTEASES

Proteases, particularly tryptases, chymases, and CPA3, expression of which is largely restricted to MCs, contribute importantly to the pleiotropic effector functions of these cells. Proteases are the major proteins of MC secretory granules, which also contain histamine, serotonin, and proteoglycans. After release by means of degranulation, these proteases primarily exert proinflammatory functions and have been implicated in the pathogenesis of MC-related disorders, but they also contribute to tissue homeostasis and host defense.[24-26]

Human MCs express 4 tryptases (α, β, γ, and δ), 2 proteases with chymotrypsin-like activity (chymase and cathepsin G [also expressed in neutrophils]), and CPA3. Tryptase β, which forms noncovalent tetramers with limited trypsin-like activity, is considered the prototypical and biological active "tryptase."[27,28] Tryptase α can assemble to virtually identical tetramers but is inactive.[29] Tryptase δ lacks the C-terminal 40-amino-acid residues,[30] and from a structural point of view, its folding and activity are enigmatic. Tryptase γ is less closely related to the other tryptases, and it is likely membrane bound in a monomeric form.[31] Although chymase and CPA3 are exclusive to MCs, chymase, cathepsin G, and CPA3 are usually expressed only in the MC_{TC} subset of MCs. MCs with distinct protease expression patterns, such as chymase-only MCs[32] and, more recently, $CPA3^+$ MC_Ts have been described in patients with eosinophilic allergic inflammatory disorders.[33,34]

Comparative genomic analysis has shown that tryptases and chymases are poorly conserved between human subjects and rodents and even between human subjects and chimpanzees.[35] The mouse genome encodes 4 tryptases: mouse mast cell protease (mMCP) 6, mMCP-7, mMCP-11, and tryptase γ/transmembrane tryptase. mMCP-6 is most likely the functional counterpart of human tryptase β, whereas mMCP-7 apparently is dispensable and not expressed in some mouse strains, such as C57BL/6.[36] The chymase locus has expanded considerably and encodes 7 chymases: mMCP-1, mMCP-2, mMCP-4, mMCP-5, mMCP-8, mMCP-9, and mMCP-10. mMCP-4 appears to be the functional counterpart of human chymase, whereas its rodent orthologs mMCP-5 and rMCP-5 have altered elastase-like activity.[37,38] Instead of being expressed in MCs, mMCP-11 and mMCP-8 are preferentially expressed in basophils,[39,40] which are virtually devoid of tryptases and chymases in human subjects. In contrast to the heterogeneity of tryptases and chymases, a single CPA3 gene is expressed in human subjects and rodents.

Considering their role in host defense versus their proinflammatory potential, it is not surprising that the expression and activity of MC proteases is extensively regulated. On the genomic level, the variation of α- and β-tryptases is complex: of the 4 tryptase genes (*TPSAB1*, *TPSB2*, *TPSG1*, and *TPSD1*), *TPSAB1* and *TPSB2* can harbor alleles encoding enzymatically active β, inactive α, or deficiency alleles.[41] All subjects initially surveyed have 2 to 4 β alleles, suggesting that the β allele has essential functions, whereas the enzymatically inactive α allele is dispensable.[41] Recently, subjects with duplications or triplications of the α-encoding *TPSAB1* gene, increased basal serum tryptase levels, and multisystem complaints have been identified, a trait now classified as hereditary α-tryptasemia syndrome.[42] On the level of gene regulation, expression of human tryptase, its mouse counterpart mMCP-6, and several mouse chymases is driven by the microphthalmia-associated transcription factor, which is also central to the development of MCs.[43,44] Posttranscriptional and posttranslational mechanisms contribute to this regulation and result in an increased number of tryptase species. For example, alternative splicing of human α- and β-tryptases has been reported, which likely affects the tetrameric architecture, stability, and enzymatic activity of these proteins.[45] Posttranslational processing further results in several forms of the proteins with slight differences in glycosylation, charge, and enzymatic activity.[46] In contrast to most other proteases, tryptases and chymases are not regulated at the level of zymogen activation. Rather, they are activated by cathepsin C and potentially by other cathepsins before storage in granules, a feature shared with other "granule-associated serine proteases of immune defense."[47,48] Within the granules, the activity of tryptases and chymases is likely controlled by compartmentalization, its acidic pH, and its close packaging. After degranulation, binding to high-molecular-weight proteoglycans continues to modulate diffusion, activity, and substrate specificity. In particular, the active β-tryptase tetramer requires stabilization by bound proteoglycans that protect it from dissociation into (almost) inactive monomers. Enzymatically active monomers with altered substrates and inhibition profiles can be formed *in vitro*,[49] but these remain to be demonstrated *in vivo*. Tetramerization is likely the main mechanism regulating tryptase β activity and selectivity *in vivo* because it restricts the access of large substrates to the active sites located within the central pore and sterically blocks inhibition by most protease inhibitors.[26,28,50] Monomeric chymases are more prone to inhibition by tissue- and plasma-derived inhibitors, but they can evade inhibition by inactivating serpins and they can retain some activity when in circulation in an α_2-macroglobulin complex.[51]

MC RECEPTORS AND SIGNALING

Immunoglobulin receptor signaling and function

MCs express FcεRI and several IgG receptors (FcγRs) on their surfaces.[52,53] FcεRI is a tetramer consisting of an α-chain that binds IgE, a membrane transversing tetraspanin β-chain, and a homodimeric disulfide-linked γ-chain.[54,55] IgE is bound at 1:1 stoichiometry at very high affinity ($K_a \geq 10^{10}\ M^{-1}$). Binding of low doses of monomeric IgE to FcεRI provides an MC survival signal,[56] and IgE levels affect surface expression of FcεRI.[57,58] Low binding of IgE or antigen to FcεRI triggers expression and secretion of chemokines and other mediators, whereas optimal binding triggers degranulation.[59] Supraoptimal cross-linking can suppress MC activation.[60] Human MCs express FcγRIIA, FcγRI, or both. Both receptors can stimulate degranulation and cytokine gene expression. In mice FcγRIIB, which is expressed also on human MCs, acts as an inhibitor, and FcγRIII is stimulatory on degranulation.

