

EDITORIAL

Mast cells: a unique and functional diversity

In this issue of *Clinical and Experimental Allergy*, Rossi *et al.* [1] offer a review of the application of mast cell culture systems to our understanding of mast cell biology, and Kobayashi *et al.* [2] report the identification of IL-13-producing mast cells isolated from the human lung. These papers illustrate the diverse nature of mast cells, and serve to remind us that although mast cells are often implicated in allergic diseases, the physiological purpose of these cells is not completely understood. Nonetheless, there may be an absolute requirement for mast cells in mammalian biology. This conclusion is drawn largely from the failure to identify individuals (normal or otherwise) that have a significant generalized deficiency of this cell type.

Mast cells, among the haematopoietically derived cells, are unique in the extent of their functional diversity. These cells have a role in tissue homeostasis, and participate in both innate and acquired immunity (Fig. 1). Mast cells reside at specific locations within the microenvironment, often poised strategically in tissues that interface with the external environment, and next to blood vessels and nerves. These cells are capable of reacting both within minutes and over hours, with either local or systemic effects, to a variety of physical, biological, and chemical stimuli. Mast cells also react in a co-ordinated and graded manner which appears to ensure an appropriate response. There is also a more sinister side to these well-engineered residents of the microenvironment in that well-meaning effector mast cell functions may result in allergic inflammation and perhaps contribute to the pathology of autoimmune diseases.

Homeostasis and wound healing

Mast cells have adhesion properties that allow them to migrate and locate at specific sites within the microenvironment. When stimulated, mast cells will thus engage specific components of the connective tissue matrix including laminin, fibronectin, and vitronectin, in particular, through integrin receptors on the mast cell surface [3,4]. This adhesion has been shown to follow activation of mast cells through Fc ϵ RI [5]. In some cases adhesion follows exposure to growth factors, such as *c-kit* ligand (SCF) [6,7], expressed by stromal cells within tissues. Mast cells also adhere to structural cells; and SCF when presented as an integral membrane protein by stromal cells, helps promote mast cell adherence via *c-kit* on the mast cell surface [8].

Mast cells make their contribution to tissue homeostasis by virtue of the biological molecules that they produce and release. In the setting of injury, mast cells have been shown to promote both connective tissue growth [9] and angiogenesis [10], critical to wound healing. These activities may also relate to bone resorption [11] and fracture repair [12]. The relevant mast cell mediators and cytokines for matrix synthesis and new vessel formation include histamine [13,14], heparin [15,16], IL-4 [17], TNF α [18], and TGF β [19]. Mast cell proteases have also been implicated in events important for tissue and organ homeostasis, such as epithelial cell proliferation [20], activation of the angiotensin-converting enzyme system [21], endothelin processing [22], and the processing of atrial natriuretic factor [23].

Innate immunity

Mast cells tend to be localized between the epithelium and the parenchyma of the skin, gut, and respiratory tract. These are therefore among the first of the inflammatory cells to come into contact with an invading pathogen. The role of mast cells in the gut has been examined with both bacterial and parasite disease models. The binding of pathogens to

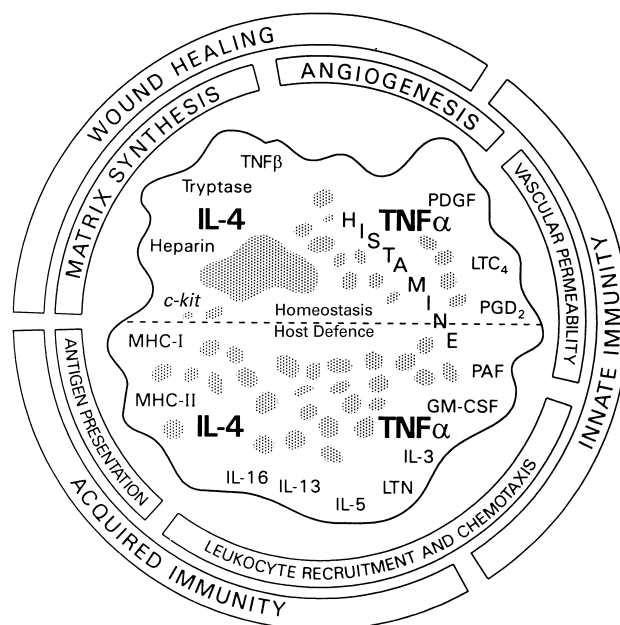


Fig. 1. The many biological functions of mast cells: mast cells participate in both homeostasis and in host defence. These biological functions are in part dependent on the mediators and cytokines that mast cells produce and release.

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mast cells, and subsequent mast cell activation, may be mediated by specific IgE and perhaps by specific IgG [24]. The importance of mast cells in innate immunity is illustrated by their ability to be activated by bacterial products, including toxins from *Clostridium difficile* [25] and *Vibrio cholerae* [26]; haemolysins [27], and lipopolysaccharide [28]. Mast cells also bind pathogens and activate through the nonspecific opsonin iC3b [29]. Other plasma factors that are generated during the inflammatory response, such as C3a and C5a [30], and subfragments of fibrinogen and fibronectin [31] also recruit and activate mast cells.

