The Role of Mast Cells in Non-Allergic Inflammation

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In 1878 Paul Ehrlich described a new type of granular cells that were mainly localized to the connective tissue compartment. These cells were prevalent in chronically inflamed human tissues. He named the cells "*Mastzellen*," meaning "well-fed cells" due to the high content of cytoplasmatic granules. These cells, better known today as mast cells, were initially considered to be part of the connective tissue. However, in the 1970s it was shown that their precursors were actually the hematopoietic stem cells. Mast cells circulate in the bloodstream and migrate into mucosal or connective tissues, where they undergo maturation into long-lived cells. These sites are the interface with the external environment (i.e., skin and mucosal surfaces), thus enabling MCs to respond rapidly to environmental stimuli, making them 'sentinels' of the immune system [1].

At first, MCs were studied in the context of allergic inflammation. For decades they were notable for their high affinity FCε receptor-I, which after binding to immunoglobulin E forms the cell's antigen receptor. The interaction with antigen and the cross-linking of the FCεRI causes degranulation of cytoplasmatic granules and the release of histamine, which increases vascular permeability and induces bronchoconstriction. The pathological consequences can be local, as in allergic rhinitis, or systemic as in anaphylaxis.

The discovery that MC granules contain preformed agents other than histamine (i.e., heparin, proteases, chondroitin sulfates and antimicrobial peptides) and their ability to selectively produce and release cytokines, chemokines, growth factors and lipid mediators (i.e., prostaglandins and leukotrienes) has led many investigators to believe that MCs participate in various biological responses other than IgE-mediated allergic inflammation. This review will focus on some of the recent advances in understanding these cells heterogeneity, mainly their role in non-allergic inflammation [2].

Mast cells and innate immunity

Both the innate and the adaptive arms of the immune system participate in host defense against infections. The unique localization of MCs to the host-environment interface, being a common site of pathogen invasion, and their ability to react to a large variety of physical, biological and chemical stimuli, raised the idea that these cells might play a role in innate immunity against infections [3,4].

MCs were initially associated with host defense against parasites since these pathogens cause IgE-associated responses. Studies have shown that intestinal parasitic infections were associated with MC hyperplasia and subsequently the release of proteases that results in expulsion of parasites by disrupting the intestinal epithelial barrier [1,5-7]. Moreover, studies of MC-deficient or IgE-deficient mice showed that these factors had a role in protection against intestinal worms [1,4,6,8]. The role of MCs in the defense against intracellular parasites was also shown in several infection models, including: malaria, *Toxoplasma gondii*, *Trypanosoma brucei*, *Giardia lamblia* and Leishmania [5,9-11].

In 1996, two groups published reports that have changed our understanding of MC biology [12,13]. They studied the ability of MC-deficient mice (lacking the MC growth factor receptor-c-kit) to fight Klebsiella peritonitis. Both groups found that normal mice overcame the bacterial infection, whereas MC-deficient mice died as a result of it. This was attributed to the rapid MC secretion of tumor necrosis factor-alpha following the inoculation of the bacteria, resulting in an augmented neutrophil response. Their findings were the first to clearly demonstrate that MCs have an important role in innate immunity, a role that is not related to parasitic infections. Shortly after, other researchers demonstrated MCs' roles in host defense against additional bacteria such as *Escherichia coli* and *Mycoplasma pneumoniae* [14-17].

MCs can be activated by host-derived signals or directly by the pathogen. The former include activated products of the complement system and endogenous peptides, which are formed quickly and in large quantities in response to infection [1,6]. For example, it has recently been shown that MCs were activated by Fv protein, an endogenous protein released by the liver during viral hepatitis [2,4,18]. Interestingly, the interaction was mediated through the Fc receptor. An example of the latter is the interaction between CD48 on the MCs and the fimbrial antigen FimH expressed by several gram-negative bacteria [2,15,17,19]. It has also been shown that MCs were activated following interaction between dengue virus and the FcγRII, resulting in the release of specific mediators that were different from those released after interaction with bacterial products [20-22].

The toll-like receptor family comprises single membrane-spanning receptors that recognize conserved molecules expressed

MC = mast cells
FCεR = FCε receptor
Ig = immunoglobulin

by different pathogens but not by the host. These molecules include factors such as bacterial peptidoglycan, lipopolysacharide, dsRNA and bacterial DNA. TLRs are considered among the key players that alert the immune system to the presence of pathogens. Since they are expressed on MCs, it was reasonable to believe that MCs participate in the recognition phase of innate immune responses [23,24]. For example, studies have shown that viruses activate MCs through interaction with TLR3 (that recognize dsRNA), resulting in the secretion of interferon-alpha, which inhibits viral replication and recruits other immune cells such as natural killer cells and macrophages [24,25].