After cross-linking by antigen, IgE-prebound FcεRI is phosphorylated by the kinase LYN at tyrosine residues in the immunoreceptor tyrosine-based activation motifs of the β- and γ-chains. This is followed by activation of SYK and other kinases. The core signaling pathways have been extensively reviewed elsewhere.[53,55,61] The relationships among the 2 classes of enzymes, other kinases and phosphatases that control MC function, are complex and sometimes hierarchical. Much has been learned from "knockout" or "knockdown" models, which need to be interpreted with caution because compensatory mechanisms might be turned on. The balance of specific signaling pathways emanating from FcεRI depends on the MC type, its site of residence, its FcεRI-independent activation status, and other biological parameters.

Cross-linking of FcεRI by IgE/antigen complexes causes it to translocate into lipid rafts.[62,63] LYN is tethered to the cytoplasmic membrane through acylation and coassembles in lipid rafts, which promote high local concentration of receptor and kinase, resulting in efficient phosphorylation of FcεRI. Other components of the FcεRI signalosome are embedded in these membrane domains as well, such as the transmembrane adapter proteins, LAT and NTAL. Not only are some proteins included in lipid rafts when FcεRI becomes cross-linked, but also others, such as certain phosphatases, are excluded from lipid rafts.[64] Thus formation of these lipid-protein domains provides a versatile mechanism for the regulation of FcεRI signaling. Other signals that modulate FcεRI-mediated degranulation likely include cell-cell contact-dependent signals from adhesion receptors (RJ; own unpublished results). Embedding MCs in appropriate tissue niches and thereby controlling MC activation might be an important mechanism to keep degranulation under finely balanced control. Many other factors that regulate the final outcome of FcεRI signals are incompletely understood, such as noncoding RNAs, membrane biophysics, intracellular liquid-phase separation, and physical interactions with other cells, including immune and nonimmune cells.

A large range of compounds from plant molecules to bacterial substances and snake venoms but also complement, Toll-like receptor (TLR) ligands, and other stimuli, such as pressure or heat, can cause MC exocytosis.[65] Thus a plethora of receptors can trigger MC degranulation independently of or in conjunction with FcεRI. MC FcεRI-mediated degranulation can also be facilitated by other pathways. Examples, such as SCF (see the section "Cytokine receptor signaling and function"), prostaglandins, nucleotides, interleukins, and chemokines illustrate the wide spectrum of ligands that modulate MC activity.[66]

MCs, at least BMMCs, can be desensitized by various pathways to keep FcεRI signaling and thus degranulation under control.[67,68] Low-dosage exposure to monomeric IgE, IgE-bound antigen, or anti-Fc receptor antibodies reduces FcεRI sensitivity.[69,70] Activation of the single-chain FcγRIIB by cross-linking it to FcεRI through immune complexes made of the immunoglobulin Fc fragments Fcγ and Fcε blocks phosphoinositide 3-kinase–mediated FcεRI signaling.[71] FcεRI can be downregulated by means of internalization, followed by either degradation or recycling to the cell surface.[61,72,73] Ubiquitination and neddylation are key signals for these endocytic processes and/or the potential subsequent lysosome- or proteasome-mediated degradation of the Fc receptor complexes.[63] Furthermore, signaling through cross-linked FcγRs can induce BMMC apoptosis.[74]

Cytokine receptor signaling and function

SCF, IL-4, and IL-33 are major cytokines regulating MC mediator release. SCF acts not only as an MC growth, survival, and chemotaxis factor but also as a regulator of mediator release by either enhancing IgE-dependent responses (both degranulation and production of leukotrienes and cytokines) or directly inducing cytokine production and release.[75,76] Mechanisms of activation of the SCF receptor KIT in MCs are quite well understood and have been reviewed elsewhere.[77,78] In contrast to the acute effects of SCF stimulation, chronic SCF treatment results in suppression of FcεRI-mediated MC activation caused by significant attenuation of cytoskeletal reorganizations.[79]

In a comparable manner acute IL-33 stimulation of MCs augments antigen-triggered cytokine production, as studied in BMMCs and human umbilical cord blood–derived MCs.[80,81] Interestingly, KIT has been shown to interact constitutively with the β-chain of the IL-33 receptor IL-1 receptor accessory protein, and it appears to be required for the full IL-33 response in BMMCs and human mastocytosis MC lines.[82] In opposition to acute stimulation with IL-33, chronic treatment of BMMCs and primary human MCs with IL-33 (>72 hours) resulted in a hyporesponsive secretory phenotype, demonstrating fundamental proteomic and regulatory changes induced by long-term IL-33 stimulation.[83]

In addition to SCF and IL-33, IL-4 is another important human MC regulator. In contrast to SCF, IL-4 does not affect matured MCs by itself but acts synergistically with SCF on MC survival, proliferation, and IgE-dependent mediator release.[3] Moreover, IL-4 alters the cytokine profile released by human intestinal and skin MCs (Fig 1).[84-86] Cytokines produced by MCs, either constitutively or on activation, vary in different species depending on the maturity of the MCs, tissue environmental factors, MC subtypes, and types of stimuli that trigger MC signaling. Below is a summary of data from primary human MCs, either MMCs from the gut[84,85] or skin.[86,87]

MMCs from the gut express constitutively small amounts of TNF-α and IL-6. On FcεRI cross-linking, expression of TNF-α and IL-6 is enhanced, and additional expression of T_H2 cytokines, such as IL-3, IL-5, and IL-13, occurs. If the MMCs are exposed to an IL-4 environment, IL-6 expression is blocked, although IL-3, IL-5, and IL-13 expression is markedly enhanced. Similar

