Physiological Roles of Mast Cells: Collegium Internationale Allergologicum Update 2019

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Abstract

Mast cells are immune cells which have a widespread distribution in nearly all tissues. These cells and their mediators are canonically viewed as primary effector cells in allergic disorders. However, in the last years, mast cells have gained recognition for their involvement in several physiological and pathological conditions. They are highly heterogeneous immune cells displaying a constellation of surface receptors and producing a wide spectrum of inflammatory and immunomodulatory mediators. These features enable the cells to act as sentinels in harmful situations as well as respond to metabolic and immune changes in their microenvironment. Moreover, they communicate with many immune and non-immune cells implicated in several immunological responses. Although mast cells contribute to host responses in experimental infections, there is no satisfactory model to study how they contribute to infection outcome in humans. Mast cells modulate physiological and pathological angiogenesis

and lymphangiogenesis, but their role in tumor initiation and development is still controversial. Cardiac mast cells store and release several mediators that can exert multiple effects in the homeostatic control of different cardiometabolic functions. Although mast cells and their mediators have been simplistically associated with detrimental roles in allergic disorders, there is increasing evidence that they can also have homeostatic or protective roles in several pathophysiological processes. These findings may reflect the functional heterogeneity of different subsets of mast cells.

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Mast cells are immune cells present in all classes of vertebrates which emerged more than 500 million years ago, before the development of adaptive immunity [1]. These cells, first identified in humans, and named by Paul Ehrlich [2], are distributed throughout nearly all tissues and are often found in close proximity to epithelia, fibroblasts, blood and lymphatic vessels, and nerves [3, 4].

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Fig. 1. Surface receptors expressed by human mast cells. Human mast cells express the high-affinity receptor for IgE (FcεRI) and FcγRIIA, and their cross-linking induces the release of proinflammatory and immunomodulatory mediators. All mast cells display the KIT receptor (CD117), which is activated by stem cell factor (SCF), whereas only certain types of mast cells (e.g., skin and synovial) express the MAS-related G protein-coupled receptor-X2 (MRGPRX2) activated by neuropeptides (e.g., substance P), opioids, and cationic drugs. Mast cells express receptors for various cytokines (IL-4Rα, IL-5Rα, IFN-γRα, and ST2), vascular endothelial growth factors (VEGFR1 and VEGFR2), neuropilin-1 (NRP1) and neuropilin-2 (NRP2), and angiopoietins (ANGPTs) (TIE1 and TIE2). These cells also display adenosine receptors (A_{2A}, A_{2B}, and A₃), corticotropin-releasing factor receptor type 1 (CRFR1), cannabinoid receptor 1 (CB1), toll-like receptor (TLR)2, TLR4,

TLR5, TLR6, histamine H₄ receptor (H₄R), prostaglandin E₂ receptor (EP₂), NGF receptor (TrkA), PGD₂ receptor (CRTH₂), 2 leukotriene B₄ receptors (BLT₁ and BLT₂), and 2 receptors for cysteinyl leukotrienes (CysLTR₁ and CysLTR₂). Mast cells express receptors for anaphylatoxins (C5aR1/CD88, C5aR2, and C3aR), several receptors for CC and CXC chemokines, and the high-affinity urokinase plasminogen activator receptor (uPAR). These cells also express coreceptors for T cell activation CD40 ligand (CD40L), TNF superfamily member 4 (OX40L), inducible costimulator ligand (ICOS-L), programmed cell death ligands (PD-L1 and PD-L2), and T cell immunoglobulin and mucin domain-containing protein 3 (TIM-3). Not shown in this figure are the inhibitory receptors CD300a, Siglec-8, Siglec-9, and CD200R expressed by human mast cells (modified from Varricchi et al. [13]).

They are associated with several physiological and inflammatory processes, including organ development [5], skin barrier homeostasis [6], wound-healing [7], angiogenesis [8], lymphangiogenesis [9], heart function [10, 11] and tumor initiation and progression [12–15].

Murine mast cells are classified into 2 main subsets: connective-tissue mast cells (CTMC), located near vessels and nerve endings in most connective tissues, and mucosal mast cells (MMC). Both CTMC and MMC are heterogeneous based on the biochemical characteristics of their secretory granule proteases [16]. Recent evidence indicates that adult CTMC originate from precursors seeded in tissues before birth and are self-maintained at steady state without bone marrow involvement [17]. Fate mapping experiments indi-

cate that there are 3 waves of mast cell differentiation [18]. The first and second waves give rise to CTMC, and the third hematopoietic wave contributes to MMC.

