PREFACE

Resident mast cells are uniquely positioned in multiple organ systems at either the tissue and/or external environment or located near nerve endings and/or blood vessels. These locations allow the mast cell to serve as a sentinel and thus play a critical role in not only inflammatory situations to promote recruitment and infiltration of other immune cells, but also homeostatic maintenance. Although mast cells have several conserved characteristics, the authors provide evidence that the micro-environment influenced differences in the phenotype of tissue-specific mast cells, control the various responses to injury, inflammation and remodeling. This book brings together the work from experts across multiple tissue/organ systems and inflammatory causes (viral, bacterial, and autoimmune) to present the most up to date knowledge regarding the role of mast cells in these regulatory and disease events.

Chapter 1 – Mast cells (MCs) have long been known as major effector cells of IgE-dependent allergic diseases, including asthma. However, during the last decade the field of mast cell biology has expanded well beyond the boundaries of atopic disorders. MCs are now recognized to play important roles in several IgE-independent physiological and pathological conditions, such as innate immunity, wound healing, chronic inflammatory and autoimmune diseases, atherosclerosis, and cancer. Scattered throughout the organism and particularly abundant in the skin and the mucosal surfaces, MCs are strategically localized at the host/environment interface and express a wide variety of receptors, suggesting their sentinel role in innate immune responses. These cells have the ability to produce, store and upon activation release a variety of vasoactive, proinflammatory, and nociceptive mediators and molecules.

Major developments have been made in the authors' understanding of the complex networks by which these products are released and exert regulation. This chapter focuses on the biological functions of MCs, the regulation of the production of their mediators, and the mechanisms by which these mediators regulate MCs functions in host defense and disease.

Chapter 2 – Mast cells are triggered to release histamine and other mediators of inflammation when immunoglobulin E (IgE) receptors on the cell membrane are brought into close proximity, i.e. aggregated. This is usually accomplished in model systems by cross-linking IgE-loaded receptors with multivalent ligands, but can also be achieved by monovalent ligands bound to a fluid lipid bilayer, which may be patterned or homogeneous. With homogeneous membranes, the receptors on the mast cell develop a spatial pattern that bears some similarity to the T cell synapse. Ligand presentation on membranes may be a good model for the interactions of mast cells with various parasites; thus, the development of

spatial patterns of receptors and the consequence for mast cell signaling is likely to be important for this most basic mast cell role. In this chapter, the authors review the role of the spatial organization of signaling components and IgE receptors in mast cell signaling.

Chapter 3 – Mast cells (MCs) derive from hematopoietic stem cells, circulate in the blood as precursors cells, differentiate and mature locally after migration into vascularised tissues. According to the tissue localization, they show different histochemical and phenotypic characteristics thus, displaying functional plasticity. In large part, MC pleiotropic functions reflect their ability to secrete a wide spectrum of preformed or newly synthesized biologically active products with pro-inflammatory, anti-inflammatory and/or immunosuppressive properties, enabling these cells to orchestrate all stages of immune response. The modulation of MC effector phenotypes relies on a wide variety of membrane molecules involved in cell–cell or cell–extracellular-matrix interaction and in the delivery of co-stimulatory signals allowing them to respond to multiple signals.

All newly described MC features led investigators to reevaluate MC role in tissue remodeling, homeostasis and regulation of innate and adaptive immune responses. This chapter focuses on recent progress in defining MC heterogeneity and in highlighting its complex and versatile role within the immune system. Specifically, the paradigm of the multiplicity of the MC functions in tumor onset and progression processes will be elucidated.

Chapter 4 – This chapter reviews published evidence that the mast cell (MC), beyond being among the first responders in host defense and the primary effector cell in Type I hypersensitivity responses to environmental allergens, also participates in more protracted, even chronic, inflammations, and can influence the natural history of such. As a legitimate immune effector cell, MCs can exacerbate a variety of hypersensitivity responses, many of which are auto-immunopathies, by regulating other immune and antigen-presenting cells through humoral and direct cell-cell contact, and by facilitating recruitment of leukocyte in early and, especially, late-phases of immune and other inflammatory reactions. Mast cells recruit leukocytes by promoting expression of adhesion molecules that effect critical leukocyte-endothelial cell interactions enabling leukocytic infiltration. These prominently include leukocyte and intercellular adhesion molecules (E-selectin; ICAM-1) induced by TNF-α, and interleukin-1 released from activated MC and other cells. Evidence that some cytokines or other MC or leukocyte mediators have prominent anti-inflammatory activity which limits immune injury and promotes tissue repair and re-modeling is also cited. Histamine, proteases, TNF-α and leukotrienes are selected as some MC mediators that have been monitored in auto-immune and other inflammatory conditions. The prospect remains speculative that these or other products of activated MC, even proteases unique to such cells, could be useful markers of clinical disease ancillary to diagnosis and follow-up.

