Trends in Immunology

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Novel Insights into Mast Cell Biology

Review

Rheostatic Functions of Mast Cells in the Control of Innate and Adaptive Immune Responses

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Mast cells are evolutionarily ancient cells, endowed with a unique developmental, phenotypic, and functional plasticity. They are resident cells that participate in tissue homeostasis by constantly sampling the microenvironment. As a result of their large repertoire of receptors, they can respond to multiple stimuli and selectively release different types and amounts of mediator. Here, we present and discuss the recent mast cell literature, focusing on studies that demonstrate that mast cells are more than a switch that is turned 'off' when in the resting state and 'on' when in the degranulating state. We propose a new vision of mast cells in which, by operating in a 'rheostatic' manner, these cells finely modulate not only immune responses, but also the pathogenesis of several inflammatory disorders, including infection, autoimmunity, and cancer.

Trends

New findings suggest that it is short-sighted to limit the classification of mast cells to two subtypes; indeed, each specific tissue has a unique mast cell type that differs significantly from those of other tissues.

Mast cells continuously sample the microenvironment, working to maintain tissue homeostasis and contribute immediately to the immune response to non-self-antigens.

A network of activating and inhibitory stimuli can modulate mast cell activity.

A mast cell is more than a switch that is turned 'off' when in the resting state and 'on' when needed; instead, mast cells show a range of modulated responses that contribute to the fine-tuning of the immune response.

Beyond a Binary View of Mast Cells

Mast cells are long-lived, tissue-resident, innate immune cells that are found primarily in sites that are in close connection with the external environment, where they have a role in host defense against parasites [1]. However, their functions are not limited to pathogen removal: they also take part in wound healing [2] and maintenance of tissue homeostasis [3], and are involved in chronic inflammation [4,5] as well as autoimmune diseases [6,7] and cancer development [8]. Different local tissue activities require mast cells to be equipped with a range of receptors that sample diverse microenvironments, allowing the immune system to mount a specific response that depends on the stimulus [9]. Guided by molecular signals exchanged with the microenvironment, mast cells in different locations adapt their repertoire of receptors and ligands to meet the diverse functional requirements of their host tissue, highlighting their incredible cell plasticity [10]. In this review, we discuss our growing knowledge of mast cell versatility and provide an updated vision of this underestimated type of immune cell.

Mast Cell Development, Tissue Migration, and Plasticity

Although mast cells are generally assumed to be long-lived cells in the periphery, they are continually replenished by rare blood-circulating precursors ($CD34^+$, $CD13^+$, c-kit^+, and $Fc\varepsilon RI^-$) released from the bone marrow into the blood stream. They are recruited via venules and mature into one of several mast cell subsets (see below) during their migration towards their