Human mast cells form a highly heterogeneous population of cells with differences in ultrastructure, morphology, mediator content, and surface receptors [19]. Classically, 2 types of mast cells have been described in humans, based on the different expression of proteases: MC_{TC}, containing both tryptase and chymase, and MC_T, expressing only tryptase [20]. Human mast cells derive from CD34+CD117+ (KIT) pluripotent hematopoietic stem cells, which arise in the bone marrow [21]. Mast cell progenitors enter the circulation and complete their maturation in the tissues. Whether the development origin of

Fig. 2. Proinflammatory and immunomodulatory mediators of human mast cells. Secretory granules of human mast cells selectively contain several preformed mediators (i.e. histamine, heparin, tryptase, chymase, cathepsin G, carboxypeptidase A3, granzyme B, and renin). Activated mast cells can produce a constellation of cytokines (SCF, TNF- α , IL-1 β , IL-3, IL-5, IL-6, IL-9, IL-10, IL-11, IL-13, IL-16, IL-17A, IL-18, IL-22, IL-25/IL-17E, TGF- β ,

NGF, FGF-2, GM-CSF, and amphiregulin), chemokines (CXCL-8/IL-8, CCL3/MIP-1 α , CXCL10/IP-10, CCL1/I-309, CCL2/MCP-1, CXCL-1/GRO- α), lipid mediators (LTC₄, PGD₂, and PAF), and angiogenic (VEGF-A and VEGF-B) and lymphangiogenic (VEGF-C and VEGF-D) factors. Mast cell activation can be accompanied by the release of extracellular vesicles containing specific proteases and the formation of extracellular DNA traps.

different subsets of human mast cells is similar to in mice remains to be investigated.

Mast cells act as sentinels of the surrounding microenvironment, with the capacity to rapidly perceive insults and initiate different biochemical programs of homeostasis or inflammation. Figure 1 schematically illustrates the constellation of surface receptors expressed by human mast cells. This characteristic explains why these cells are activated not only by antigens [4] and superantigens [22, 23], the main mechanisms which account for their role in allergic disorders, but also by a plethora of immunologic and nonimmunologic stimuli [19]. Several reviews have examined the roles of mast cells in allergic disorders [19, 24], so we do not do so here.

Upon activation, mast cells store and release a large repertoire of biologically active mediators that have potential positive or negative effects on various target cells [25, 26]. These cells and their mediators have been ca-

nonically associated with a detrimental role in allergic diseases [4, 27]. However, due to their presence in nearly all tissues, their proximity to blood vessels, lymphatic vessels, and nerves, the plethora of proinflammatory and immunoregulatory mediators they produce, and their capacity to interact with many immune and nonimmune cells, mast cells are involved in several pathophysiological processes. Figure 2 illustrates the powerful arsenal of preformed and de novo synthesized mediators released from human mast cells. These cells also release extracellular vesicles [28] and form extracellular DNA traps [29].

Mast Cells in the Homeostasis of the Immune System

Figure 3 schematically illustrates the constellation of interactions between mast cells and nearly all immune cells. Histamine (H₁ and H₂ receptors) [30], cysteinyl leu-

Fig. 3. Schematic representation of the multiple interactions between mast cells and several cells of the immune system through the release of mediators. Mast cells can interact with monocytes (histamine, LTD₄, VEGF-A, and PAF), macrophages (histamine, IL-13, IL-6, PAF, and PGD₂), dendritic cells (histamine, PGE₂, PGD₂, VEGF-C, and IL-13), ILCs (IL-1β, IL-9, PGD₂, and LTD₄), NK cells (histamine and heparin), T cells (histamine, LTC₄, LTD₄, and TNF-α), T_H1 (histamine) and T_H2 (histamine, LTC₄, LTD₄, and PGD₂) cells, T_{FH} cells (IL-6), B cells (histamine, PAF, and IL-5), Treg cells (histamine), eosinophils (histamine, IL-5, IL-9, SCF, LTD₄, PAF, PGD₂, and VEGF-A), neutrophils (histamine, LTB₄, PAF, and heparin), basophils (histamine, PAF, and PGD₂), and platelets (PAF).