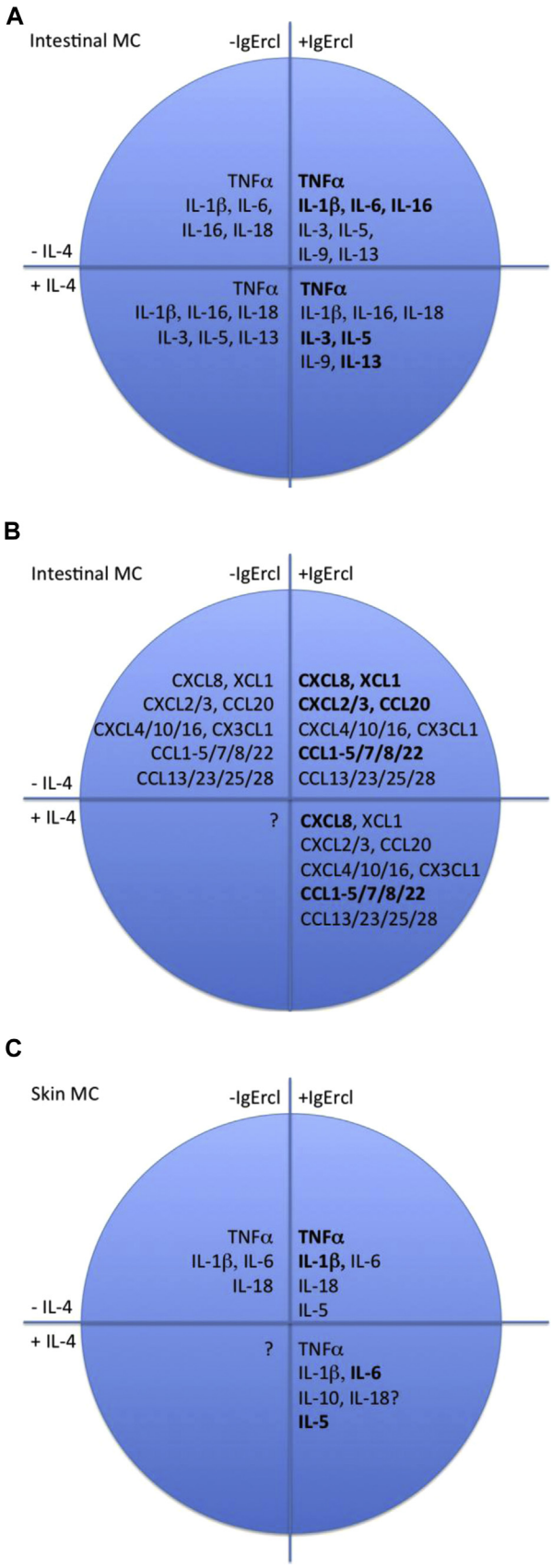

FIG 1. Expression of cytokines (**A** and **C**) and chemokines **(B)** in human MCs. Intestinal MCs were isolated from gut (Fig 1, *A* and *B*) and skin MCs from the foreskin and breast skin (Fig 1, *C*). Cytokine/chemokine mRNA expression without stimulation *(upper left quarter)*, after stimulation with IgE receptor cross-linking (*IgErcl*, *right quarters*), and after priming with IL-4 *(lower quarters)* are shown. Cytokine/chemokine mRNA expressions in boldface letters in the *upper right quadrants* were enhanced by IgE receptor cross-linking, whereas cytokine/chemokine mRNA expressions in boldface letters in the *lower right quadrants* were enhanced by IL-4.[84-86]

variations in cytokine expression can be observed in human skin MCs depending on FcεRI cross-linking and IL-4 treatment. However, no T_H2 cytokine expression has been described in this cell type (Fig 1, *C*). Human MMCs are also a rich source of several chemokines, expression of which is again regulated by FcεRI cross-linking and IL-4 (Fig 1, *B*).

Human skin MCs produce chemokines also, namely CCL2, CCL3, and CCL4, on activation by CD30, but their regulation has been less extensively studied.[87] The priming effect of IL-4 is likely not restricted to intestinal or skin MCs but has been observed also in lung MCs, the human MC line LAD2, and other human MCs.[88-91]

IL-4 is a key mediator of allergic inflammation, considering that it also induces development of T_H2 cells and IgE switching in B cells.[3] Thus SCF and IL-4 can be considered primary costimulatory mediators because they not only enhance FcεRI-mediated signals but also induce upregulation of secondary stimulatory receptors, such as the substance P (NK-1) receptor. Such costimulation draws comparisons between MC and T-cell signaling because both require cooperation of 2 signals for optimal activation: an antigen-dependent signal, such as from the T-cell receptor or IgE-bound FcεRI, and a costimulatory molecule, such as CD80, in T cells or SCF/IL-4 in MCs.

The priming effect of IL-4 in human MCs is possibly not restricted to FcεRI-mediated stimulation. In human cord blood–derived MCs, IL-4 pretreatment enhances TNF production after stimulation with the TLR2 agonist peptidoglycan and enables MCs to produce TNF in response to LPS.[92] In the LAD2 human MC line, IL-4 pretreatment enhances IL-31 production after stimulation with IL-33.[91] These 2 studies are probably insufficient for generalization of IL-4–priming effects in IgE-independent signaling in human MCs but demonstrate that the priming effects are not restricted to FcεRI-mediated stimulation.

The intracellular mechanisms connecting SCF and the IL-4 signaling pathway have been analyzed in human MC_Ts isolated from gut mucosa.[93] Activation of MC_Ts by means of FcεRI cross-linking alone results in phosphorylation of extracellular signal-regulated kinase (ERK) and mitogen-activated protein kinase (MAPK) p38 but not AKT. Stimulation with SCF alone also induces phosphorylation of ERK and MAPK p38 and additionally of AKT. As opposed to human MC_Ts, in murine BMMCs both KIT- and FcεRI-mediated stimulation results in ERK, MAPK p38, and AKT activation.[76] IL-4 priming of human intestinal MC_Ts enhanced activation of ERK but blocked activation of MAPK p38. Because activation of MAPK p38 is required for IL-6 production, the reported negative effect of IL-4 on MAPK p38 explains the inhibitory effect of IL-4 on IL-6 expression in human MCs. Moreover, IL-4 priming that antecedes FcεRI cross-linking induces activation of AKT. Combined treatment of MCs with IL-4, SCF, and FcεRI cross-linking substantially upregulates activation of AKT, whereas blocking of AKT inhibited the pronounced production and release of cytokines and chemokines in response to the 3 MC agonists.[93]

Innate immune receptors

The particular localization of MCs makes their expression of receptors recognizing microbial constituents meaningful and mandatory. MCs are equipped with different TLRs, which can productively interact with various pathogen-associated molecular patterns present on bacteria, viruses, and fungi. Differential types of MCs of different species have been reported to express various TLRs (investigated mainly at the mRNA level). TLR1 to TLR9 have been found in murine and human MCs,[94-96] whereas TLR10 can only be detected in human lung MCs.[97] By far most studies in the field of TLR function and signaling have been published for TLR4 and its ligand LPS. In macrophages LPS is bound by mCD14 and eventually transferred to the TLR4–MD-2 complex, hence activating the myeloid differentiation response gene–88 (MyD88)-dependent and TIR domain–containing adapter-inducing IFN-β (TRIF)–dependent pathway. The former induces production of proinflammatory cytokines, and the latter induces generation of type I interferons.[98] Intriguingly, BMMCs and human intestinal MCs lack mCD14, with the consequence that they recognize R-chemotypes of LPS but not S-chemotypes.[99,100] In correlation, macrophages deficient in CD14 show an LPS recognition phenotype comparable with MCs.[101]

Moreover, both murine BMMCs and murine peritoneal mast cells (PMCs) were found to lack the adaptor protein TRIF-related adapter molecule, resulting in their inability to activate the TRIF pathway and hence to produce type I interferons on LPS stimulation.[102,103] With respect to MyD88-dependent proinflammatory TLR4 signaling, B-cell lymphoma 3, a member of the inhibitor of nuclear factor κB family, has been shown to play a suppressive role in PMCs, which was not obvious in BMMCs.[104] Most likely, many more differences between diverse MC types are to be found at the level of signal transduction as well.

