



Review

Mast Cells and Inflammation

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Abstract. Mast cells have long been recognized as potent producers of a large panel of biologically highly active mediators such as biogenic amines, arachidonic acid metabolites, cytokines and chemokines, but most of their biological functions have been elusive and speculative. By taking advantage of mast cell-deficient mice, the role of mast cells in a variety of experimental settings can now be studied in detail and such approaches have dramatically altered and enlarged our knowledge about mast cell biology and function. Herein we will focus on the role of mast cells in inflammatory reactions of diverse origin, such as delayed type hypersensitivity, atopy, immune complex-mediated inflammation and innate immune responses. From the current standpoint, there is no doubt that the most outstanding and beneficial feature of mast cells is their recently discovered ability to induce a life-saving inflammatory response rapidly upon encountering microbes and microbial constituents. Nevertheless, the picture is also emerging that mast cells are deeply involved in the induction and maintenance of a variety of severe allergic and autoimmune diseases. However, a deeper understanding of their activation and immune-modulatory capacity might open a new window for the development of curative strategies.

Key words: mast cells; inflammation; IgE-independent activation; innate immune response.

Introduction

Inflammation is a rather general term, traditionally characterized by the symptoms of pain, redness, heat and swelling at the affected sites, which are due to changes in the caliber of vessels, exudation of fluid and plasma proteins, and the emigration of leukocytes, predominantly neutrophils. In this classical sense, the inflammatory response is a local immune reaction triggered by the invasion of microorganisms which initiate the recruitment of inflammatory cells able to combat and neutralize the causative pathogens. In this context, inflammation is the result of a very rapid and effective

interaction of soluble as well as cellular components of the innate immune system which prevents the spread of infection within minutes to hours. Therefore, these early events are also termed “acute inflammatory response”. On the other hand, a persisting infection, and also a variety of allergic and autoimmune diseases, lead to a state of chronic inflammation, often accompanied by severe tissue-destruction by the host’s own immune system.

It has been recognized that mast cells fulfill a variety of biological functions due to their ability to respond to diverse stimuli, leading to the release of a large panel of mediators, such as biogenic amines,

Abbreviations used: CLP – cecum ligation and puncture, DTH – delayed type hypersensitivity, LT – leukotriene, SCF – stem cell factor.

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arachidonic acid metabolites, cytokines and chemokines²⁹. Undoubtedly, impressive progress in the understanding of mast cell biology and function has been made possible by the characterization of naturally occurring mutations of stem cell factor (SCF) and its receptor, the tyrosine kinase c-kit (CD117). SCF is now regarded as the most important growth and differentiation factor for both murine and human mast cells *in vivo*³. A milestone in mast cell biology has been the use of the mouse strain WBB6F₁-*Kit*^W/*Kit*^{W-v}, which is devoid of mast cells due to mutations in both copies of c-kit. The *Kit*^W mutant allele encodes a truncated c-kit protein without a transmembrane region, and the mutant *Kit*^{W-v} allele has a point mutation within the cytoplasmic tyrosine kinase domain which leads to a strong decrease in the kinase activity of c-kit²². By using such mice, the question can be answered as to what happens under defined experimental conditions without mast cells *in vivo* compared with mast cell-sufficient congenic wild-type littermates. As a proof of the principle, it is also possible to reconstitute mast cell-deficient mice with mast cells grown *in vitro* from bone marrow-precursors or embryonic stem cells in order to reverse the observed symptoms⁴⁵.

In this review, we will summarize the current knowledge about the role of mast cells in inflammatory responses of diverse origin, namely in innate immunity against infection, immune complex-mediated reactions, allergic inflammation and delayed hypersensitivity reactions, the latter regarded as the basis of some severe autoimmune diseases.