kotriene D₄ (LTD₄) [31], platelet-activating factor (PAF) [32], and vascular endothelial growth factor A (VEGF-A) [33] modulate the functions of monocytes. Mast cells interact with macrophages through the release of histamine (H₁, H₂, and H₃ receptors) [34, 35], IL-6 [36], IL-13 [37], PGD₂ [38], and PAF [32]. PGD₂ [39], PGE₂ [40], VEGF-C [41], and histamine (H₁ and H₂) [42, 43] influence the activity of dendritic cells. PGD₂ and LTD₄ [44, 45] and cytokines (e.g., IL-1β and IL-9) modulate innate lymphoid cells (ILCs) [46]. Histamine [47] and heparin [48] affect natural killer (NK) cells. On their surface, T cells express histamine H₁ and H₂ receptors [49] and CysLTR₁ [50], and they can be activated by TNF-α [51]. Specifically, helper T1 (T_H1) cells express H₁ and T_H2 cells express H₂ and H₄ receptors [49]; the latter express the CysLTR₁ activated by LTC₄ and LTD₄ [52] and the CRTH2 activated by PGD₂ [53]. IL-6-produced mast cells can indirectly favor the differentiation of follicular T_H cells (T_{FH}) [54]. PAF [55], IL-5 [56], and histamine (H₂ receptor) [57] can modulate B cells. Histamine H₂ and H₄ receptors are expressed by FoxP3⁺ regulatory T (Treg) cells [58]. Several functions of eosinophils can be influenced by histamine (H₄ receptor) [59], LTD₄ [60], PGD₂ [61], PAF [62], IL-5 [63], IL-9 [64], VEGF-A [65], and stem cell factor (SCF) [66]. Histamine (H₄ receptor) [67], LTB₄ [68], PAF [69], and heparin [70] affect neutrophils.

Mediator release from human basophils can be modulated by histamine (H₂ receptor) [71], PGD₂ [72], and PAF [73]. Platelets can be aggregated by PAF [74]. Collectively, these findings indicate that mast cells can influence the functions of nearly all the cells of the immune system via the release of a wide spectrum of mediators.

The central role of mast cells in a variety of pathophysiological processes is also supported by the observation that their mediators affect several nonimmune cells (Fig. 4). In particular, tryptase activates the PAR-2 receptor on fibroblasts [75], keratinocytes [76], and cardiomyocytes [10]. Histamine (H₁ receptor) [77], LTC₄ and LTD₄ (CysLTR₁ and CysLTR₂) [78], PGD₂ [79], and tryptase (PAR-2) [80] act on smooth-muscle cells. IL-13 [81], TNF-α [82], TGF-β [83], IL-9 [84], and PGD₂ [85] activate bronchial epithelial cells. VEGF-A increases the vascular permeability of blood endothelial cells (BECs) [86], whereas VEGF-C and VEGF-D modulate lymphatic endothelial cells (LECs) [9]. IL-13 [87], IL-1β [88], TGF-β [89, 90], TNF-α [91], and PGD₂ [92] activate fibroblasts. PAF activates keratinocytes [93]. Histamine (H₁ and H₂ receptors) [94], LTC₄ and LTD₄ [95], PAF [96], PGD₂ [97], IL-1β [98], and IL-13 [99] activate specific receptors on BECs. IL-13 [100] and LTE₄ [101] elicit mucin release from goblet cells. IL-13 is induced in the adipose tissue of obese humans and activates IL-13Rα2

Fig. 4. Schematic representation of the multiple interactions between mast cells and various nonimmune cells through the release of mediators. Mast cells can interact with blood endothelial cells (histamine, LTC₄, LTD₄, PGD₂, PAF, VEGF-A, IL-13, and IL-1β), lymphatic endothelial cells (VEGF-C and VEGF-D), bronchial epithelial cells (IL-13, TNF-α, IL-9, TGF-β, and PGD₂), smooth-muscle cells (histamine, LTC₄, LTD₄, PGD₂, and tryptase), goblet cells (IL-13 and LTE₄), adipocytes (IL-13), neurons (histamine, NGF, SP, and PGD₂), cardiomyocytes (tryptase), osteoblasts/osteoclasts (histamine and osteopontin), keratinocytes (tryptase and PAF), and fibroblasts (tryptase, PGD₂, TNF-α, TGF-β, IL-13, and IL-1β).