C-type lectin receptors have also been found to be involved in MC signaling activated by certain bacteria. MCs differentiated from murine BM or peritoneal cells express mannose receptor and macrophage galactose-type lectin, for which roles in the recognition of *Bordetella pertussis* have been demonstrated.[105] In addition, expression of the C-type lectin receptor Dectin-1, which participates in antifungal immunity, has been reported in different types of MCs, such as BMMCs,[106] human MCs generated from peripheral blood $CD34^+$ progenitors,[107] and cord blood–derived MCs.[108] Thus MCs are well endowed with different features for pathogen recognition.

Regulation of Ca^{2+}-dependent MC activation

MC activation by numerous stimuli relies on Ca^{2+} entry. Numerous stimuli, including antigen acting on IgE-bound FcεRI, adenosine, endothelin-1, or compound 48/80, for which the receptor in MCs (ie, MRGPRB2 in mice and MRGPRX2 in human subjects) was identified only 3 years ago,[109] trigger a marked increase in free cytosolic Ca^{2+} concentration to evoke MC activation. Degranulation achieved by means of regulated exocytosis of secretory vesicles requires an increase in free cytoplasmic Ca^{2+} concentration similar to the production of leukotrienes or activation of several transcription factors, which drive cytokine synthesis. Before degranulation can occur, vesicles loaded with, for example, inflammatory mediators are transported to the plasma membrane, where they fuse with the plasma membrane. This process of regulated exocytosis is initiated by an increase in the Ca^{2+} concentration in the vicinity of the membrane, which depends on Ca^{2+} influx through Ca^{2+}-permeable channels in the plasma membrane.[110,111]

A major downstream target of FcεRI stimulation is phospholipase C (PLC) γ1, which leads to generation of inositol-1,4,5-trisphosphate (IP_3). IP_3-mediated Ca^{2+} release from intracellular stores is subsequently followed by an influx of Ca^{2+} from the extracellular space, a process called store-operated Ca^{2+} entry (SOCE).[112] SOCE has been described in MCs,[111,113] and ionic currents mediating this Ca^{2+} influx were first characterized as Ca^{2+} release–activated Ca^{2+} (CRAC) channels.[114] Molecular constitutions of this Ca^{2+} entry pathway include proteins of the ORAI family. Depletion of intracellular Ca^{2+} stores through IP_3 generation can be achieved by several agonists mentioned above that act on G protein–coupled receptors (GPCR), leading to stimulation of PLCβ. These signaling pathways are also shown to activate transient receptor potential (TRP) channels.

Ca^{2+} entry into MCs through channels consisting of ORAI proteins. The ORAI family of cation channels consists of 3 members, ORAI1, ORAI2, and ORAI3, all of which are sufficient to build SOCE channels (see references in Tsvilovskyy et al[115] and (Table I).[115-128] In murine BMMCs in which the *Orai1* gene has been targeted by a gene-trap approach,[116] CRAC currents (I_{CRAC}) were reduced by 66%, and FcεRI-mediated Ca^{2+} entry and release of inflammatory mediators were reduced to a similar extent. In contrast, in *Orai2*$^{-/-}$ mice, antigen-evoked Ca^{2+} levels increase, and degranulation of PMCs and passive systemic anaphylaxis were increased.[115] This finding was initially surprising because overexpression of *Orai2* or *Orai1* cDNA leads to a pronounced enhancement of both SOCE and I_{CRAC} (see references in Tsvilovskyy et al[115]). An increase in SOCE was also observed in *Orai2*$^{-/-}$ T cells and macrophages,[129] which was explained by a role of ORAI2 proteins in fine-tuning the magnitude of SOCE mediated in ORAI1:ORAI2 heteromeric channels.[129] A Ca^{2+} increase triggered by compound 48/80 is increased in *Orai2*$^{-/-}$ PMCs, suggesting that Ca^{2+} entry channels triggered by MRGPRB2 receptors contain ORAI2 proteins.[115]

In human lung MCs, all 3 *ORAI* genes (also termed *CRACM* in some studies) are expressed. Adenovirus-mediated knockdown of *ORAI1* in human lung MCs resulted in a significant reduction of approximately 50% in Ca^{2+} influx and in FcεRI-dependent release of β-hexosaminidase and leukotriene C_4, whereas *ORAI2* knockdown had only marginal effects.[117] However, it is still unknown whether any of the 3 ORAI proteins contribute to Ca^{2+} entry and MC activation triggered by other agonists, such as those acting through GPCRs.

TRP channels determine Ca^{2+} entry into MCs. Twenty-eight mammalian TRP proteins are classified into 6 subfamilies according to structural homology: TRPC, TRPV, TRPM, TRPA, TRPML, and TRPP (see references in Freichel et al,[110] Table I). TRP channels not only contribute to Ca^{2+} entry across the plasma membrane but also play an important role in electrogenesis, regulating the driving force for Ca^{2+} entry through other Ca^{2+}-permeable channels, such as CRAC or other store-operated channels. In BMMCs indirect regulation, as a limiting factor of SOCE, was found to be a characteristic feature of TRPM4 channels, which act as Ca^{2+}-activated cation channels primarily conducting Na^+. TRPM4 channels depolarize the membrane after FcεRI stimulation, thereby critically decreasing Ca^{2+} influx through CRAC channels. Accordingly, TRPM4 deletion results in an increased Ca^{2+} entry and excessive release of

TABLE I. Summary of data concerning cation channel functional importance in primary MC models obtained by using knockout and knockdown approaches

