Editorial

Mast Cells: Fascinating but Still Elusive after 140 Years from Their Discovery

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1. Preface

Some of the basic characteristics of tissue mast cells were described over 140 years ago by Paul Ehrlich, the founder of modern immunology [1]. At that time, the mast cells’ distinguishing feature was the affinity of their cytoplasmic granules for certain basic dyes. For several decades, mast cells and their mediators were essentially considered to play mainly a proinflammatory role in allergic disorders, such as bronchial asthma [2–4], allergic rhinitis [5], urticaria [6,7], food allergy [8,9], anaphylaxis [10,11], atopic dermatitis [12], and angioedema [13]. With the appreciation of these cells as major potential sources of a myriad of cytokines and chemokines, it became evident in the 1990s that mast cells may express immunoregulatory functions [14,15]. During the last decades, it was demonstrated that mast cells can also produce different proangiogenic [16–18] and lymphangiogenic factors [19,20], suggesting that they may actually play a role in tumor initiation and growth [21–24]. Moreover, these cells can be activated by different viral [25,26] and bacterial proteins [27,28] and thereby represent a potentially important cell during microbial infections. Therefore, the spectrum of diseases in which mast cells and their mediators have been implicated has extended to include bacterial, fungal, viral, and helminth infections [26,29–31]; several diseases of the cardiovascular [14,32,33] and gastrointestinal systems [34–36]; and the joints [37,38]. Figure 1 schematically summarizes the wide spectrum of pathophysiological conditions in which mast cells and their mediators have been implicated during the last decades.

This volume contains contributions by several established investigators in the field of mast cell biology. The volume starts with a collaborative paper by Stephen J. Galli, Gilda Varricchi, and Gianni Marone, illustrating initial and more recent studies which have attempted to identify distinct “subpopulations” of mast cells based on the analyses of transcriptomes of anatomically distinct mouse mast cell populations [39–42]. The authors illustrate the important roles played by mast cells to the control of homeostasis in different pathophysiological conditions. Moreover, they discuss the possibility that distinct subpopulations of mast cells could play different roles in cardiovascular disorders and in tumorigenesis. Finally, the authors speculate that at least two major subsets of mast cells, MC1 and MC2, like macrophages (M1 and M2 subtypes) [43], dendritic cells (D1 and D2) [44], and neutrophils (N1 and N2) [45,46], could play distinct or even opposite roles in different pathophysiological conditions.
Kirshenbaum and collaborators describe the biochemical and immunological characteristics of a novel human mast cell line (LADR) which they have established [47]. LADR cells are characterized by a slower proliferation rate and more advanced development compared to the classical LAD cell line. This new cell line appears to be a valuable addition for in vitro studies of human mast cell biology.

Mekori and coworkers illustrate the possible roles of various miRNAs in IgE-mediated allergic and non-allergic diseases involving mast cell activation [48]. Theoharides and collaborators report that IL-27, produced by activated macrophages, can be modulated by mast cell mediators, such as heparin and tryptase [49]. Kwon and Kim report that leukotriene B₄ (LTB₄) can activate the low-affinity LTB₄ receptor, BLT₂, on mast cells. Engagement of BLT₂ mediates the synthesis of the most potent proangiogenic molecule, vascular endothelial growth factor (VEGF-A), and IL-13 from mast cells. The authors speculate that novel strategies aimed to block BTL₂ could contribute to the treatment of allergic disorders [50].

It is well established that mast cells are strategically localized in different sections of the human heart, such as the myocardium [51,52], the atherosclerotic plaque [33], and the aortic valve [53]. Kovanen comprehensively reviews the complex role of mast cells throughout the progression of early to late lesions of human atherosclerosis [32]. Immunohistochemical studies in autopsied patients and studies in cell culture systems and in atherosclerotic mouse models have collectively provided evidence that mast cell mediators may promote atherogenesis at various stages of lesion development.

Mastocytosis is a hematopoietic neoplasm characterized by abnormal expansion and focal accumulation of clonal mast cells in various organs [54–56]. The disease is highly heterogeneous and exhibits a complex pathology and different clinical presentations. Valenti and a group of international leaders reviewed the WHO classification of mastocytosis and their different prognosis. The authors also illustrate the different symptoms and associated co-morbidities of various forms of mastocytosis. Finally, they emphasize the multidisciplinary aspects of the disease and discuss related challenges in daily practice [57]. Another group of mastocytosis experts demonstrate the expression of programmed death ligand 1 (PD-L1) on mast cells from patients with mastocytosis [58]. PD-L1 is expressed on tumor cells [59,60] and also on several activated immune cells, including CD4⁺ and CD8⁺ T cells, B cells, NKT cells, and mast cells [61–63]. PD-L1 expression has been shown to be upregulated in several tumor cells as a mechanism of immune suppression and evasion [64]. The authors review the literature on PD-L1 expression on mast cells from patients with mastocytosis.