Chapter 5 – Mast cells are well known as key effector cells in IgE dependent allergic reactions. Upon activation, they release preformed or *de novo* synthesized inflammatory mediators such as histamine, proteases, eicosanoids, cytokines and chemokines. In the last years, mast cells are also recognized as guardians in innate immune response. Activation of mast cells in host defense results from different pathways which can be divided in a complement-dependent and complement-independent mechanism. The contribution of mast cells *via* complement system is caused by their ability to express complement receptors (CR). In case of complement-independent mechanism, mast cells recognize pathogens by Toll-like receptors (TLRs), nucleotide-binding oligomerization domain (NOD)-like receptors (NRLs) and mannose-binding receptor CD48. Activated mast cells release mediators such as TNFα

responsible for the recruitment of granulocytes and the initiation of the immune response. The intestinal immune system faces a considerable challenge in tolerating commensal flora while preventing the dissemination of potential pathogens. The authors observed that the functional responsiveness to TLR ligands is down-regulated in mast cells isolated from the intestinal mucosa compared with mast cells from other origin. The present article provides an overview on the role of mast cells in host defense against Gram-negative bacteria and bacterial products such as lipopolysaccharide (LPS) in general and at the gastrointestinal barrier in particular.

Chapter 6 – First recognized in 1991 and finally termed such in 2007, "mast cell activation syndrome" (MCAS) is a large, likely quite prevalent collection of illnesses resulting from MCs which have been inappropriately activated but which, in contrast to the rare "mastocytosis," are not proliferating, or otherwise accumulating, to any significant extent. Due to the marked diversity of direct and indirect, local and remote biological effects caused by the plethora of mediators released by MCs, MCAS typically presents as chronic, persistent or recurrent, waxing and waning or slowly progressive multisystem polymorbidity generally, but not necessarily, of an inflammatory theme. Suspected to be of clonal origin in most cases, MCAS usually is acquired relatively early in life via unknown mechanisms; interaction of environmental factors with inheritable risk factors is one possibility. Initial manifestations often occur in childhood or adolescence but are non-specific; in fact, virtually all of the syndrome's manifestations are non-specific, leading to decades of mysterious illness (and incorrect diagnoses often poorly responsive to empiric therapies) prior to diagnosis. A large menagerie of mutations in MC regulatory elements has been found in MCAS patients; most patients appear to have multiple such mutations, with no clear patterns, or genotype-phenotype correlations, yet apparent. Such mutational heterogeneity likely drives the heterogeneity of aberrant MC mediator expression, in turn causing the extreme heterogeneity of clinical presentation. Different MCAS patients can present with polar opposite clinical aberrancies. All of the body's systems can be affected by MCAS. In addition to clinical heterogeneity, diagnosis is confounded by difficulty not only in detecting sensitive and specific biomarkers of primary MC disease but also in finding histologic evidence of a non-proliferative disease wrought by cells capable of great pleomorphism. For example, in contrast to proliferative mastocytosis which usually drives significantly elevated tryptase levels, relatively non-proliferative MCAS usually presents with normal tryptase levels; instead, histamine, MC-specific prostaglandins, and other mediators need to be assessed in evaluations for MCAS. Although the World Health Organization 2008 classification scheme for myeloproliferative neoplasms does not recognize MCAS, proposals for diagnostic criteria have been published recently and generally require presence of symptoms consistent with chronic/recurrent aberrant MC mediator release, laboratory evidence of such release (or of mast cell proliferation not meeting WHO criteria for systemic mastocytosis), absence of any other evident disease which could better explain the full range of findings in the patient, and, ideally but not necessarily, at least partial response to therapy targeted against MCs or MC mediators. Systemic MC disease of any form is not presently curable. Therapies for MCAS generally aim to control and ameliorate the disease by inhibiting aberrant mediator production and release, blocking released mediators, and/or managing the consequences of aberrantly released mediators. Many such therapies are available. Although there presently is no method to predict which set of therapies will best control the individual patient's disease, a methodical, persistent, trial-and-error approach usually succeeds in finding significantly

helpful therapy. Lifespan for most MCAS patients appears normal, but quality of life can be mildly to severely impaired absent correct diagnosis and effective treatment.

Chapter 7 – Mast cells (MCs) are resident cells containing many histamine and heparin rich granules. Although best known for their roles in allergy and anaphylaxis, accumulating evidence has strongly suggested that MCs have also been intimately involved in, or apparently coordinating numerous other physiological and pathophysiological processes. The authors will review the roles of MCs in bone disorders, especially heterotopic ossification (HO), a common clinical complication, or a rare but life-threatening hereditary condition, and briefly discuss the current major challenges and potential future directions.