Early Indications for the Contribution of Mast Cells in Inflammatory Responses

Mast cells are prominent on all potential entry sites for pathogens, especially in the mucosa of the respiratory and digestive tracts, and in skin. They are also located around blood vessels, particularly in the vicinity of postcapillary venules, which are the predominant site for the emigration of leukocytes from the blood vessels into the surrounding tissue and for the leaking of macromolecules and fluid, the latter being responsible for the swelling of an infected site. These findings, in combination with the ability of activated mast cells to release a variety of inflammatory mediators, led to the assumption that mast cells might be the first cell type stimulated by an inflammatory agent, well-suited as they are to induce the recruitment of neutrophils as an early step of many inflammatory responses³². In order to examine this hypothesis, the authors induced an in-

flammatory response in the peritoneal cavities of mast cell-deficient *Kit*^W/*Kit*^{W-v} mice and their congenic wild-type littermates by local injection of thioglycollate and monitored the time course and magnitude of neutrophil influx, assayed by counting cells in the peritoneal lavage. In these experiments, the influx of neutrophils into the peritoneal cavities of *Kit*^W/*Kit*^{W-v} mice was delayed, starting at 12 h with the maximum being reached at 18 h, whereas in the control animals the influx started at 4 h and the maximum was observed 14 h after the administration of thioglycollate. Furthermore, the length of time during which the neutrophil count was elevated was shortened in *Kit*^W/*Kit*^{W-v} mice. Nevertheless, there was a difference in neither the total number of neutrophils in the two sets of animals at their respective maxima nor in the total monocyte counts. Importantly, the adoptive transfer of wild-type-derived mast cells in mast cell-deficient mice compensated for the delay in neutrophil influx, proving that mast cells contributed to the thioglycollate-induced inflammation. In addition, the activation of mast cells was corroborated by the observed decrease in the fluorescent intensity of berberine sulfate staining (selective for heparin-containing granules) of mast cells in the peritoneal lavage after thioglycollate administration. This indicates that mast cells had undergone degranulation. Using phorbol 12-myristate 13-acetate (PMA) as a stimulus of acute inflammation, it was also reported that mast cells are required for a full-blown inflammatory response in a model of cutaneous inflammation in mice⁴⁷. Epicutaneous application of PMA to the ears of *Kit*^W/*Kit*^{W-v} mice resulted in a decreased tissue swelling and recruitment of neutrophils compared with their wild-type littermates, and the symptoms could be restored upon local reconstitution of *Kit*^W/*Kit*^{W-v} mice with cultured wild-type mast cells. Also in this model, local degranulation of mast cells was observed upon the application of PMA²¹.

Immune Complex-Mediated Inflammation

Immune complex-mediated inflammation and injury is characteristic for a variety of diseases, such as arthritis, glomerulonephritis, serum sickness and systemic lupus erythematosus, hence the broad interest in the underlying mechanisms.

In a mouse model for IgG immune complex-induced peritonitis, RAMOS et al.³³ described a delayed and decreased influx of neutrophils into the peritoneal cavities of *Kit*^W/*Kit*^{W-v} mice compared with their wild-type controls, both of which could both be restored by

reconstitution with mast cells. In these experiments, staining for heparin also revealed an intensive degranulation of mast cells, which preceded the influx of neutrophils.

Prototypic for immune complex-mediated reactions is the Arthus reaction, classically based on the formation of immune complexes in immunized animals encountering the respective antigen. In a reverse passive Arthus reaction in mice, elicited by i.v. injection of antigen followed by intradermal injection of specific antibody, ZHANG et al.⁵¹ demonstrated that mast cells contributed strongly to the inflammatory response. Neutrophil influx, edema and hemorrhage were decreased in *Kit^W/Kit^{W-v}* mice and could be reconstituted upon the transfer of mast cells. Since inhibition of 5-lipoxygenase *in vivo* significantly decreased the above-mentioned symptoms in wild-type mice but not the weak response of *Kit^W/Kit^{W-v}* mice, the authors concluded that mast cell-derived leukotrienes (LT), as potent chemoattractants and activators of neutrophils, profoundly contribute to the reverse Arthus reaction. Consequently, in mast cell-reconstituted *Kit^W/Kit^{W-v}* mice the inhibition of lipoxygenase led to a strong reduction of the symptoms. These findings, i.e. reduced edema, neutrophil influx and hemorrhage in *Kit^W/Kit^{W-v}* mice as well as the contribution of LT, could also be confirmed using the selective deposition of basement membrane-specific antibody in the mouse skin⁵¹.