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final location within the tissue. Although the signals that lead to the migration and localization of mast cells are not yet completely understood, analysis of the chemokine receptors involved can provide useful information. Indeed, mast cells express numerous surface receptors for many ligands with chemoattractant properties [11,12], including CXCR2, CXCR4, CCR3, CX_3CR1, CCR5 [13,14], c-Kit [15,16], and integral membrane-bound G-protein-coupled receptors (GPCRs), which bind and respond to eicosanoids [17–19]. However, it is unclear whether these chemokine receptors lead to the selective tissue homing of mast cells or whether they are involved in cell maturation. CCR3 is present on the cell surface during mast cell maturation and, because it binds to CCL11, CCL24, and CCL26, it might have a role in tissue cell homing [13]. Additionally, CCL11 acts synergistically with stem cell factor (SCF) to increase the number of embryonic mast cell progenitors [20], suggesting that chemokines also have a role in mast cell development. Mast cells are the only terminally differentiated hematopoietic cells that express the c-Kit receptor. SCF binds to this receptor on immature and mature mast cells, activating them and inducing their chemotaxis and survival at steady state in mice [21,22]. It is likely that mast cell precursors are attracted by SCF produced by fibroblasts and endothelial cells for entry into peripheral tissues. However, the tissue localization of mast cells requires tissue-specific signals. In fact, the interaction of the $\alpha4\beta7$ integrin expressed on mast cell progenitors with the mucosal addressin cellular adhesion molecule-1 (MAdCAM-1) is required for homing to the mouse small intestine [23] and this process is specifically dependent on CXCR2, as demonstrated by using CXCR2-deficient mice, which are defective only in intestinal mast cells [24]. Additionally, inflammatory mediators, such as leukotriene D4 (LTD4) and B4 (LTB4), induce the passage of mast cell precursors across the endothelium into peripheral tissues [25–27]. These studies indicate that different receptor–ligand pairs may be required for mast cell entrance and terminal maturation into different peripheral tissues. Nevertheless, the precise chemokines involved remain unclear, given that chemokine receptor expression varies greatly among the *in vivo* subsets. In the periphery, tissue mast cells locate near blood and lymphatic vessels, glands, smooth muscle, and nerves. In these sites, mast cell precursors can either remain as a homeostatic pool or complete their differentiation process into mature mast cells upon exposure to the local environment, a process that is also modulated by the genetic background in different mice strains. Indeed, compared with the C57BL/6 strain, BALB/c mice display higher levels of IL-5, IL-13, and CCL11 in the lung and show greater airway reactivity to methacholine [28]. Additionally, circulating mast cell precursors were found to be more mature in BALB/c than in C57BL/6 mice [29]. Thus, a real 'circulating' mast cell does not exist and, therefore, this cell type can be considered only as a tissue-resident cell. Other nonterminally differentiated immune cell types circulate in the blood but, in contrast to mast cell precursors, they share some characteristics with their fully differentiated counterpart. Indeed, monocytes actively patrol the vascular endothelium under homeostatic and inflammatory conditions [30] and, together with circulating neutrophils, they store in their cytoplasmic granules cytokines typically present in macrophages and activated neutrophils. Therefore, the lack of a circulating mast cell is unique among the different cell types of the immune system, but should not be considered a restriction. Indeed, the capacity of the mast cell to differentiate into a fully mature and functional cell only within the tissue gives rise to an extremely heterogeneous population.

Classically, mast cells have been classified depending on their tissue distribution and granule content. Based on the proteases produced, human mast cells have been categorized into those that contain predominantly tryptase (MC_T) or chymase (MC_C) or both (MC_{TC}) [31]. The two proteases have distinct substrate specificities and are part of the large array of effector molecules contained in mast cell granules. A similar scenario can be observed in mice, where mast cell populations of connective or serosal tissues (CTMC) contain abundant heparin in their granules, while mucosal mast cells (MMC) have little or no heparin. However, the factors that can regulate the molecules expressed and stored in these granules will subsequently modulate the functions exerted by mast cells [32]. Thus, it is possible to argue that tissue-specific mast

cells display differences in their granule content, cytokine expression pattern, and tissue-specific receptors that provide context-related functions to the cell. In support of this consideration, a recent transcriptional analysis carried out by Dwyer and colleagues on 14 lymphoid and myeloid cell populations identified the mast cell as the most transcriptionally variable cell type of the immune system [33]. The authors demonstrated that murine mast cells purified from different tissues shared a 'mast cell-specific' transcriptional signature of more than 100 genes and also showed tissue-specific regulation of their transcriptomes [33]. Among these, there were genes encoding serine proteases (*MCPT*) and metalloproteases (*ADAMTS*), and molecules required for the generation of preformed and newly synthetized mediators [5-lypoxygenase (*ALOX5*) and oxidized lipoprotein receptor (*ORL1*)], as well as genes encoding cytokines (*IL3*) and adhesion molecules (*CD59a* and *ITGB2*). Similarly, an *in silico* data analysis performed by Saito and coworkers provided evidence of a different gene expression profile depending on the specific environmental context [34]. Interestingly, the upregulation of specific mRNAs associated with the MC_{TC} phenotype (*CMA1*, *HEY1*, and *C5R1*) was observed in tonsil- and skin-derived but not in lung-derived mast cells.