The host response to certain enteric bacteria suggests a protective role for mast cells. In the case of *E. coli*, binding to mast cells is mediated by a specific lectin–glycoprotein interaction between the Fim H1 component of the bacterial fimbriae and the cell surface [32]. This binding results in mast cell activation and piecemeal degranulation with the release of histamine and TNF α [33]. This response of mast cells has been demonstrated to have a protective function *in vivo* in a mouse model of bacterial peritonitis [34]. The W/Wv mouse, which is deficient in mast cells, has a greater susceptibility to sepsis than their mast cell replete litter mates in this model. This protection has been shown to be in part dependent on the release of TNF α from mast cells.

The case for mast cell involvement in the host defences against parasitic infections is diverse. Mast cell hyperplasia and activation are observed in intestinal helminthic infections [35]. Mast cell precursors have been shown to migrate from the peripheral blood and bone marrow to the intestine during parasitic infections [36]. The proliferation of mast cells in the intestine appears to be T cell dependent, and involves the cytokines IL-3, IL-4, IL-5 and IL-9 [37]. During primary infection, mast cells may be activated by parasite components [38]; and later in the course of infection, by parasite-specific IgE [39]. Mast cell products may either cause direct damage to parasites [40], or lead to expulsion by promoting mucus hypersecretion and increased intestinal motility [41], as well as affecting ion transport and fluid influx [42]. However, there does not seem to be a strict requirement for mast cells in the successful resolution of these infections. Depending on the model system employed, mast cells thus enhance parasite expulsion to varying degrees [43,44].

Acquired immunity

Mast cells participate in acquired immunity by virtue of the release of mediators that lead to enhanced vascular permeability and aid in the initial recruitment of inflammatory cells to sites of infection or injury. While mast cells have now been shown to produce an array of cytokines, the contribution of mast cell cytokine production to subsequent inflammatory processes, especially the generation of

specific immune responses, is poorly understood. It has been hypothesized that mast cell cytokine production may contribute to the differentiation of T cells into the TH₂ compartment. Mast cells are also candidate cells for the initial production of the IL-4 required for TH₂ differentiation [45]. It has been shown that mast cell cytokine production stimulates the production of IgE from B cells [46], and mast cells may process and present antigen [47,48]. Such biological activities may help initiate, amplify or perpetuate the development of the specific TH₂ immune response that characterizes the response against helminths, or when perturbed, results in the pathology of allergic diseases.

Kobayashi's report in this issue provides further data to support the concept that mast cell cytokine production is relevant in both normal human biology and disease. They were able to demonstrate the SCF-mediated induction of IL-13 from the lung mast cells of an asthmatic subject. In contrast, IL-13 production from nonasthmatic lung mast cells required both SCF and anti-IgE. The kinetics of IL-13 production appeared to be different as well, with sustained production of IL-13 by the nonasthmatic vs a pattern of transient production in the asthmatic lung. While the conclusions based on this observation should be taken with caution, given the small sample size of the study, the authors justifiably suggest that the microenvironment present in the asthmatic lung may predispose mast cells for IL-13 production.

What is the evidence that mast cell cytokine production, or mast cells themselves, modulate subsequent immune responses? Mast cells synthesize cytokines, but are there studies that show that a deficiency or excess of mast cell cytokines alter the development of an acquired immune response? A recent investigation using a mouse model of allergic airway inflammation, for instance, failed to show a role for mast cells [49]. However, it should be noted that the W/Wv mouse was employed as a model of mast cell deficiency. Despite the utility of this approach, there are several caveats. First, the W/Wv mouse is deficient in mast cells, but they are not absent [50]. This is presumably due to a low level of signalling through a hypofunctioning *c-kit* (the Wv mutation). Mice homozygous for Wv do not survive. Also, it has been shown that IL-3 dependent mast cells may be cultured from W/Wv bone marrow [51]. And, in models of chronic cutaneous inflammation, nests of mast cells are present at sites of inflammation, even in the W/Wv mouse [52]. In addition, the models of mouse asthma used adjuvant-based parenteral sensitization techniques that, while invoking what appears to be a TH₂ type inflammatory response, are not necessarily restricted to the production of IgE-dependent diseases [53]. Almost certainly, other classes of immune reactions including delayed type hypersensitivity [54] and immune complex deposition are involved in the inflammatory process. Finally, although cell types with

morphological criteria for mast cells are markedly decreased in the W/W^v mouse, there remains the possibility that functional mast cell precursors may remain in tissues and are not visible by the standard criteria. Thus, conclusions derived from W/W^v data must be interpreted in the context of the experimental design.

Do mast cell culture systems help us understand the physiological role of mast cells? These systems have proven their utility in defining mast cell signal transduction pathways, mediator release and cytokine synthesis. Rossi *et al.* [1] point out the importance of these techniques in bridging the gap between basic and clinical studies. The initial observation of a gain-of-function mutation of *c-kit* in a mast cell line was later extended in our laboratory when this mutation was identified in a subgroup of patients with systemic mastocytosis [55]. Now and in the near future, the ability to culture mast cells from transgenic or knockout mice, and then adoptively transfer them into the appropriate host system, should permit the identification of mast cell cytokine and signal transduction pathways that are relevant to both normal physiology and to disease.

Although the physiological intention of the mast cell remains enigmatic, its unparalleled diversity of function suggests its value. With its ability to respond instantly to injury and maintain homeostasis, the mast cell appears to have been appointed by nature to serve as both the guardian and conservator of the tissue microenvironment. It would also be a cumbersome waste of physical space and cellular energy if the multiple reactivities and responses of mast cells were sequestered in multiple cell types. Mast cells thus have a unique and functional diversity apparently essential to normal health.

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