Fig. 5. Human cardiac mast cells can be activated by several immunologic stimuli (e.g., anti-IgE, anti-FcεRI, immunoglobulin superantigens, eosinophils cationic protein [ECP], major basic protein [MBP], and C5a). The activation of cardiac mast cells induces the release of, among other mediators, renin, chymase, and tryptase. Renin, acting independently of angiotensin-converting enzyme (ACE), cleaves the leucine-valine bond in angiotensinogen to generate ANG I. Chymase cleaves the phenylalanine-histidine peptide bond in ANG I to form ANG II. ANG II activates AT₁R on the sympathetic nerves, inducing the release of norepinephrine

which contributes to arrhythmias. ANG II may also exert cardioprotective effects by activating AT₂R resulting in the production of vasodilating mediators (e.g., nitric oxide and prostanoids). Tryptase activates the PAR-2 receptor on sensory nerve fibers, to release substance P which activates the MRGPRX2 receptor. The PAR-2 receptor is also expressed on cardiomyocytes and myofibroblasts. Stem cell factor (SCF) can be released from human cardiac mast cells [174] and activate the KIT receptor on mast cells. Chymase can also cleave SCF¹⁻¹⁶⁶ to form 2 peptides, SCF¹⁻¹⁵⁹ and SCF¹⁶⁰⁻¹⁶⁶, that are biologically active in human mast cells [215].

on adipocytes [102]. Histamine [103] and osteopontin [104] activate H₁ and osteopontin receptor on osteoblasts and osteoclasts, respectively. Finally, H₁, H₃, H₄, and PGD₂ receptors are present in the peripheral and central nervous systems [105]. Activated mast cells can release NGF and substance P that stimulate nerve endings [106, 107]. Collectively, these findings demonstrate that mast cells and their multiple mediators can participate in the homeostasis of several systems.

Mast Cells in the Host Defense against Pathogens

Mast cells, strategically located at host-environment interfaces (e.g., the skin and intestinal mucosa), act as sentinels that sense pathogens and initiate a metabolic immune response. They participate in the first line of defense against the bacterial and viral antigens entering the body, due to their location in the skin and mucosa [108]. Mast cell density increases during certain parasitic infections and the cells degranulate when exposed to parasite antigens [109]. Studies using KIT mutant Kit^{W/W-v} and/or Kit^{Wsh/Wsh} mice suggested that mast cell deficiency, among other abnormalities, affects host immunity against primary infection by several parasites [110–112]. Experiments with KIT mutant mice led to conclusions ranging from no contribution [113] to pathogenic [114] and protective [115] roles of mast cells in leishmaniasis. Interestingly, a recent study using KIT-independent mast cell-deficient Cpa3^{Cre} mice provided evidence that mast cells are not involved in cutaneous leishmaniasis [116].

Several bacterial proteins can induce the release of mediators (e.g., histamine, PGD₂, TNF- α , and cysteinyl leukotrienes) from human mast cells [22, 117–119]. Initial studies with KIT mutant mice showed that mast cells are crucial for protection against enterobacterial infection in the cecal ligation and puncture (CLP) model of sepsis [120, 121]. This observation was confirmed by different groups indicating that mast cells protect against several bacterial infections [122–124]. Toll-like receptor 4 (TLR4) is apparently required for mast cell protection during CLP [125]. These studies indicate that mast cells contribute to host defense by promoting inflammation and/or the ability for myeloid cells to clear bacteria [121, 126]. The protective role of mast cells in CLP has been attributed to TNF- α . However, mast cells are not the main source of TNF- α during CLP [126], and it has been proposed that mast cell-derived IL-6 contributes to a positive outcome after CLP [127]. The possibility exists that mast cells are activated by endogenous peptides (e.g., comple-

ment components, endothelin-1, and neurotensin) during CLP [128]. Mast cells can produce antimicrobial peptides such as cathelicidins [129]. They can also recruit inflammatory cells to exert antibacterial activity. Finally, KIT mutation-associated hematologic abnormalities, such as a reduction in neutrophils, may explain some of the protective roles of mast cells. Ablation of connective tissue mast cells in *Mcpt5-Cre⁺i DTR⁺* mice provided evidence that these cells and CXCL1/2 contribute to neutrophil recruitment into the peritoneal cavity after LPS-induced endotoxemia [130].

