

Mast cells: makers and breakers of allergic inflammation

Kayvan Hakim-Rad, Martin Metz and Marcus Maurer

Department of Dermatology and Allergy, Allergie-Centrum-Charité/ECARF, Charité-Universitätsmedizin Berlin, Berlin, Germany

Correspondence to Marcus Maurer, MD, Professor of Dermatology and Allergy, Department of Dermatology and Allergy, Allergie-Centrum-Charité, Charité-Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany
Tel: +49 30 450 518 043; fax: +49 30 450 518 972; e-mail: marcus.maurer@charite.de

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Purpose of review

Recent findings have developed, changed, challenged and extended the established view of mast cell biology and of their role in inflammation. The purpose of this review is to present and discuss recent research in this area relating to allergic inflammation.

Recent findings

Mast cells are traditionally viewed only as IgE-activated histamine-providing effector cells of allergic inflammation. Yet, recent findings also support a role for mast cells in the sensitization to allergens, and early released human mast cell tryptase has been shown to break down IgE, hence breaking the key maker of allergic inflammation. Furthermore, mast cells demonstrate proinflammatory action through nonhistamine and non-IgE-mediated routes. For example, the role of platelet-activating factor in contributing to allergic inflammation and anaphylaxis in mice is now starting to be shown in humans. Most surprisingly, mast cells have also emerged as modulators and downregulators of allergic inflammation. For example, the newly discovered siglec-8 receptor might act as an inhibitor of mast cell degranulation and thus of mast cell-mediated allergic inflammation. Also, mast cell-derived IL-10 is shown to be a modulator of allergic inflammation, demonstrated in a murine model of contact hypersensitivity.

Summary

Understanding the mast cell's divergent phenotypes based on situation and setting is required to truly discover their role in allergic inflammation.

Keywords

histamine, IgE, IL-10, mast cell, platelet-activating factor, urticaria

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Introduction

The consensus view of the evidence for the widening array of mast cell activators and responses is that the ultimate goal of mast cells is to facilitate optimal protective immune responses [1–5]. It would, therefore, seem short sighted to continue categorizing mast cell action, in allergic inflammation, as one of only inducing and exacerbating immediate hypersensitivity responses seeing how these cells demonstrate such a potential for more. In light of this, we present and discuss selected recent reports that have identified and characterized novel mechanisms and effects of mast cell action across stages of allergic inflammation.

Makers: allergic sensitization

Allergic inflammation is a paradoxical immune response given that the very action of inflammation is not in itself a malfunction but instead protective in purpose and allergens are rarely harmful to any physiology. The primary source of allergic disease is inappropriate sensitization or rather the host's symptomatically invisible mechanism of incorrectly classifying benign substances (i.e. allergens) as threats. Rarely has a convincing case been made for

mast cell involvement in sensitization to allergens, apart from indirectly related to mast cell responsibility for epithelial barrier integrity [3]. Yet, there is an increasing interest in the interactions of mast cells with cells known to be involved in the adaptive immune response as a whole, which includes sensitization. For instance, mast cell-dependent antigen-specific deficiencies observed during the course of *Leishmania major* infections in mast cell-deficient *Kit^W/Kit^{W-v}* mice have been described [6]. These include impaired local recruitment of dendritic cells, absent major histocompatibility complex (MHC) class I-dependent T cell priming and marked reduction in proliferation of both CD4⁺ and CD8⁺ T cells [6]. Also observed was a shift in cytokine production toward a Th2 response, categorized by reduced Th1 antigen-dependent IFN γ and IL-12 production, coupled with increased Th2 cytokines, IL-4 and IL-10 [6].

Another study proposes direct involvement in sensitization by showing that mast cell-derived tumor necrosis factor (TNF) enlarges draining lymph nodes through promoting T cell migration to the site [7]. Mast cell-deficient mice did not develop the same lymph node hypertrophy unless engrafted with bone marrow-derived cultured mast cells (BMCMCs) and also not if the

engrafted cells were TNF-deficient [7]. Although these findings were demonstrated in a mouse model of skin bacterial infection and not in an allergic context, they at least implicate mast cells in the processing of environmental antigens. The same group expanded on this theme by using the mast cell activator compound 48/80 alongside a protective protein antigen from *Bacillus anthracis* to manufacture a specific adaptive immune response [8[•]]. Indeed, when mast cells were activated in this way a lasting protective antigen-specific IgG and IgA response was observed compared with the same procedure in mast cell-deficient mice or with protective antigen alone in wild-type mice [8[•]]. Although again not proposed in an allergic model, it demonstrates a fabricated means to bring about sensitization, which in this article is proposed as a possible vaccine route [8[•]]. If this forced sensitization was instead achieved with ovalbumin (OVA) or birch pollen, for example, then the case immediately switches from vaccination to one of mast cell contribution to allergen sensitization.