A cornerstone has been the observation that mast cell-derived TNF- α is responsible for the recruitment of neutrophils in immune complex-induced peritonitis in mice⁵². In this study, two peaks of TNF- α were evident in the lavage fluid of wild-type mice after challenge. The first peak within 5 min declined within 15 min, but the level of TNF- α still remained elevated, and a second wave of greater magnitude appeared 4 to 8 h after challenge. In *Kit^W/Kit^{W-v}* mice, the early peak of TNF- α was missing, and the second peak was reduced by 60%. Furthermore, a delayed and decreased influx of neutrophils was observed. All these symptoms were restored upon the transfer of mast cells. Evidence was also given that only the first peak of mast cell-derived TNF- α was critical for the recruitment of neutrophils, the TNF- α produced later probably being derived from activated monocytes and neutrophils. Obviously, the immediate release of TNF- α at the onset of an inflammatory response is due to the unique ability of mast cells to store preformed TNF- α in their granules^{15, 16}.

A variety of studies have been undertaken in order to answer the question as to how mast cells are activated in immune complex-mediated inflammation, and it has been convincingly shown that the complement

component C5a, possibly generated independently of C3, and the immune complex low-affinity receptor for IgG, Fc γ RIII (CD16), play important roles^{17, 18, 34, 43, 44}. The relative contributions of complement and Fc γ R vary in different models, but this is most likely due to tissue-specific requirements for the initiation of immune complex-mediated inflammation^{5, 6}. Thus, IgE-independent activation of mast cells by complement and aggregated IgG is critical for immune complex-induced inflammation.

Innate Immune Responses

The findings demonstrating that mast cells are crucial effectors of an innate immune response against microbes can be regarded as a long-sought missing link for the understanding of a protective mast cell function. Their ability to initiate an inflammatory response as a first line of defence might now answer the question as to why these potentially hazardous allergy effector cells developed and have been preserved in evolution.

The contribution of mast cells to combat bacterial infections was studied by ECHTENACHER et al.¹² using cecum ligation and puncture (CLP) as a model for acute septic peritonitis in mice. Strikingly, 100% mortality of mast cell-deficient *Kit^W/Kit^{W-v}* mice was observed within 5 days following CLP, as opposed to 25% in the respective wild-type controls, and the adoptive transfer of mast cells protected *Kit^W/Kit^{W-v}* mice from the lethal effects of CLP-induced peritonitis. Furthermore, neutralization of TNF- α immediately after CLP suppressed this protective effect of mast cells, confirming that mast cell-derived TNF- α is responsible for recovery from peritonitis¹¹. Besides TNF- α , evidence has been provided that mast cell-derived LTs also contribute in mediating early recruitment of neutrophils, which are critical for phagocytosis and killing of bacteria in septic peritonitis²⁵. Using the CLP model, it has also been reported that repetitive treatment with SCF improves the survival of wild-type and mast cell-reconstituted *Kit^W/Kit^{W-v}* mice, but not of mast cell-deficient animals, indicating that this protective effect of SCF depends on the presence of mast cells and is most likely based on an SCF-mediated increase in mast cell number²⁸. Accordingly, mice with reduced peritoneal mast cell numbers exhibit increased mortality from bacterial peritonitis, accompanied by decreased neutrophil influx and increased bacterial burden³⁶. Using a mouse-virulent strain of *Klebsiella pneumoniae* injected into the peritoneal cavities or lungs of wild-type