Extracellular DNA trap formation is a feature of the cells of the innate immune system (e.g., neutrophils, eosinophils, mast cells, and basophils) [131–134]. Neutrophil extracellular traps (NETs) formation involves the citrullination of histones leading to the decondensation of chromatin, nuclear envelope disintegration and spilling into the cytoplasm, and the extracellular ejection of DNA and granule proteins [133, 135]. Similar to NETs, mast cells also form extracellular DNA traps (MCETs) [29]. In addition to DNA and histones, MCETs contain tryptase [29]. *Streptococcus pyogenes* [136] and *Enterococcus faecalis* induce the formation of MCETs and the antibacterial activity appears to be mediated by the release of LL-37 [137]. The release of NETs from human neutrophils and eosinophils occurs via 2 pathways [138]. The first is a cell death pathway, mainly activated by phorbol-12-myristate-13-acetate (PMA) which occurs within hours after cell activation [139]. The second is a vital form occurring within minutes of activation, independently of cell death [135, 140–142]. It has not yet been elucidated whether mast cells do elaborate these 2 forms, and their distinct pathophysiological roles have also not been established. Whatever the mechanisms, MCETs represent a novel mechanism by which mast cells contribute to host defenses against bacterial and fungal pathogens.

Mast cells contain and release several proteases (e.g., chymase, tryptase, and carboxypeptidase A3 [CPA3]) [19], which can proteolytically inactivate some of the pro-inflammatory mediators. For instance, CPA3 and neurolysin promote homeostasis through the downregulation of endothelin (ET)-1 and neurotensin, respectively [128]. Mouse mast cell protease-1 (MCPT1) can contribute to the clearance of *Trichinella spiralis* [143] through the degradation of occluding [144], and MCPT4 decreases the severity of Gram-positive bacterial infection [145]. It is important to note that some mast cell mediators (e.g., TNF- α and IL-10) can be detrimental to the outcomes of certain bacterial infections and can aggravate multiorgan dysfunction associated with sepsis [126, 146].

Mast cells are strategically located to respond to inhaled and cutaneous fungi. *Aspergillus* activates mast cells [147] and contributes to the allergic response in vivo [148]. *Aspergillus fumigatus* [149] and *Candida albicans* activate mast cells [150]. Interestingly, human mast cells mount an initial response toward *C. albicans* characterized by rapid release of enzymes, neutrophil recruitment, and reduced fungal viability, followed by a later stage that includes the secretion of anti-inflammatory cytokines such as IL-1ra [151]. *C. albicans* affects differently mucosal and stromal mast cells. Mucosal mast cells did not kill fungi and can actually be killed by them. In contrast, stromal mast cells kill ingested yeasts. Interestingly, mast cells also modify the local microbial composition in *Candida*-infected mice, indicating that these cells can modulate gut microbiota. Recent evidence indicates that *C. albicans* can stimulate the release of several cytokines from mast cells [36].

In conclusion, the role of mast cells in the host response against pathogens has been investigated using KIT-dependent and KIT-independent mast cell-deficient mice and mice with specific mast cell-mediator deficiencies. These studies indicate that mast cells can either promote host resistance to infection or contribute to a dysregulated immune response that can increase host morbidity and mortality. Unfortunately, there is no model to study how mast cells contribute to infection outcomes in humans, so several questions remain unanswered.

Mast Cells in Angiogenesis and Lymphangiogenesis

The formation of new blood (angiogenesis) and lymphatic vessels (lymphangiogenesis) occurs vigorously during embryogenesis but is restricted during adulthood [152]. In adults, angiogenesis/lymphangiogenesis is limited to sites of wound-healing, inflammation, and cancer [8]. Angiogenesis and lymphangiogenesis are finely modulated by several stimulatory and inhibitory signals [153]. VEGF-A is the most potent angiogenic factor acting on VEGF receptor 2 (VEGFR2) in BECs [154]. VEGF-C and VEGF-D are crucial for the survival, proliferation, and migration of LECs by engaging VEGFR3 [155]. VEGF-A also influences lymphangiogenesis by recruiting immune cells (e.g., macrophages and mast cells) that produce VEGF-C and VEGF-D [9, 156]. Angiopoietins (ANGPT1 and ANGPT2) also modulate angiogenesis and lymphangiogenesis through the engagement of TIE1 and TIE2 receptors [157]. ANGPT1, expressed by pericytes, supports BEC survival whereas ANGPT2, secreted by BECs, acts

autocrinally and paracrinally as the TIE2 ligand to promote angiogenesis and lymphangiogenesis [158]. TIE1 and TIE2 mRNAs are expressed in human lung mast cells and ANGPT1 induces migration of these cells through the engagement of TIE2 [159]. Angiogenesis and lymphangiogenesis are also modulated by certain chemokines [160].