The mast cell's role in sensitization is then taken a stage further by introducing a means of non-MHCII-dependent mast cell antigen presentation [9[•]]. Mast cells have evolved lysosomes that store content without degradation enabling their preformed mediators to stay intact before degranulation [10]. It is shown that allergens could also be stored in this way after first being internalized by high-affinity IgE receptor-mediated phagocytosis [10]. Live cell imaging has been used to demonstrate this action showing labelled bone marrow-derived dendritic cells immediately taking up labelled OVA [9[•]]. The OVA, however, is shown to be among the remains of a nearby apoptotic BMDC, hence demonstrating the production of compartmentalized intact fragments proposed in this article as mast cell-derived antigen reservoirs [9[•]]. The same group then provides the right conditions to induce mast cells to express MHCII and so to propose direct antigen presentation to T cells by mast cells [11^{••}]. Mast cells were shown to maximally express MHCII after 72 h when stimulated with physiological concentrations of lipopolysaccharide (LPS) and IFN γ *in vitro* [11^{••}]. Furthermore, LPS injected in mice induced a marked increase in the number of mast cells in the lymph nodes that were also found to express MHCII [11^{••}]. It has to be considered, however, that in most settings, mast cells fail to express MHCII. Yet, in support of this sort of specific tailored functionality is the view that even mature mast cells display high levels of plasticity so as to adapt functionally as required [4]. Alternatively, progenitors could mature and differentiate into functionally divergent mast cell subclasses [4]. Either way, these changes would be based on which location cells migrate to and exactly what is going on in the microenvironment. Hence, such tailored in-vitro manipulations could, if

related to real biological settings, provide plausible evidence for mast cell action.

Makers: the onset of allergic inflammation

When it comes to the onset of allergic inflammation, much is understood regarding the frontline position of an appropriately sensitized mast cell in bringing about allergic inflammation through releasing preformed mediators such as histamine [3]. Both in mice and humans, platelet-activating factor (PAF) is also among the potent proinflammatory substances produced by mast cells [12]. There is now further evidence of its importance in humans, taken from a sample of allergic patients [13^{••}]. Vadas *et al.* [13^{••}] describe a strong correlation between serum PAF levels and severity of allergic reaction, including fatal anaphylaxis. Then, the same severity scale is also shown to have an inverse relationship to PAF acetylhydrolase, an enzyme responsible for breaking down PAF [13^{••}]. Mast cell-derived IL-1 β is also being recognized as a key proinflammatory mediator [14[•]]. Very recently, IL-1 β , produced and released from mast cells, has been identified to be responsible for the urticaria-like symptoms in cryopyrin-associated periodic syndrome patients [14[•]]. The occurrence of wheals in these patients is completely histamine independent and is instead brought about by a genetic defect that causes constitutive production of IL-1 β by mast cells [14[•]].

Although IgE-mediated induction of allergic inflammation has a well deserved reputation for being the key mechanism for mast cell activation in allergic responses, there are alternative pathways [15]. For example, activation of the complement system, and not IgE-mediated mast cell activation, has been shown to be the relevant mechanism in peanut allergen-induced anaphylaxis in mice [16[•]]. A systematic approach was taken to induce peanut extract-induced anaphylaxis in various immune-deficient mice models. It was found that even without B cells or T cells, a response was observed, induced by the complement component C3a [16[•]]. PAF was again found to be the major mediator and, to a lesser extent, histamine. In relation to this, mast cells were only participants in a response that was led mainly by macrophages and basophils [16[•]]. IgE-mediated mast cell action is not to be diminished as a maker of peanut allergy anaphylaxis, but instead shown to be part of a wider mechanism. Hence, it is proposed that peanut extract consists of multiple allergens that trigger a range of synergistic mechanisms invoking both the innate immune system and the adaptive immune system to produce allergic inflammation [16[•]].

Irrespective of what is understood in any model of allergic reaction, it seems there is still room for new layers of complexity. It has been somewhat of a surprise to see that mast cells and nerve cells seem to be highly collaborative units in terms of proximity and direct cell-to-cell

communication. A fascinating example of this has been the description of anaphylaxis in guinea pigs by a learned histamine release induced purely through sensory conditional release reflex [17]. As instructive as this early work was in implicating neurogenic signals in mast cell-mediated inflammation, subsequent research in this area has been slow to develop. It has recently been shown, however, that sensory skin nerves are directly involved in allergic reactions as surgical denervation of sensory nerves in the back skin of mice lead to impaired mast cell-driven passive cutaneous anaphylaxis [18*].

In addition to directing a nerve cell to mast cell action, it seems an effect can be transmitted in the other direction as shown during IgE-mediated mast cell degranulation in the asthma model of allergic inflammation [19]. Interestingly, the neural fibre and behavioural changes observed did not occur through IgG-mediated mast cell mechanisms or through eosinophil-induced inflammation [19]. The study suggests that IgE-mediated allergic inflammation includes an appropriate behavioural response to a perceived threat and, therefore, places mast cells as the sensory arm of this expanded allergic response.