Channel	Consequence of knockout or knockdown on: Ca^{2+} entry	Inflammatory mediator release	*In vivo* function in channel-deficient mice	References
Orai1	Decrease	Decrease	Regulation of passive cutaneous anaphylactic reaction	116,117
Orai2	Increase	Increase	Regulation of passive systemic anaphylaxis	115
TRPC1	Decrease; decreased frequency of Ca^{2+} wave initiation	Decrease	Regulation of recovery in passive systemic anaphylaxis	120-122
TRPC3	Decreased frequency of Ca^{2+} wave initiation	ND	ND	120
TRPC5	Decrease	Decrease	ND	123
TRPV1	No effect	No effect	ND	124
TRPV2	No effect on PMCs	Decrease	ND	124,125
TRPV4	No effect	No effect	ND	124
TRPM2	Decrease	Decrease	ND	126
TRPM4	Increase	Increase	Regulation of acute cutaneous anaphylaxis	118,119
TRPM7	ND	Decrease	ND	127
TRPM8	No effect	Decrease	Regulation of passive systemic anaphylaxis	128

ND, Not detected.

histamine, leukotrienes, and TNF-α and aggravates acute cutaneous anaphylaxis.[118] A similar role has recently been described in PMCs[119] in a study that demonstrated that TRPM4 proteins localize to the plasma membrane in response to FcεRI stimulation, suggesting that increased translocation of TRPM4 to the plasma membrane is part of the mechanism that limits MC activation.

The other TRP channels that contribute to MC activation do so by directly mediating Ca^{2+} entry. First evidence of the involvement of TRPC in MC activation came from knockdown experiments of TRPC1 and TRPC3 in RBL-2H3 cells, which resulted in decreased sensitivity to antigen stimulation.[120] Also, in BMMCs deficits in FcεRI-triggered MC activation were observed after TRPC1 downregulation.[121] However, contrary to expectations, analysis of *Trpc1*$^{-/-}$ mice showed a delayed recovery in passive systemic anaphylaxis, and *Trpc1*$^{-/-}$ BMMCs responded to antigen stimulation with an enhanced increase in intracellular Ca^{2+} compared with wild-type controls. Intriguingly, Ca^{2+} entry and degranulation triggered by antigen stimulation were unchanged.[122] Concerning the TRPC5 channel, Ma et al[123] found that TRPC5 downregulation in RBL-2H3 cells reduced SOCE and proposed an association of TRPC5 with STIM1 and ORAI1.

Within the TRPV subfamily, several studies have described expression of TRPV1, TRPV2, and TRPV4 in different types of mouse, rat, and human MCs,[110] including mouse PMCs.[124] However, the Ca^{2+} increase triggered by either antigen, endothelin-1, or compound 48/80 was unchanged in PMCs from TRPV1-, TRPV2- and TRPV4-deficient mice, respectively. In a similar manner degranulation triggered by antigen or compound 48/80 was unchanged.[124] Although degranulation induced by physical stimuli was found to involve TRPV2 activation in HMC-1 MCs,[125] the heat-evoked Ca^{2+} increase and degranulation were unchanged in *TRPV2*$^{-/-}$ PMCs.[124]

Within the TRPM subfamily, expression of TRPM2, TRPM4, TPRM7, and TRPM8 has been reported in different types of mouse, rat, and human MCs.[110] In *Trpm2*$^{-/-}$ BMMCs a heat-evoked cation current was lacking, and the antigen-evoked Ca^{2+} increase and degranulation were reduced.[126] Interestingly, SOCE levels were also reduced in *Trpm2*$^{-/-}$ BMMCs, and the authors raised the concept that TRPM2 can act as a store-operated channel independently of ORAI1. TRPM7, like TRPM6, serves as a bifunctional protein, with the protein kinase domain fused to an ion channel. TRPM7 is permeable to divalent cations including Mg^{2+} and Ca^{2+}. TRPM7 currents and histamine release evoked by either macrophage inflammatory protein 1α or substance P are significantly reduced in PMCs from mice lacking the TRPM7 kinase domain.[127] TRPM8 can be activated by cold and cooling compounds, such as menthol. *Trpm8*$^{-/-}$ mice showed enhanced passive systemic anaphylaxis, which could not be explained by alterations in the antigen-evoked Ca^{2+} increase or degranulation measured in BMMCs, suggesting that TRPM8 expressed on non-MCs can contribute to the protective role of TRPM8 during anaphylaxis.[128]

Taken together, it is commonly accepted now that the intracellular [Ca^{2+}] increase is indispensable for MC activation, and numerous studies demonstrate that proteins of the ORAI and TRP families are essential constituents or modulators of antigen-induced Ca^{2+} entry; however, the Ca^{2+} entry pathways evoked by stimulation of GPCRs in MCs remain unclear and will be the subject of upcoming studies.

Phosphatase regulators of MC signaling

MC effector functions are controlled by regulatory systems that act to counterregulate excessive activation that would otherwise lead to disease. One of these regulatory systems is represented by phosphatases that inhibit the action of the kinases whose activity is triggered by the activation of different MC receptors.

The role of phosphatases in different MC models has been reviewed in recent years. Although most of them have predominantly negative regulatory activities through removal of differential phosphorylation in the MC signaling cascade (eg, protein tyrosine phosphatase α[130] and ε,[131] SH2 domain–containing inositol-5′-phosphatase 1[132,133] and 2,[134] phosphatase and tensin homolog,[135] the phosphatidate phosphatase LIPIN-1,[136] and T-cell ubiquitin ligand 2[137]), others exert positive activities (eg, dual-specificity phosphatase [DUSP] 2[138]) and some even possess both regulatory properties (positive and negative; eg, CD45[139,140]

TABLE II. Phosphatase regulators of MC functions

Phosphatase	Function in BMMCs	Function in mice	References
Negative regulators			
PTPα	FcεRI-mediated degranulation	FcεRI-mediated anaphylaxis	130
PTPε	Degranulation and cytokine production	FcεRI-mediated passive systemic anaphylactic reaction	131
SHIP1	Degranulation and FcεRI-mediated IL-6, TNF, and IL-5 production	Allergic inflammation and MC hyperplasia	132,133
SHIP2	FcεRI-mediated degranulation and cytokine (IL-4 and IL-13) gene expression	—	134
PTEN	FcεRI-mediated degranulation and cytokine (IL-3 and IL-6) production and survival	Antigen and SCF-induced allergic response	135
LIPIN-1	FcεRI-mediated degranulation and prostaglandin D_2 release	FcεRI-mediated passive systemic anaphylaxis	136
TULA-2	FcεRI-mediated degranulation	—	137
Positive regulators			
DUSP2	FcεRI-mediated IL-6 and TNF expression	Promotes the "K/BxN" model of inflammatory arthritis that depends on MCs and macrophages	138
Dual positive and negative regulators			
CD45	Negative: degranulation and IL-3–dependent proliferation Positive: Degranulation and cytokine secretion	Positive: FcεRI-mediated systemic anaphylaxis	139,140
SHP-1	Negative: IL-4, IL-13, IL-6, and TNF expression on H_2O_2, LPS, and FcεRI cross-linking Positive: IL-3–dependent proliferation	Negative: allergic response	141-144
SHP-2	Negative: Ca^{2+} mobilization Positive: FcεRI-mediated TNF secretion	—	146