Chapter 8 – Mast cells are crucial elements in several physiological and immunological functions in the body. The role of mast cells in allergic reactions, and parasitic infections is well established. Recently, their role in non-allergic phenomenon is getting more attention. Mast cells phagocytize and process antigens and play an important role in immune response against bacterial infections. Mast cells not only act as the first line of defense against parasitic and bacterial challenges but several studies indicate that mast cells also play a very important role in the pathology and pathogenesis of viral infections through intracellular and extracellular antiviral defense mechanisms. Furthermore, studies indicate that mast cells and several mast cell mediators are angiogenic, regulate endothelial cell proliferation and promote angiogenesis and progression of tumor malignancies in humans and animals. In this chapter, the role of mast cells in neoplasm angiogenesis and progression and in bacteria- and virus-induced inflammatory processes will be covered.

Chapter 9 – Although mast cells are normally present in the human testis and ovary, little is known about their phenotypic characteristics and their gonadal roles in heath or disease. Recently, however, it became clear that mast cell-specific genes are robustly increased in the testes of men with impaired spermatogenesis as compared to samples with normal spermatogenesis. Furthermore, immunohistochemistry and morphometric studies, as well as electron microscopy, revealed a massive accumulation of activated, tryptase-immuno-reactive mast cells in the wall of seminiferous tubules, bearing impaired spermatogenesis. The normal architecture of this wall, which consists of smooth-muscle-like peritubular cells and extracellular matrix (ECM), is fibrotically altered in these cases, as well. These observations led to the hypothesis that mast cells may target peritubular cells, resulting in fibrosis and unexplored consequences, which impair spermatogenesis and male fertility. Studies with cultured *h*uman *t*esticular *p*eritubular *c*ells (HTPCs) have allowed us to explore aspects of this topic. The authors found that the products of testicular mast cells, tryptase and tumor necrosis factor alpha (TNFalpha), stimulated the production of decorin, an ECM-proteoglycan with multiple functions, including interference with growth factor signaling and activation of toll-like receptors (TLRs). TNFalpha also stimulated the production of interleukin-6 and monocyte chemo-attractant protein-1 (MCP-1) by HTPCs. MCP-1, as a potent chemo-attractant cytokine, may be involved in the increase in testicular macrophages, which are likewise significantly elevated in number in infertility patients and thus may enhance an inflammatory milieu. An inflammatory milieu in testes of sub- and infertile men may also include increased levels of prostaglandins and reactive oxygen species (ROS). A metabolite of prostaglandins induced the generation of ROS in HTPCs, and ROS caused a loss of the contractile abilities of HTPCs. Prostaglandins may originate from different cells, including mast cells. Testicular mast cells in states of partial degeneration of seminiferous tubules express the prostaglandin-synthesizing enzyme cyclo-oxygenase 2 (COX-2). Antagonistic

actions of products of mast cells emerge with regard to nerve growth factor (NGF), a product of peritubular cells with an assumed role in mast cell maturation and spermatogenesis. TNFalpha increases the production of NGF at the transcriptional level, while tryptase enzymatically cleaves both NGF and its precursor, proNGF, thus altering the levels of bioactive proNGF and NGF. These results suggest a key role for mast in the human testis in states of sub-/infertility. A better understanding of these multi-facetted cells in the human gonads may lead to novel therapeutic approaches in infertility.

Chapter 10 – Mast cells are resident cells in a variety of organ tissues, and are known as a key cell type involved in type I hypersensitivity. However, recent studies suggest that these cells may be capable of regulating inflammation, host defense, and innate immunity.

Moreover, these cells have been associated with the pathophysiology of inflammatory bowel disease (IBD), which consists of ulcerative colitis and Crohn's disease. IBD is characterized by chronically relapsing inflammation of the bowel of unknown origin. Markedly increased numbers of mast cells were observed in the mucosa of the ileum and colon of patients with IBD, which was accompanied by elevated degranulation of chemical mediators and cytokines such as histamine, tryptase, substance P and Tumor necrosis factor (TNF)-α. These data indicate the mast cell contribution to the pathophysiological process in IBD, suggesting that regulation of mast cells could be a therapeutic strategy for IBD.

Regulation of mast cell activation by mast cell stabilizing agents could reduce inflammation and fibrosis of intestinal lesions of the experimental colitis. Additionally, it was shown that attenuation of experimental colitis was observed in mast cell-deficient mice as compared with wild type mice.

In clinical settings, oral or rectal administration of tranilast, *N*-(3', 4'-dimethoxy-cinnamonyl)-anthranilic acid, a mast cell stabilizing agent, has been used empirically for patients with ulcerative colitis in Japan. Oral administration of tranilast also improved the stenotic lesions of small bowel of the patients with Crohn's disease. However, the therapeutic mechanisms of tranilast for the intestinal lesions of IBD are largely unknown.

In this review, the authors discussed about the role of mast cells in IBD, especially their role in intestinal fibrosis of Crohn's disease. The authors proposed a hypothesis of a crosstalk between mast cells and mesenchymal cells, including fibroblasts, in the gut wall of patients with Crohn's disease. The authors suggest that mast cells could be potential therapeutic targets in intestinal inflammation and fibrosis of IBD.