Breakers of allergic inflammation

What is of course more surprising and complex is the discovery that mast cells can break an allergic response. If mast cells do have the potential to suppress allergic inflammation, then it would seem logical that they would first need to sense when to do this. Such an action could be the purpose of siglec-8 (sialic acid-binding, immunoglobulin like lectin-8), which was found to be expressed on human eosinophils. Details of its discovery in humans and search for the equivalent in mice would not suit the focus of this piece but is very well reviewed by Bochner [20]. Although the physiological function of siglec-8 is not yet understood, *in-vitro* antibody activation has been shown to cause apoptosis in eosinophils [21] and mast cell inhibition of IgE-mediated histamine, prostaglandin D₂ release but not IL-8 [22*]. In support of these findings, it is worth mentioning that there exists more established knowledge of such regulatory mechanisms in mast cell biology. One of the best examples is the tyrosine kinase network, which is central to the function of the two main mast cell activation receptors, namely IgE receptor FcεRI and stem cell factor receptor KIT, and has been recently well reviewed [23].

A stronger case for the modulation by mast cells would require demonstrating the existence of released substances that can directly suppress inflammation. The most effective target to suppress would be the proinflammatory storm evoked by crosslinking mast cell-bound IgE [24**]. Hence, there is much interest in the discovery that IgE itself can be cleaved by an initially released mast cell

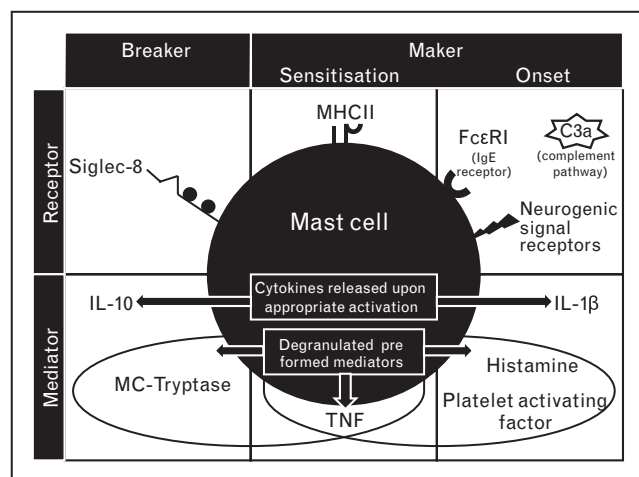
protease [24**]. The effect was first observed using recombinant human β-tryptase showing IgE cleavage in both the constant Fc region and the variable Fab region [24**]. These cleavage sites respectively implied impaired binding to FcεRI and to allergen, which was subsequently shown *in vitro* by showing the existence of corresponding cleavage products [24**]. To then further implicate this action as a direct mast cell response, these expected IgE cleavage products were shown to be only present in supernatant from calcium ionophore-degranulated mast cells cocultured with IgE [24**]. Demonstrating an *in-vivo* biological response involved pretreatment with protamine, a heparin-dependent protease inhibitor, which resulted in an increased late phase allergic reaction in human trials [24**]. Although not in an allergic setting, studies have been conducted demonstrating that endogenous and exogenous toxic peptides such as endothelin-1, neurotensin and snake venom components induce degranulation of mast cells and are then cleaved by mast cell proteases, hence modulating the peptide's otherwise harmfully toxic effects [25–27].

Altogether, it builds up to a convincing case stating that immediately released proteases can break the onset of inflammation, allergic or otherwise. In addition to this rapid mechanism for maintaining homeostasis, mast cells appear to also be important in modulating chronic inflammatory changes, for example in bacterial toxin-induced long-lasting skin inflammation or in skin changes after chronic ultraviolet B exposure [28,29]. Furthermore, recent findings strongly indicate that mast cells also contribute to the control of chronic inflammatory processes in type IV allergic responses. Grimaldeston *et al.* [28] have elegantly demonstrated that mast cell-derived IL-10 is critical for the limitation of chronic skin inflammation following contact hypersensitivity responses to urushiol, the allergen-containing component of poison oak and poison ivy.

Conclusion

Recent findings show that the trend of discovering diverse mast cell functionality is still going strong. With respect to allergic inflammation their role is introduced in sensitization, extended in onset and developed to also be one of modulation (Fig. 1). A valid criticism of some recent reports supporting mast cell plasticity required to enable such diversity is that *in-vitro* findings reflect neither the true nature of mast cells nor their setting. Furthermore, mouse model-generated biological responses are not guaranteed to be transferable in humans. The challenge is, therefore, to clarify the relevance of these findings in real and relevant biological conditions. Only then can the true implications of mast cell action be understood across all the phases of allergic inflammation. This could open up new therapies but also introduces the concept of treatment

Figure 1 Schematic summary of the reviewed mast cell receptors and mediators as examples of makers and breakers of allergic inflammation



MHCII, major histocompatibility complex II; TNF, tumor necrosis factor.

timing and focus. Purely targeting mast cells as a whole for instance would suggest missing out on their late phase modulatory protease cleavage or IL-10 suppression of inflammation. The answer, it would seem, lies in understanding the mast cell's divergent phenotypes based on situation and setting.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

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- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 484).

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