Based on the above results, the historical classification of mast cells based on their tissue distribution and granule content can be now revisited based on insights from gene expression profile analyses (Table 1). The further extension and validation of differential gene expression analyses of both human and murine mast cell subsets could help to better define this multifaceted cell and to clarify its specific role in different pathophysiological contexts.

Rheostatic Functions of Mast Cells

Mast cells have long been considered critical effector cells during IgE-mediated allergic disease and their role has consequently been linked to massive degranulation with 'all or nothing' effects on the immune response. This commonplace interpretation has restricted our view of the function of mast cells only to promoting or suppressing the immune response in relation to, or as a consequence of, cell activation, following a specific stimulation. However, given their continuous sampling of the microenvironment, 'resting' mast cells do not exist. Indeed, the mast cell can be considered as a rheostat that can modulate the intensity of its response based on the signals it receives from the microenvironment (Figure 1).

In a physiological context, mast cells have primarily a homeostatic function. For example, given their association with blood vessels, lymphatics, epithelial surfaces, and smooth muscle, these cells release mediators to modulate fluid flow, permeability, secretion, and contraction in many sites [35,36]. Numerous papers have described the ability of mast cells to control, expand, and influence the activities of regulatory and effector B [37,38] and T lymphocytes [39,40] as well as the activities of innate immune cells (myeloid-derived suppressor cells, eosinophils, and stromal cells) [9] by direct crosstalk and, importantly, in the absence of external activation signals and classical degranulation (Figure 1A). Co-stimulatory molecules belonging to the TNF/TNFR families (CD40L, OX40L, 4-1BB, GITR, CD153, Fas, TRAIL-R, and HVEM) are implicated in these interactions [41–43]. Notably, these receptors and ligands are constitutively expressed by mast cells and their levels of expression are not significantly affected by mast cell activation [9,43]. Moreover, under resting conditions (i.e., in the absence of specific triggering and, therefore, of 'classical' exocytosis), mast cells incessantly communicate with the microenvironment via two elegant secretion mechanisms, namely piecemeal degranulation (PMD) and exosome release [32,44]. PMD has been principally described in basophils, mast cells, and eosinophils, and comprises the gradual and prolonged emptying of cytoplasmic secretory granules via vesicular transport, in the absence of direct granule-to-plasma membrane fusion events [45]. One of the first demonstrations of PMD in mast cells dates to the early 1990s, when the slow release of mast cell granule content was described in the eyelid lesions of IL-4 transgenic mice [46]. Since then, mast cells functioning via PMD have been detected in several

Table 1. Classification of Human and Murine Mast Cells Based on Anatomical Localization, Granule Composition, and Differential Gene Expression[a]

Organ/Tissue	MC subtype	Granule composition	Upregulated genes	Downregulated genes	Refs
Mouse					
Trachea	MMC	Hist; MMCP1-2; chondroitin sulfate E	*Cd34, Cd59, Lipf*		[33]
Esophagus	MMC	Hist; MMCP1-2; chondroitin sulfate E	*Cd34, Cd59, Mcpt1, Mcpt2*		[33]
Tongue	MMC	Hist; MMCP1-2; chondroitin sulfate E	*Cd34, Cd59*		[33]
Ear	MMC	Hist; MMCP1-2; chondroitin sulfate E			
Skin	CTMC	Hist; 5-HT; MMCP-3,4,5,6; carboxypeptidase; heparin	*Cd59, Mrgprb8, Mrgprb13, Adamts1, Adamts5, Il-3, Sox7* [33]	*Cd34, Alox5. Alox5ap*	[33]
Peritoneum	CTMC	Hist; 5-HT; MMCP-3,4,5,6; carboxypeptidase; heparin	*Cd34, Itgb2, Bmp2*	*Cd59, Orl1*	[33]
Human					
Alveoli	MC_T	Hist; tryptase; heparin		*CMA1*	[34]
Bronchi	MC_T MC_C	Hist; tryptase; heparin; chymase			
Tonsils	MC_{TC}	Hist; tryptase; chymase; cathepsin G; carboxypeptidase; heparin	*C5R1, CMA1, HEY1*		[34]
Nasal mucosa	MC_T	Hist; tryptase; heparin			
Nasal submucosa	MC_{TC}	Hist; tryptase; chymase; cathepsin G; carboxypeptidase; heparin			
Intestinal mucosa	MC_T	Hist; tryptase; heparin			
Intestinal submucosa	MC_{TC} MC_C	Hist; tryptase; chymase; cathepsin G; carboxypeptidase; heparin			
Skin	MC_{TC}	Hist; tryptase; chymase; cathepsin G; carboxypeptidase; heparin	*CMA1, HEY1*		[34]
Conjunctiva	MC_{TC}	Hist; tryptase; chymase; cathepsin G; carboxypeptidase; heparin			
Axillary lymph nodes	MC_{TC}	Hist; tryptase; chymase; cathepsin G; carboxypeptidase; heparin			
Breast parenchyma	MC_{TC}	Hist; tryptase; chymase; cathepsin G; carboxypeptidase; heparin			