and *Kit^W/Kit^{W-v}* mice, it has been shown that the number of surviving bacteria was about 20-fold higher in the latter and that the limited bacterial clearance correlated with impaired neutrophil influx, but both could be reversed upon reconstitution of mast cells²⁷. Regarding the activation of mast cells in such settings, a variety of microbes and microbial components, such as cell wall constituents, bacterial DNA and toxins, have been reported to stimulate mast cells *in vitro* independently of IgE, inducing the release of mast cell-mediators such as histamin, TNF- α and LTs¹³. In principle, the activation of mast cells can be the result of a direct microbe/mast cell interaction or can be mediated by opsonizing molecules. To date, the best known example for the former case is the interaction between enterobacteria via FimH, a minor constituent of the fimbrial filament, and CD48 on the mast cell membrane²⁶. Evidence has also been presented, that opsonization via C3b is involved in the binding of mast cells to salmonellae as well as to the helminth *Schistosoma mansoni*³⁸⁻⁴⁰. Experimental evidence for a link between mast cell-dependent natural resistance and the complement system also came from the observation that degranulation of mast cells and bacterial clearance in mast cell-dependent CLP-induced peritonitis is impaired in C3-deficient mice³¹. This is in line with the recent observation that mice deficient for the complement receptors CD21 (CR2) and CD35 (CR1) also exhibit decreased survival following CLP along with impairments in the release of early TNF- α and the recruitment of neutrophils¹⁴. The fact that mice deficient in secreted IgM are also highly susceptible to peritonitis and display reduced neutrophil recruitment and decreased levels of TNF- α ⁹ also argues for a critical role of complement in the immediate defense against bacterial infection, since natural IgM is a potent activator of the classical complement pathway³⁰.

Atopic Diseases

The crosslinking of specific IgE bound on the mast cell membrane by challenging sensitized individuals with the respective antigen (allergen) elicits 3 types of associated responses. The acute allergic reaction, which develops immediately within seconds to minutes, is followed several hours later by the more widespread late-phase reaction and, finally, the state of chronic inflammation, which can persist for years⁴⁶. Passive cutaneous anaphylaxis (PCA) in mice, elicited by local i.d. administration of hapten-specific IgE in the ear followed by systemic i.v. application of hapten-carrier conjugate,

has been used to demonstrate that mast cells are indeed responsible for acute- and late-phase reactions in this model⁴⁸. Cutaneous swelling, characteristic for the acute phase, and neutrophil infiltration, as a measure for the late phase, have been severely impaired in mast cell-deficient mice. These symptoms could be elegantly reversed by reconstitution of mast cells in one ear only, leaving the contralateral ear as an untreated control. Furthermore, neutralization of TNF- α partially inhibited the neutrophil infiltration associated with IgE-dependent PCA, confirming the importance of this cytokine for the influx of neutrophils.

However, contradictory results were obtained regarding the contribution of mast cells in murine atopic asthma, another widely used and important model for allergic diseases. It is commonly accepted that genetic and environmental factors contribute to this exceptional disease, which is characterized by airway-hyperresponsiveness (AHR), inflammation of the airways by infiltrating eosinophils, mast cells, T cells and macrophages, as well as mucus plugging and airway remodeling^{10, 50}. Regarding the diversity of contributing factors and the complex network of different effector cells and bioactive molecules in the inflamed tissue, it should be expected that there might be no master switch responsible for the entire pathology. As outlined by WEDEMEYER and GALLI⁴⁶, the focus is clearly on Th2 cells and eosinophils, since each cell type is likely to contribute, but the major task should be to identify the extent to which these and other cells contribute to clinically important symptoms of the disease.

The questions whether and under which conditions mast cells assist in acute-phase and late-phase reactions in a model for murine atopic asthma have been recently answered by WILLIAMS and GALLI⁴⁹. Using ovalbumin in combination with adjuvant in a short-time immunization protocol, no differences in terms of AHR (acute phase) and airway-eosinophilia (late phase) were obvious between mast cell-deficient mice and their wild-type littermates following challenge with ovalbumin. In contrast, mast cell-deficient mice sensitized to ovalbumin by repeated injection of low-dose antigen without adjuvant over a long period of time only marginally exhibited AHR and eosinophilia. However, this weak response could be restored upon reconstitution of such mice with mast cells. Hence, this approach demonstrates that mast cells play a role in more physiologically relevant settings.