Aldehyde dehydrogenase 2 (Aldh2) is the most efficient isoenzyme within the ALDH enzymes to remove toxic metabolites from the metabolism of alcohol [65]. A genetic polymorphism (rs671) in ALDH2 is present in approximately 40% of Eastern Asian populations [65,66] and is associated with alcohol flush syndrome [67]. Kim and coworkers demonstrate that bone-marrow-derived mast cells from mice with a genetic deletion of Aldh2 have increased proliferation and IL-6 production after activation by stem cell factor (SCF), as well as when co-stimulated with SCF and an antigen [68]. These findings provide insight into the regulation of mast cell responsiveness in relation to alcohol-associated flushing.

There is increasing evidence that mast cells and their mediators can be involved in several aspects of tumor initiation and growth [21,39,69,70]. However, their impact on experimental and human tumors remains controversial [22,23]. Several papers in this volume address this complex and still controversial issue. Redegeld and collaborators, by using a 3D co-culture model, elegantly investigated the role of mast cells in colon cancer. By comparing the transcriptomic profile of colon cancer-co-cultured mast cells versus control mast cells, they identify several deregulated genes which can contribute to cancer development. This experimental model could represent a novel approach to investigate the role of mast cells in tumorigenesis [71].

Sammarco and collaborators investigated the role played by mast cells in the modulation of angiogenesis and lymphangiogenesis in human gastric cancer [21]. They report that mast cell density is increased in gastric cancer and there is a correlation with angiogenesis [72,73]. They also report that gastric mast cells express PD-L1, a relevant checkpoint, and that several undergoing clinical trials are targeting immune checkpoints in gastric cancer. The authors suggest that elucidation of the
role of subsets of mast cells in different human gastric cancers will demand studies of increasing complexity beyond those assessing merely mast cell density and microlocalization. Antonelli and coworkers, based on their long-lasting experience, comprehensively reviewed the roles of immune and inflammatory cells, cytokines, and chemokines in the thyroid cancer microenvironment [74]. Ribatti and Vacca illustrate the role of bone marrow angiogenesis in the pathogenesis and progression of hematological malignancies [75]. Based on their extensive experience, they discuss the roles played by mast cells in the modulation of angiogenesis in patients with multiple myeloma. Sagi-Eisenberg describes a novel mechanism by which adenosine, released by activated mast cells, can autocrinally activate the A3 adenosine receptor [76].

Mast cells are strategically located at sites that interface with the external environment, such as the skin [77], lung [78], and intestine [34,79]. These locations allow mast cells to act as sentinels for tissue damage and pathogen invasion [4]. Moreover, the association between mast cells and blood vessels [32,52] is optimal to foster the rapid recruitment of immune cells out of the bloodstream and into the inflamed tissues. This process is facilitated by the mast cell production of TNF-α [80–84] and IL-1β [85,86] that activate endothelial cells, the release of vasoactive mediators (i.e., histamine and cysteinyl leukotrienes) [87,88], and chemokines that promote the recruitment of inflammatory and immune cells [24,70,89–92]. Marshall and coworkers elegantly reviewed the complex roles of mast cell responses to viruses and pathogen products [26]. This review highlights the complexity of mast cell biology in the context of innate immune responses. Di Nardo and collaborators elegantly demonstrated that mast cells express lipocalin 2 (LPCN2), a known inhibitor of bacterial growth. Using mast cells derived from mice deficient in LPCN2, they show that this antimicrobial peptide is an important component of mast cell activity against Escherichia coli. They also demonstrate that sphingosine-1-phosphate (SIP) activates a specific receptor (SIPR) on mast cells to release LPC2, which exerts antimicrobial activity against several bacteria such as Staphylococcus aureus and E. coli [93]. Piliponsky and collaborators extensively reviewed the role of mast cells and their mediators in viral, bacterial, and fungal infections [29]. They discuss recent studies focused on mast cell interactions with flaviviruses and Candida albicans, and mast cell functions in a model of cecal ligation and puncture. Collectively, the results of these studies illustrate that mast cells can either promote host resistance to infections or contribute to a dysregulated host response that can increase host morbidity and mortality.