[a]Abbreviations: 5-HT, 5-hydroxytryptamine; CTMT, connective mast cell; Hist, histamine; MC_C, mast cell containing chymase; MC_T, mast cell containing tryptase; MC_{TC}, mast cell containing tryptase and chymase; MMC, mucosal mast cell.

other settings, such as in antral biopsies from patients with *Helicobacter pylori* 'active' gastritis [47] and in the context of gastric carcinomas [48]. Interestingly, signs of PMD were observed following mast cell interaction with different cell types, such as regulatory T cells [49] and conjunctival epithelial cells [50]. The observation that mast cells could release exosomes is even more recent. In 2001, the research group of Mécheri described for the first time the ability of bone marrow-derived mast cells (BMMC), peritoneal mast cells, and mast cell lines to constitutively secrete exosomes [44]. These authors provided crucial evidence of the fact that mast cells use these extracellular vesicles as sophisticated messengers with immunoregulatory functions on B and T lymphocytes [44,51] and dendritic cells [52]. More recently, mast cell exosomes were found to express CD40L [37] and OX40L [53] and to expand the pool of IL-10-competent B cells [37] as well as to promote the proliferation and differentiation of Th2 cells [53]. Another recent study demonstrated that exosomes from IFN-α-treated mast cells contained a cytoplasmic isoform of PLA2 (PLA2G4D) that can be transferred to neighboring CD1a-expressing cells, contributing to a CD1a-reactive T cell response in patients with psoriasis [54].