Mast cells and adaptive immunity

There is a growing body of evidence that bidirectional interactions between MCs and T lymphocytes have a major role in adaptive immunity [26]. MCs are able to phagocyte bacteria, process its antigens, and present it to T lymphocytes in the context of major histocompatibility complex class I and II, thus serving as antigen-presenting cells [5,27,28]. During induction of an immune response, MCs migrate into lymph nodes where they further secrete chemokines and cytokines that induce lymph node hypertrophy and aggregation of additional lymphocytes [26,29]. TNFα induces T lymphocyte recruitment to the lymph node while interleukin-6 promotes these cells' activation [4,30]. On the one hand, most of the cytokines secreted by MCs induce Th2 differentiation, thereby escalating the allergic immune response. On the other hand MCs can secrete IL-12 and INFγ that support Th1 response, suggesting in fact that MCs are able to regulate the equilibrium between Th1 and Th2 responses [5].

MCs regulate T lymphocytes' specific immune responses indirectly by modulation of dendritic cells [5,31,32]. They promote recruitment, maturation and migration of immature dendritic cells from the circulation to the lymph nodes, where they present antigens to T lymphocytes [23,29,33]. Moreover, MCs have a regulatory effect on B cells through expression of MHC class II, stored in exosomes that release through exocytosis [5,34]. MCs express a wide variety of surface receptors and adhesion molecules that can be implicated in the co-stimulation process during the adaptive immune responses and enable them to interact with other inflammatory cells. Examples of such receptors are intercellular adhesion molecule-1, β2-integrins and CD40 ligand [2,34-36].

Snake bites and bee stings

For many years MCs were believed to contribute to the complications caused by snake bites and bee stings through the release of tissue-damaging molecules. These molecules promote an increase in vascular permeability, local inflammation, disturbance of the clotting and the fibrinolysis systems, and eventually might lead to shock and death. In 2004, Maurer and colleagues [37] published a study where they investigated the association between MCs and endothelin-1 [37]. ET-1 is an endogenous vasoconstrictor peptide that participates in the vascular changes occurring during sepsis. It is also known to activate MCs by binding to the ET-1 receptors, leading to degranulation and release of mediators. Interestingly, the authors showed that MCs promote the degradation of ET-1, thereby increasing survival during acute bacterial peritonitis [37].

ET-1 has high homology (> 70%) to sarafotoxin, the most potent toxic components of the venom of the Israeli mole viper (*Seraph Ein Gedi*). This raised the question whether MCs have a protective role in envenomation. In 2006, Metz and Galli [38] challenged this question. They found that MC-deficient mice were more susceptible to hypothermia and death as a result of injection of either sarafotoxin or complete Israeli mole viper venom, compared to normal mice or MC-deficient mice engrafted with normal MCs. Moreover, they showed that the levels of sarafotoxins in the peritoneal cavity of these mice were significantly lower than in the control group, suggesting that MCs have a role in reducing the toxin levels. They generated two groups of mice that contained MCs that either expressed or lacked the ET-1 receptor and found that those lacking the receptor failed to clear sarafotoxins and died quickly, indicating that sarafotoxins activate MCs, at least in part, through binding to this receptor.

In their search for a potential mechanism by which MCs reduced the venom toxicity, they found that carboxypeptidase A, a protease found in MC granules, was responsible for degrading the venom. Normal mice given an inhibitor of CPA, or MC-deficient mice engrafted with MCs expressing an inhibitory RNA that silenced CPA, died within an hour after injection of sarafotoxins or whole venom. Further studies showed that MCs had a protective role against other venoms that did not contain ET-like peptides such as the American pit vipers, the western diamondback rattlesnake, and the southern copperhead [38]. It was also reported that MCs provided protection against honeybee venom, although it is still unclear if CPA is the major anti-venom agent in this case [39]. Despite the fact that human MCs are different from mice MCs, it is reasonable to assume that they share similar protective roles [40].

Conclusions

It was not too long ago that the role of MCs was restricted to allergic inflammation. However, in the last two decades MCs have emerged as one of the most important factors at both the innate and the adaptive arms of the immune system. There is no doubt that we are only at the beginning of the journey towards better understanding of MC biology and extensive research is definitely needed.

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TLR = toll-like receptor
TNFα= tumor necrosis factor-alpha
IL = interleukin
INFγ = interferon-gamma
MHC = major histocompatibility complex
ET-1 = endothelin-1
CPA = carboxypeptidase A

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