Coeliac disease is a human autoimmune-like disorder characterized by chronic inflammation of the small intestine induced by proline- and glutamine-rich wheat gluten [94,95]. Coeliac disease is the result of complex interactions of genetic, environmental, and immunological factors [96]. Although coeliac disease is considered a prototype of T-cell mediated disease [96], the innate immune system can contribute to its pathogenesis. Frossi and collaborators’ review has interesting results, indicating that mast cells and their mediators could play a role in the pathogenesis of coeliac disease [94].

Rheumatoid arthritis is a chronic systemic autoimmune disease primarily affecting the joints [97]. Mast cells are present in healthy synovial tissue [98] and their density is increased in rheumatoid arthritis synovitis [99,100]. However, the exact functions and the correlations of mast cell density with disease development and progression are still largely unknown. Moreover, contradictory data have been obtained in animal models and from patients with long-lasting disease [101–103]. Rivellese and coworkers present a careful revision of the literature on mast cells in rheumatoid arthritis, including recent observations from patients with early disease indicating that these cells are relevant markers of disease severity [37,38].

In recent years, accumulating evidence has revealed the close anatomical contact and functional interactions between neurons and mast cells [104–106]. Theoharides and coworkers present a careful revision of the literature and recent findings on mediators released from activated mast cells that could activate microglia [107,108], causing localized inflammation [109–111] and some symptoms of autism spectrum disorder [112].

Boo and collaborators present original results in a mouse model of allergen-provoked localized vulvodynia, supporting the hypothesis that mast cells are involved in this painful disorder [113].
2. Conclusions and Future Directions

This is a wonderful time in mast cell research. Indeed, the last years have witnessed unprecedented progress in our understanding of the development of mast cells [40–42]. Moreover, extraordinary progress has been made in understanding the complex homeostatic and protective roles of these cells in different pathophysiological conditions [31,39,114,115]. Mast cells, known for decades for their detrimental role in allergic diseases, are now recognized to play crucial roles in a diverse array of physiological and pathologic functions [15,30,116]. We would like to speculate that such different, sometime opposite effects of mast cells are made possible by the plurality of mast cell subpopulations. Recently, comprehensive analysis of the transcriptome of individual anatomically distinct mast cells [117] and fate-mapping system [40,41,118] demonstrate that rodent mast cells form a highly heterogeneous population of immune cells [40–42], similar to macrophages [43,119] and T cells [120,121]. These fascinating results indicate that much more remains to be discovered in development, migration to tissues, biochemistry, and functions of different subsets of rodent and human mast cells.

Figure 1. This figure schematically illustrates the wide spectrum of pathophysiological conditions in which mast cells and their mediators have been implicated. For several decades mast cells were considered to play mainly proinflammatory roles in several allergic disorders, such as bronchial asthma [2–4,122], allergic rhinitis [3], urticaria [6,7], food allergy [8,9], anaphylaxis [10,11], atopic dermatitis [12], and angioedema [13]. During the last years, it became evident that mast cells represent an important cell during bacterial [26,27,29], fungal [29], viral [25,29], and helminth infections [30,31]. Elegant studies have demonstrated that mast cell-derived mediators can play protective roles against several venoms [114,115]. Mast cells and their mediators can be involved in several aspects of tumor initiation and growth [21,39,69–71], presumably through the production of several angiogenic and lymphangiogenic factors [19,20,75]. Systemic mastocytosis is a clonal disease associated with a somatic gain-of-function KIT mutation [56,57,123]. Mast cells, strategically located in different sections of the human heart [51,52] and atherosclerotic plaque [32,33], are involved in different phases of atherosclerosis and myocardial infarction. These cells can be involved in several autoimmune disorders, such as rheumatoid arthritis [37], coeliac disease [94], multiple sclerosis [124], and bullous dermatoses [125]. Mast cell–nerve communications are involved in stress, pain, pruritus [126,127], and in inflammatory bowel diseases [35,36].

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After 140 years from their discovery, mast cells remain fascinating but still elusive cells of the immune system. The characterization of subpopulations of mast cells by single-cell RNA-seq, together with analysis of encoded proteins, will be of paramount importance to modulate the injury- or repair-inducing abilities of these immune cells.

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**Abbreviations**

- Aldh2: Aldehyde dehydrogenase 2
- BTL2: Low-affinity leukotriene (LT) B4 receptor
- E. coli: Escherichia coli
- IL-13: Interleukin-13
- LPCN2: Lipocalin 2
- LTB4: Leukotriene B4
- NKT: Natural killer T-cell
- PD-L1: Programmed Death Ligand 1
- S1P: Sphingosine-1-phosphate
- S1PR: Sphingosine-1-phosphate receptor
- SCF: Stem cell factor
- TNF-α: Tumor Necrosis Factor-α
- VEGF-A: Vascular Endothelial Growth Factor-A

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