PTEN, Phosphatase and tensin homolog; *PTP*, protein tyrosine phosphatase; *SHIP*, SH2 domain–containing inositol-5′-phosphatase; *SHP*, SH2 domain–containing phosphotyrosine phosphatase; *TULA-2*, T-cell ubiquitin ligand 2.

and SH2 domain–containing phosphotyrosine phosphatase 1[141-144] and 2[145,146]). Almost all the studies on the role of phosphatases in MC function were performed on phosphatase-deficient mice or BMMCs, which are mucosal-like MCs (Table II).[130-144,146] Because reports have been made on subtle differences in phosphatase function in different types of tissue-resident MCs,[133] future studies will be needed to compare the role of phosphatases in different MC types.

A number of the phosphatases are transcriptionally regulated by glucocorticoids (GCs), which are famous therapeutically for their antiallergic and anti-inflammatory actions. GCs in general are known to exert their antiallergic actions on MCs by binding to an intracellular receptor (the GC receptor) that then interacts with a number of proinflammatory transcription factors, such as activator protein 1 or nuclear factor κB, to downregulate their activity.[147] However, GCs also acting through the GC receptor activate the expression of certain phosphatases as an indirect means of downregulating MC action.

DUSP1 (also known as MAPK phosphatase 1) was the first GC-inducible phosphatase gene reported to inhibit MC action through dephosphorylation of the MAPKs ERK1 and ERK2 in RBL-2H3 rat basophilic leukemia cells, which have been widely used as rat MMCs.[148,149] Later studies carried out in BMMCs showed a more complex regulatory effect of GCs. GC-induced activation of DUSP1 was found to be important for dephosphorylation of the MAPK p38 at early time points (4-8 hours), whereas it did not alter the phosphorylation of ERK1/2 or c-Jun N-terminal kinase. This shows a difference in the regulatory action of DUSP1 in BMMCs compared with RBL-2H3 cells that have been used repeatedly in many MC signaling studies. The results of the GC-induced DUSP1 expression also showed that only a subset of MAPKs was regulated by DUSP1 in BMMCs.[150] Therefore it was not surprising that GC-mediated inhibition of proinflammatory cytokine and chemokine gene expression (*Ccl2*, *Il6*, and *Tnf*), as well as degranulation, were unaltered in BMMCs from *Dusp1*$^{-/-}$ mice.[150]

A search for other mechanisms that might accompany GC regulation of MC function showed that several other phosphatases were transcriptionally upregulated by GCs in MCs. Intriguingly, in *Dusp1*$^{-/-}$ BMMCs GC upregulated the expression of phosphatases, such as DUSP2, DUSP4, DUSP9, and PEST domain-enriched tyrosine phosphatase (PEP).[150] Of these GC-regulated phosphatases, PEP is the most studied. Unlike the other GC-regulated phosphatases, PEP is exclusively expressed in hematopoietic cells.[151] In addition, disease-associated studies showed that alterations in *LYP*, the gene that codes for the human homolog of PEP, is a risk factor for human diseases, including inflammatory conditions, such as rheumatoid arthritis,[152] for which GC therapy is used.[153]

PEP is a potent negative regulator of T-cell receptor signaling that acts on receptor-coupled protein tyrosine kinases in T cells.[154,155] However, in BMMCs *Pep* gene deletion resulted in reduced antigen-mediated MC responses, such as serum histamine release, and a decreased number of degranulated MCs in the skin of knockout compared with wild-type mice, suggesting a positive regulatory function of this phosphatase.[156] GC-mediated inhibition of c-Jun N-terminal kinase 1/2 and PLCγ1 phosphorylation and Ca^{2+} mobilization after FcεRI cross-linking was abolished in *Pep*$^{-/-}$ BMMCs.[156] These studies show that although PEP expression is positively regulated by GCs, PEP is not a negative regulator of MC action, an apparent discrepancy in the putative role of this phosphatase in GC action.

Thus whole-genome expression profiling has recently been carried out using RNA sequencing analysis on $Pep^{+/+}$ and $Pep^{-/-}$ BMMCs to find a mechanistic explanation for the action of PEP in the regulation of MC activity and GC action (see GSE108972 for expression profiling data). These results identify PEP as a positive and negative regulator of MC functions. In its absence cytokine and chemokine gene expression (eg, *Tnf*, *Il13*, and *Csf2*) was downregulated, whereas expression of other genes (eg, *Il33*, *Ccr1*, *Il1r1*, and *Tnfrsf12a*) was upregulated in response to antigen (see GSE108972).[157] Furthermore, PEP was needed for the antiallergic action of GCs in MCs because GC-induced negative regulation of antigen-mediated *Cox2* gene expression was attenuated in $Pep^{-/-}$ BMMCs (GSE108972),[157] showing that PEP is a promising target in antiallergic therapy. In this light some attempts have already been made to inhibit PEP activity by using small-molecular-weight compounds. The first attempt was with an Au(I)-phosphine complex, but because this was less specific,[156] a more selective inhibitor, L75NO4, has since been described.[158] Further studies will be needed to determine whether PEP/LYP is a valid target for future therapeutic approaches for MCs in human subjects.