Several immune cells are involved in the modulation of angiogenesis and lymphangiogenesis [8, 9, 13, 161–165]. Various immunologic and nonimmunologic stimuli induce the production of VEGF-A from human mast cells [166, 167]. Human lung mast cells express several isoforms (121, 165, 189, and 206) of VEGF-A, and activation of these cells induces the release of VEGF-A [9]. These cells also express VEGF-B, VEGF-C, and VEGF-D. VEGFs induce mast-cell chemotaxis in vitro [9] and in vivo [168] through the activation of both VEGFR1 and VEGFR2.

Recently, we demonstrated that immunologic (anti-IgE) stimuli and bacterial and viral immunoglobulin superantigens (proteins A and L) activate primary human cardiac mast cells to release angiogenic (VEGF-A) and lymphangiogenic (VEGF-C) factors [169, 170]. Mast cells are strategically located in the human and murine heart [171, 172] and their mediators are involved in several cardiometabolic diseases [173–176]. Interestingly, lymphangiogenic factors can contribute to blood pressure homeostasis [177], lipid metabolism [178], and coronary artery development [179]. Understanding how cardiac mast cells participate in physiological and pathological angiogenesis and lymphangiogenesis could contribute to the development of targeted therapies for important cardiometabolic disorders.

Mast Cells in the Immune Landscape of Cancer

Immune cells recognize and eliminate cancer cells that are constantly generated [180]. However, immune-resistant cancer cells can make trickery and proceed to develop tumors [181]. A normal microenvironment (consisting of immune cells, fibroblasts, blood and lymphatic vessels, and interstitial extracellular matrix) plays a pivotal role in maintaining tissue homeostasis and is a barrier to tumor initiation [182]. Incorrect signals (e.g., proinflammatory cytokines/chemokines, reactive oxygen species, adenosine, and lactate, or hypoxia) from an aberrant microenvironment alter tissue homeostasis and promote tumor growth. Several cells of the innate and adaptive immune system (macrophages, mast cells, lymphocytes,

neutrophils, eosinophils, T_{FH} cells, NK cells, and NK T cells) are components of the microenvironment that physiologically protect from or promote the development of tumors [183–185].

Mast cells are present in the microenvironment of several human solid and hematologic tumors [13, 14]. In several tumors, such as thyroid [168, 186], gastric [187], pancreas [188, 189], and bladder [190] cancer, Merkel cell carcinoma [191], Hodgkin's [192] and non-Hodgkin's lymphoma [193, 194], and plasmacytoma [195], mast cells are associated with a poor prognosis. In breast cancer, mast cells appear to play an antitumorigenic role [196]. Collectively, these results indicate that the contribution of mast cells to cancer is tumor-dependent.

The role of mast cells in cancer varies according to the stage of tumorigenesis. A low density of mast cells in invasive melanomas correlates with a poor prognosis, but the mast cell count is not correlated with survival in superficial melanomas [197]. In prostate cancer, mast cells are initially protumorigenic, but become dispensable at later stages [198, 199]. In stage I non-small-cell lung cancer (NSCLC), increased peritumoral (but not intratumoral) mast cell density confers a survival advantage [200].

There is also evidence that the role of mast cells in tumors varies according to their microlocalization. In NSCLC, the presence of mast cells in tumor islets is a favorable prognostic factor [201]. In pancreatic carcinoma, mast cell density in the intratumoral border zone, but not in the peritumoral or intratumoral zones, is associated with a poor prognosis [202]. In prostate cancer, increased intratumoral mast cell density is associated with a good prognosis [203]. It has also been found that intratumoral mast cells inhibit tumor growth, but that peritumoral mast cells stimulate human prostate cancer [204]. Mast cell density is increased, particularly at the tumor periphery, and correlates with disease progression in both cutaneous T cell and B cell lymphomas [205]. Collectively, these findings suggest that the contribution of mast cells in several tumors varies according to their microlocalization.