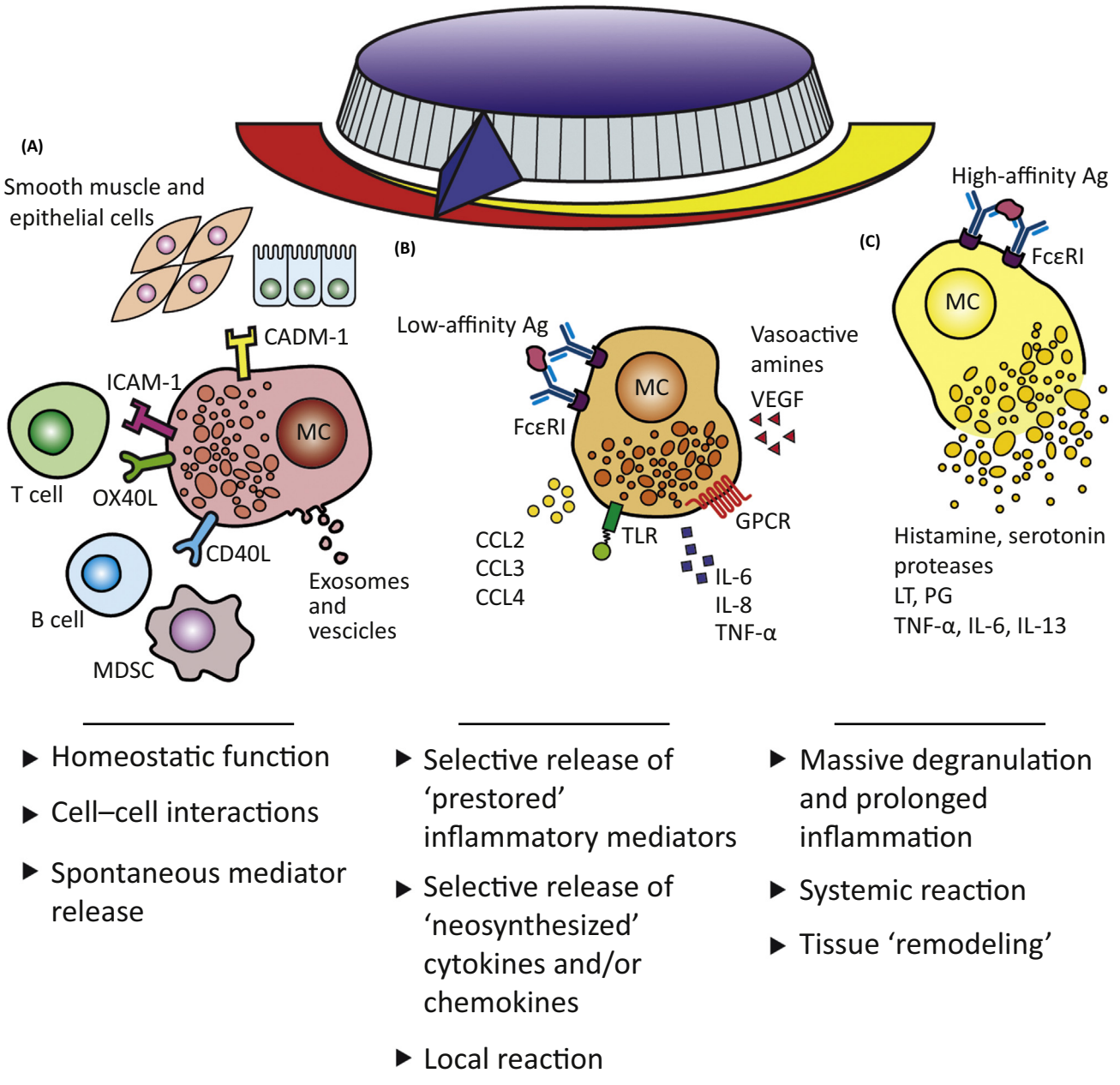

Figure 1. Schematic Representation of the Mast Cell As a Rheostat That Modulates the Type and Amplitude of the Immune Response. In the absence of external stimulation, the homeostatic function that the mast cell exerts on innate and acquired immune cells, via cell–cell contact or the spontaneous release of soluble mediators, is predominant (A). Following the activation by specific endogenous and exogenous signals, mast cells respond differently in terms of the amount, type, and kinetics of mediator release (B). Strong mast cell activation causes massive and extended secretion of preformed and newly synthetized mediators that cause local and systemic reactions (C). Representative examples of cellular partners, membrane-bound receptors and soluble mediators are reported. Abbreviations: CADM-1, cell adhesion molecule-1; ICAM-1, intercellular adhesion molecule-1; IL, interleukin; LT, leukotrienes; PG, prostaglandins; TLR, Toll-like receptor; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

Nevertheless, mast cells are best known for the consequences deriving from the loss or release of their granules upon activation by external signals. The triggering of one of the countless receptors that a mast cell expresses on its surface results in the release of the proteases stored in the cytosolic granules, in the secretion of neosynthesized lipid-derived mediators, and in the