PHYSIOLOGIC FUNCTIONS OF MCs

Chemotaxis and phagocytosis

Generally, MCs are thought of as long-lived tissue-resident cells with little turnover. The traditional thought is that there is a continuous stream of MCps from the BM, circulating in the blood and replenishing peripheral sites in which final maturation happens. This view has very recently been challenged by using lineage-tracing experiments that show very little MC replenishment of peripheral tissues from the BM.[23] In many inflammatory settings, however, MC numbers strongly increase in target tissues. Local cell divisions alone, if mature and terminally differentiated MCs would proliferate at all, could not account for the massive increase in MC numbers.[17] Thus MC migration remains an important and insufficiently understood aspect of MC biology.[6,12,159-162]

MC chemotaxis is often assayed *in vitro* by using transwell assays or similar approaches and less often *in vivo* by using injection of labeled MCs through the tail vein and analysis of their arrival at certain anatomic locations, including the skin, peritoneal fluid, and small intestine. However, many of these experiments used mouse models carrying deficiencies in the KIT/KITL system that have multiple effects and thus are problematic. Depletion of specific MC populations, such as through MC-specific diphtheria toxin expression, followed by their reconstitution from BM transfer, has proved an important tool in many studies.[163-165] Yet, under nonchallenged conditions, reconstitution was slow and seemed to occur from endogenous MCps not affected by the toxin.[23]

The most prominent receptors described above, FcεRI and KIT, were also found to act on MC migration, and thus IgE and SCF are potent inducers of MC migration. Antigen-mediated migration (ie, IgE/antigen-triggered FcεRI activation that causes MCs to migrate) was observed, for example, after sensitizing mice and challenging their lung airways with aerosolized antigen. KIT-triggered pathways are involved not only in proinflammatory MC activation but also in migration. Key to migratory behavior and the required F-actin– and tubulin-dependent cytoskeletal dynamics[162] are RHO GTPases, particularly RAC, RHOA, and CDC42, and their regulatory factors.[166,167] Chemotaxis toward SCF expressed by endothelial cells and fibroblasts has been demonstrated numerous times *in vitro* for mouse and human cultured MCs.[168,169] Because some MCp populations express only low levels of KIT, in such cases SCF can support chemotaxis that is mainly triggered by chemokines, such as CCR2.[170]

The chemotactic landscape, even for the same tissue, is highly complex and depends on a plethora of parameters, including species, strain, age, activation status, cell type involved, and sex, and thus generalized predictions are very difficult, as is the assignment of direct effects of chemoattractant to a specific MC type. MC chemotaxis is also induced by many other agents as diverse as lipid mediators, such as sphingosine-1-phosphate (S1P), leukotriene B_4, and prostaglandins (prostaglandin E_2), and by CC or CXC chemokines.[171-173] The respective receptors are found on the surfaces of MCs, including 2 S1P receptors (S1P1 and S1P2) and chemokine receptors, such as CCR3, CCR5, CXCR2, and CXCR4. For example, in CXCR2-deficient mice MCs do not home efficiently to the intestines.[10,16,160]

Cytokine signaling can result in stimulatory or inhibitory effects on migration; for example, the anti-inflammatory IL-10 inhibits TNF-α– or nerve growth factor–induced MC migration.[174] Migration is affected by the environment through which MCs migrate, such as the extracellular matrix and/or other cell types. Indeed, some immune cells substantially support reconstitution of MC-depleted tissues. Dendritic cells, for example, but not lymphocytes, promote MCp trafficking to the intestine.[175]

When immature MCs reach a site of inflammation or mature resident MCs become locally activated near that site, these MCs (potentially further matured) not only rapidly degranulate and express further mediators but also can become actively involved in phagocytosis. MCs are strategically located in the skin, airways, gut, and other surface-exposed places to defend attacking microbes. In the skin MCs are estimated at a density of 3000 to 7000 cells per cubic millimeter and thus are prone to contact and attack invading pathogens.[176]

Studies using BMMCs indicate that to combat pathogens, the cells can phagocytose using complement and FcγRs, as well as CD48 and TLRs, and thus are involved in opsonin-dependent and independent means of defense, respectively.[177] Bacteria, such as *Escherichia coli*, *Klebsiella pneumoniae*, and *Enterococcus faecium*, are phagocytosed by using mouse BMMCs or human cord blood–derived MCs. The endosome-lysosome axis in MCs was reported to internalize and kill pathogens through either reactive oxygen species or nonoxidative means.[178] These conclusions are debatable because other authors did not find intracellular destruction of bacteria but rather extracellular attachments. Furthermore, some bacterial strains can enter MCs and thereby protect themselves from immune attack, although at least some of the bacteria, such as *Staphylococcus aureus*, will be destroyed intracellularly.[179,180]

The pathogenic fungus *Candida albicans* is found on mucosa and thus at a site prominently populated by MCs. The contribution of MCs to defense against *Candida albicans* is controversial because some authors suggest that MCs primarily fight the fungi through extracellular means,[181] whereas others describe phagocytotic killing of the fungus. After recognition through TLR2 and Dectin-1 receptors, *Candida albicans* was reported to be phagocytosed by BMMCs and killed by a nitric oxide–dependent mechanism.[182]

After phagocytosis, MCs display pathogenic peptides on their surfaces, thus supporting the adaptive immune response through this antigen-presenting activity. A further twist of the defense strategies used by MCs, although suicidal, is formation of extracellular traps.[183] Here MCs release DNA to trap microbes that stick to the viscous material. The MCs die, but this process is not accidental but rather a programmed mechanism that apparently involves high reactive oxygen species production.

Host defense against pathogens

MC_Ts are important immune cells that fight off selected species of intestinal nematodes (eg, *Trichinella spiralis* and *Strongyloides venezuelensis*), and worm expulsion is closely associated with intestinal mastocytosis. Different kinetics of resolution of infection correlate with the ability of different mouse strains to mount intestinal MC_T responses.[184] Immune elimination of primary nematode infection in rats correlated with secretion of the neutral protease rat MC protease II from MMCs.[185] Moreover, glycosaminoglycans, such as chondroitin sulfate A and heparin, stored in secretory lysosomes of MCs have been found to inhibit attachment and invasion of adult worms into the intestinal epithelium, hence promoting worm expulsion.[186]

About 20 years ago, a critical protective role of serosal-type MCs was described by using a murine model of acute septic peritonitis, cecum ligation, and puncture.[187,188] MC-secreted TNF-α on bacterial recognition acted as a chemotactic ligand for neutrophils necessary for the eradication of bacteria. These data were collected comparing WT and *Kit* mutant MC-deficient $Kit^{W/Wv}$ mice, which are known to exert additional hematopoietic abnormalities, such as neutrophilia and deficiency of peritoneal macrophages.[189,190] Piliponsky et al[190] advised caution in formulating general statements because they found the effect of MC deficiency to depend on mouse strain background, the nature of the mutation causing MC deficiency, and both the type and severity of infection.[190] In particular, MC engraftment of MC-deficient C57BL/6-$Kit^{W\text{-}Sh/W\text{-}Sh}$ mice even resulted in increased mortality during severe cecum ligation and puncture or on intraperitoneal inoculation of *Salmonella typhimurium*.[190] Moreover, when using a *Kit* mutant–independent mouse model, allowing conditional ablation of MCs, MCs were found to aggravate severe septic peritonitis by secreting IL-4, which in turn acted on peritoneal macrophages, attenuating their phagocytosis of bacteria.[165] Nevertheless, although the role of MCs in infection and immunity obviously is multifaceted, it is without a doubt that MCs are important actors in infectious and immunologic scenarios by secreting various mediators and/or regulating responses of myeloid and lymphoid immune cells.