Obviously, mast cells are well-suited to mediate the often life-threatening acute phase reactions of atopic asthma due to their ability to release a variety of mediators such as histamine and LTs. On the other hand, the

question of how mast cells participate in the late phase or chronic phase has not been entirely resolved. Most likely, this is due to the production of mast cell-derived Th2 cytokines, such as IL-4, IL-5, IL-9 and IL-13, which have been recognized as being deeply involved in the pathogenesis of asthma³⁵. IL-5 is essential for the recruitment of eosinophils, and both IL-9 and IL-13 have been found to be critical factors contributing to airway inflammation, AHR and excessive mucus production. In this context, the proinflammatory cytokine IL-1 might additionally amplify the local production of mast cell-derived IL-5, IL-9 and IL-13, thereby promoting and amplifying the late-phase state of the disease^{19, 41, 42}. Nevertheless it should be noted that it is still less clear to which extent mast cells contribute to the production of these pleiotropic cytokines *in vivo*, but mast cells could thereby generally act as local amplifiers of Th2-driven reactions.

Delayed Type Hypersensitivity and Autoimmune Diseases

A variety of severe diseases such as rheumatoid arthritis, Crohn's disease, psoriasis and multiple sclerosis are considered to be based on delayed-type hypersensitivity reactions (DTHR) induced by IFN- γ -producing type 1 T cells. Although strictly T cell-dependent, it has long since been recognized that mast cells are involved in the effector phase of murine DTHR^{1, 23}. Mast cell-deficient mice displayed impaired DTHR, but adoptive transfer experiments clearly indicated that the ability to elicit DTHR could be transferred using T cells from sensitized mast cell-deficient to wild-type mice, whereas sensitized T cells from wild-type mice could not restore DTH responsiveness in mast cell-deficient mice. These findings implicated that mast cell deficiency is not correlated with the ability to generate DTHR-mediating effector T cells, but with an impaired effector response².

Using a mouse model of DTHR with trinitrochlorobenzene as skin-sensitizing agent, it has recently been shown that mast cells control the recruitment of neutrophils by their ability to secrete TNF- α and the CXC-chemokine macrophage inflammatory protein 2 (MIP-2), the functional analogue of human IL-8⁸. In this study, extractable MIP-2 was found in and around mast cells from wild-type mice, but not in mast cell-deficient mice during DTHR; furthermore, neutrophil recruitment could be reduced by 60% using neutralizing anti-MIP-2 antibodies. Importantly, mast cells from wild-type mice efficiently restored DTHR and MIP-2 levels in

Kit^W/Kit^{W-v} mice, whereas mast cells from TNF- α knock-out mice did not.

Experimental allergic encephalomyelitis (EAE) in rodents has been intensively used as an experimental model for the demyelinating human disease multiple sclerosis. It has long been assumed that mast cells play an important role in EAE, possibly by enabling the entry of autoreactive T cells and monocytes across the blood-brain barrier, while neutrophils are virtually absent from the inflamed tissues⁷. Using a myelin oligodendrocyte glycoprotein-induced model of EAE, SECOR et al.³⁷ recently reported that mast cell-deficient mice displayed a delayed onset of the disease and decreased clinical scores compared with their wild-type littermates, the symptoms being reconstitutable by mast cell transfer. However, it is still unclear how mast cells are being activated in the above-mentioned experimental settings, but it is reasonable to assume that a functional communication between antigen-specific T cells and mast cells will occur, leading to the activation of mast cells^{4, 20, 24}.

Conclusions

For a long period of time, mast cells were thought to be the "bad guys" as they represent the main effectors in atopic diseases, especially via an IgE-mediated secretion of an array of detrimental disease-promoting mediators. This view has been profoundly enlarged and altered in the last years by reports which have revealed that mast cells obviously represent a key player in the immediate induction of protective inflammatory immune responses. A central finding of these studies is that mast cells can be activated not only by crosslinked IgE and complement (C3a, C5a), but also by complexed IgG and different bacterial components. Thus, mast cells exert Janus-faced properties; on the one hand, they are found to be essential disease-promoting effector cells in the course of an anaphylactic shock syndrome, immediate early allergic reactions as well as DTHR. On the other hand, at the beginning of bacterial infections, mast cells are involved decisively in a very rapid beneficial and curative immune response that is mainly characterized by the recruitment of neutrophils through locally activated mast cells secreting cytokines (TNF- α , MIP-2) and vasoactive mediators.

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