production and secretion of a wide variety of cytokines and chemokines. However, once again, the mast cell stands out for its versatility, since it can respond differently in terms of the kinetics of release, as well as in the quality and quantity of the mediators produced following a specific signal (Figure 1B). The engagement of pattern recognition receptors, such as Toll-like receptors (TLRs), results in a selective mast cell response, with the secretion of a distinct and specific array of cytokines and chemokines, rather than in the release of histamine. Indeed, when stimulated with peptidoglycan, murine BMMC released TNF-α, IL-4, IL-5, IL-6, and IL-13, but not IL-1β. By contrast, lipopolysaccharide (LPS)-treated BMMC secreted TNF-α, IL-1β, IL-6, and IL-13, but not IL-4 or IL-5. Moreover, while TLR2 stimulation elicited degranulation, engagement of TLR4 did not [55]. In addition, several membrane receptors for endogenous molecules can also evoke a mast cell specific response. These include GPCRs that bind inflammatory mediators (cytokines, complement fragments, and β-defensin), cationic ligands (e.g., substance P), hormones, and neuropeptides (e.g., somatostatin, neurotensin, and endothelin). The engagement of these GPCRs triggers the selective release of specific molecules, such as serotonin, IL-6, vascular endothelial growth factor (VEGF), and others, but not of histamine [56]. Last but not least, mast cells are characterized by the presence of the high-affinity IgE receptor, FcεRI, on their surface. This receptor is arguably the most-studied mast cell activator and is thought of as a classical inducer of degranulation. However, it is also possible to obtain different types of response as a result of the binding of this single receptor. Indeed, the affinity of the interaction between an IgE and its cognate antigen can vary, influencing the size and stability of FcεRI clusters and, consequently, the type of cell response [57,58]. Antigens with either weak or low affinity for IgE result in similar receptor phosphorylation, although differences in receptor cluster size, mobility, distribution, and, therefore, mast cell effector responses, are present. Indeed, low-affinity stimulation boosted FcεRI association with the Src family kinase Fgr and shifted signals from the adapter LAT1 to the related adapter LAT2 [57]. This, in turn, led to a response characterized by enhanced chemokine production, but reduced degranulation and cytokine secretion (Figure 1B). This means that low-affinity interactions between IgE and its cognate antigen can elicit a cellular response without the release of the classical preformed allergic mediators. By contrast, strong interactions between an antigen and IgE cause the generation of highly dynamic FcεRI clusters that form a tight synapse-like structure [58]. This causes massive emptying of the granule content and promotes the neosynthesis and release of mediators that orchestrate and sustain local and systemic inflammatory reactions (Figure 1C). Recently, an elegant study by Gaudenzio and colleagues compared the nature and kinetics of the degranulation induced by the engagement of FcεRI with the hapten dinitrophenyl (DNP) plus anti-DNP IgE and by the engagement of the GPCR MRGPRX2 with substance P [59]. The authors demonstrated the existence of spatiotemporally distinct patterns of mast cell degranulation and associated these differences with pathological responses *in vivo*. FcεRI-mediated mast cell activation was characterized by slower but sustained Ca^{2+} influx and inhibitor of kappa-B kinase (IKK-β) activation that allowed the fusion of cytosolic granules to the plasma membrane and the formation of large granules. These were slowly released and could be transported throughout the lymphatic circulation, inducing a systemic immune response. By contrast, the activation of the mast cell by substance P induced a rapid and transient release of individual small secretory granules responsible for the brief local inflammatory reaction, developing a quick vascular reaction that also rapidly resolved [59].

All these differences in the timing, amount, and type of mediator released allow the mast cell to intervene adequately in specific pathophysiological contexts, promoting the suppression or the amplification and diversification of the immune response. This evidence has led us to propose that, similarly to some other immune cells, mast cells also function as a rheostat and not simply as an 'on-off' switch, as classically thought (Figure 1).

Towards a Broader Understanding of Mast Cells Functions *In Vivo*

As underlined in this review, beyond their well-known role in IgE-mediated reactions, mast cells contribute to the regulation of both innate and adaptive immune responses. Although this has been a key area of investigation in the mast cell field for the past three decades, little attention has been paid to the role that these cells have in a physiological context or in interactions with both immune and non-immune cells, which occur in the tissues and underpin tissue homeostasis. A lesson is provided by the analysis of mast cell-deficient mice, despite the caveats that have been raised about these models and their reconstitution. Indeed, compared with wild-type mice, mast cell-deficient $Kit^{W\text{-}sh/W\text{-}sh}$ (Wsh) mice or mast cell protease 4 deficient (*Mcpt4*$^{-/-}$) mice present altered intestinal barrier functions, modifications in the intestinal morphology, as well as dysregulated claudin-3 crypt expression [3]. Interestingly, the reconstitution of Wsh mice with *in vitro* differentiated mast cells replenished the intestinal barrier function, which could be because the lack of mast cells deprives the small intestine of a source of the anti-inflammatory factor MCPT4, which degrades TNF-α [60–62]. Additionally, mast cells are important in the differentiation of follicular helper T cells via ATP signaling [63], and have a role in IgA switch and expression and in the overall homeostasis of gut bacteria [64,65]. Furthermore, the analysis of unstimulated mast cell activities could be pivotal to our understanding of the importance of mast cells in a physiological context. All the resting activities of mast cells can be influenced by the mutual signaling exchange with the microenvironment. For example, the interaction between mast cells and regulatory T cells sustains tolerance and sets a threshold of activation for allergic or parasitic inflammation; however, mast cells are also able to rapidly revert their behavior and polarize a strong immune response [40,66].