Protection and regulation of tissue barriers

MCs are favorably located at boundaries where the host and environment meet, such as the skin or the mucosa of the lung and gastrointestinal tract. The intestinal mucosa is the largest boundary of the human body (estimated to be 200-400 m^2) and a most challenging one because the intestine hosts a large number of bacteria that need to be controlled to prevent host invasion. The second largest boundary is the respiratory mucosa (estimated at 100-200 m^2), whereas other mucosal sites (<1 m^2) and the skin (2 m^2) are rather small. Such boundaries are equipped not only with MCs but also with numerous cells of the innate and adaptive immune system, suggesting tight communication between these cells, as well as with tissue cells, including epithelial cells, endothelial cells, fibroblasts, and keratinocytes. The boundaries form unique functional barriers to protect the host against toxins, pathogens, and other harmful agents. MCs contribute to such barrier functions. In the intestine MCs regulate blood flow, smooth muscle contraction and peristalsis, mucosal secretion, and innate and adaptive immune responses.[191,192] This explains why MCs are involved in so many different types of gastrointestinal diseases, not only allergic disorders but also gastrointestinal infections and chronic inflammatory disorders, colon cancer, and other malignancies.[193]

The most effective stimulus for MMCs is cross-linking of cell surface–bound IgE, either by allergen in sensitized subjects or by parasitic antigens. However, this pathway is likely of no importance in healthy nonallergic subjects. It is not yet clear which stimuli might play a role in MC activation in healthy persons. Little is known about IgE-independent triggers of human MMCs of the lung or gastrointestinal tract. They might differ from triggers for human skin MCs or MCs from other species.[91,92] Important progress has been made in understanding MC regulation through the discovery of several inhibitory mechanisms that might balance the agonistic activities of mediators discussed previously.[194] Of particular relevance to the gastrointestinal tract are the anti-inflammatory cytokines TGF-β1 and IL-10, which are highly expressed in the healthy intestine. TGF-β1 inhibits SCF-dependent growth of human gastrointestinal MCs *in vitro* and modulates the mediator profile released on FcεRI aggregation by reducing proinflammatory mediator release, except for prostaglandin D_2 production, which is enhanced by TGF-β1.[195]

Multiple studies in rodents and, to some extent, also in human subjects have shown that MCs have a central role in host defense against bacteria, viruses, and parasites (see the "Host defense against pathogens" section). More recently, it was shown that gastrointestinal MCs interact also with commensal bacteria in the intestine. For example, intestinal commensal bacteria regulate the migration of murine MCs into the intestine through induction of CXCR2 ligands from intestinal epithelial cells in a TLR-dependent manner. Germ-free mice have lower MC densities in the small intestine than normal mice.[196] On the other hand, commensal bacteria, such as *Enterococcus faecalis*, suppress degranulation of MCs, at least *in vitro*, in a MyD88-independent manner, for example through partial inhibition of Ca^{2+} signaling on FcεRI cross-linking.[197]

It is tempting to speculate that MC–commensal bacteria interactions play a role in the gastrointestinal barrier and in protection against barrier-related diseases. By using *in vitro* models, it could be demonstrated that MC proteases are directly responsible for the increase in epithelial paracellular permeability.[198] The MC-dependent modulation of intestinal permeability was confirmed in human subjects exposed to stress.[199] The fact that gastrointestinal MCs are in intimate contact with the epithelium and nerves suggests further that MCs are involved in regulating mucosal permeability and intestinal barrier function.

Most of the physiologic functions of MCs described for the gut also apply to the lung. However, a comprehensive study of MC functions in normal lung physiology is lacking. Most work focuses on MC functions in the pathogenesis of asthma and other pulmonary diseases. It was only recently pointed out that MCs and their activation contribute to lung health through innate and adaptive immune responses to respiratory pathogens.

Human skin MCs are quite distinct in their development, functions, and biological properties compared with human MMCs. Skin MCs are sensitive to stimulation by substance P, compound 48/80, and other basic nonimmunologic stimuli. Moreover, skin MCs are also important players in protective immune responses against pathogens.

The fact that MCs are largely found at interfaces between the environment and the internal milieu predestines them to be involved in wound healing and tissue remodeling. Wound healing is a complex process of lysis and reconstitution controlled by a series of cell-signaling proteins. MCs have been shown to play a significant role in the early inflammatory stage of wound healing and also to influence proliferation and tissue remodeling in the skin.[200] In the skin, but also in the lung and intestinal mucosa, MCs are located around small vessels that are involved in vasodilation. MCs intimately communicate with endothelial cells providing MC growth factors, and in consequence of this communication, MCs are involved in regulation of extravasation of blood-derived immune cells.[201] In summary, MCs regulate a large number of physiologic tissue functions, namely maintenance of tissue barriers.

CONCLUSIONS

The mechanisms underlying pleiotropic MC functions to support the host's homeostasis have been unraveled to a large extent within the last few decades. MCs vary considerably depending on their grade of maturation, growth and trigger factors, tissue environmental conditions, and presence or absence of pathogens. MCs express a large variety of receptors, allowing them to respond specifically to particular conditions. Their major effector functions, the physiologic importance of which has to be elucidated in many cases, comprise the generation and release of proteases, amines, and cytokines, as well as chemotaxis and phagocytosis. These functions are regulated by SCF, IL-4, and other cytokines and chemokines; IgE and IgG receptor–dependent mechanisms; and innate immune receptors and other mechanisms and depend on an intracellular Ca^{2+} increase that is mediated or modulated by TRP and ORAI channels in many cases. Such mechanisms explain how MCs, both in human subjects and in different animal species, can exert a number of physiologic functions, including host defense against pathogens and regulation of mucosal and skin functions. The understanding of such mechanisms not only explains particular body functions but also offers novel opportunities for pharmacologic interventions.

We regret that we are unable to cite all relevant studies because of space limitations, and we apologize to our colleagues whose work has not been cited.

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