Mast Cells and the Renin-Angiotensin System

The renin-angiotensin system (RAS) plays a central role in the homeostatic control of the cardiovascular and renal systems, and in regulating the volume of extracellular fluid [206, 207]. The RAS consists of several enzymatic reactions that generate angiotensin II (ANG II). Initially, renin cleaves angiotensinogen to produce ANG

I, which is then hydrolyzed by the angiotensin-converting enzyme (ACE) to produce ANG II. This peptide acts on ANG II type 1 receptor (AT₁R) and AT₂R. ANG II promotes vasoconstriction, inflammation, salt and water reabsorption, and oxidative stress via the activation of AT₁R [206, 207].

Silver et al. [208] discovered that cardiac mast cells store and release renin. This observation was extended to the human mast cell line, HMC-1, and also human heart and lung mast cells [209]. We have shown that human cardiac mast cells store and release chymase [174], a protease also involved in the formation of ANG II [210], independently of ACE. Chymase cleaves the phenylalanine-histidine peptide bond in ANG I to generate ANG II and is an important enzyme in the formation of ANG II in the heart [211, 212]. ANG II activates AT₁R on the sympathetic nerves, promoting the release of norepinephrine [213] which contributes to the development of cardiac arrhythmias [11]. Figure 5 schematically illustrates that activation of human cardiac mast cells can induce the release of renin, chymase, and tryptase. These mediators can exert multiple effects in the homeostatic control of the cardiovascular system.

An additional link exists in the heart between sensory nerves and renin-containing mast cells, in that in ischemia/reperfusion cardiac sensory nerves release neuropeptides such as substance P and CGRP. Figure 5 also illustrates that tryptase released from mast cells can activate the PAR-2 receptor on nerve fibers, cardiomyocytes, and myofibroblasts. PAR-2-activated sensory nerve fibers release substance P, which, in turn, activates the MRGPRX2 receptor on human cardiac mast cells [169]. Interestingly, recent provocative results suggest that the activation of PAR-2 on cardiomyocytes by tryptase might exert a protective effect during experimental myocardial infarction [10].

Conclusions and Perspectives

Mast cells have a widespread distribution at strategic locations in nearly all human tissues. For decades, mast cells were viewed simplistically as effector cells in allergic disorders. During recent years, these cells have gained recognition for their involvement in various physiological and pathological processes. There is now evidence that mast cells and their different products (soluble mediators, extracellular vesicles, and extracellular DNA traps) communicate with nearly all immune cells and contribute to the homeostasis of the immune system. The role of these

cells in a variety of pathophysiological processes is also supported by the observation that their products affect a variety of nonimmune cells.

Mast cells and their mediators trigger a cascade of events that can be either protective or detrimental to the outcomes of microbial infections. The controversial role of mast cells in host defense against pathogens could be revealed by deploying different experimental models (e.g., KIT-dependent and KIT-independent mast cell-deficient mice). Diversity is an essential feature of immune cells, as they must respond to innumerable pathogens. We would like to suggest that different subtypes of mast cells could exert opposite effects under different pathophysiological conditions.

Activated cells can produce both angiogenic and lymphangiogenic mediators. Both processes occur vigorously in wound-healing, e.g., following myocardial infarction and tumor growth. Lymphangiogenesis is also involved in the resolution of inflammation [214]. The recent demonstration that the activation of human cardiac mast cells leads to the production of both angiogenic and lymphangiogenic factors [169, 170] could open up new perspectives for the pathophysiology of cardiovascular diseases.

The role of mast cells in the onset and progression of different human tumors is far from being understood. Intriguing results from several studies indicate that the pro- or antitumorigenic role of mast cells in different human tumors is cancer-specific, depending on the microlocalization of these cells and the stage of tumorigenesis. It is quite possible that different subtypes of mast cells play a protective role whereas other types play a protumorigen-

ic role. Single-cell mapping of peri- and intratumoral mast cells could help to elucidate the functions of different subsets of mast cells in the various stages of tumorigenesis.

In conclusion, although mast cells and their mediators have been simplistically associated with a detrimental role in allergic diseases, there is overwhelming evidence that these cells can also have multiple homeostatic and protective roles in several pathophysiological processes.

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