Further lessons on the regulatory activity of mast cells emerge from mastocytosis, a rare disease in which there is uncontrolled cell activation dependent on a c-Kit mutation, or from other diseases characterized by mast cell hyper-responsiveness. In these conditions, the regulatory properties of mast cells, as well as the control of tissue homeostasis, are lost. Indeed, the existence of a link between mastocytosis and the development of lymphoproliferative diseases of B cells (chronic lymphocytic leukemia, lymphoblastic leukemia, hairy cell leukemia, monoclonal gammopathy of undetermined significance, and plasma cell myeloma) has been reported, supporting a key role of mast cells in B cell tumor development and growth [67,68]. Moreover, it is suggestive that the increase in mast cell number and their functional hyperactivation exacerbate their normal capacity to support the expansion of clonal populations and this is dependent on changes in the microenvironment [8]. In the context of solid tumors, it has been reported that mast cell accumulation contributes to modeling the tumor microenvironment (TME) during cancer progression [8]. In the TME, mast cell can release mediators that support tumor growth, such as proteases (chymase), matrix-degrading enzymes (MMP9), and angiogenic factors (VEGF), as well as inflammatory mediators (IL-6, IL-1β, and TNF-α) that inhibit tumor progression [69]. In addition to the release of this multitude of biologically active factors, mast cells were shown to interact with several cell types of the TME, such as myeloid-derived suppressor cells [70], regulatory T cells [8,39], and the cancer cell itself. It is via this mutual and continuous dialog with several cell types that mast cells shape and model the TME [8].

Concluding Remarks

The overriding consideration of mast cells as cells responsible only for allergic reactions has been largely overcome, given that new roles for this cell type within the immune system are continuously being proposed. This will help provide a new perspective on an old cell that appeared early during evolution [71], before other classical immune effector cells, such as neutrophils [72], monocytes [72], and lymphocytes [73,74]. In this review, we have highlighted two main concepts. The first is the pivotal role of the microenvironment in guiding mast cell tissue distribution, localization, and maturation, resulting in a multifaceted and versatile cell. The

Outstanding Questions

Mast cells are among the most phenotypically variable cells of the immune system, because of their tissue-specific differentiation from a circulating immature precursor and switch from a pro-to anti-inflammatory phenotype. How do these phenotypic changes relate to those of other immune tissue-resident immune cells?

Which are the physiological and the pathophysiological roles of different mast cell subtypes in the context of diseases localized in different tissues?

In terms of therapeutic approaches, how should we consider the different responsiveness of the diverse mast cell subtypes?

How might we use mast cells to restore tissue homeostasis in pathological conditions?

second concept concerns a new vision of a cell that never rests. Mast cells can be fine-tuned by a wide range of receptors and the production of mediators is specifically regulated by the signals received. Under 'resting conditions', the mast cell uses this plastic repertoire to control several immune cell functions in the absence of external activation. However, under appropriate conditions, the mast cell uses the same repertoire to sense specific changes in the microenvironment and, consequently, to establish an appropriate reaction. Considering these new lines of evidence reveals the critical role of mast cells in the fine-tuned modulation of both homeostatic and inflammatory responses, and extends new avenues of research into their functions, beyond their role in allergic responses through the release of histamine and other mediators (see Outstanding Questions).

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