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HIGHLIGHTS

COMMENTARY

Mastering gut permeability: New roles for old friends

Michael Bramhall and Colby Zaph

Infection and Immunity Program, Department of Biochemistry and Molecular Biology, Monash Biomedicine Discovery Institute, Monash University, Clayton, VIC, Australia

Mast cells are innate immune cells that respond rapidly to infection in barrier tissues such as the skin and intestinal mucosa. Expulsion of parasitic worms in the gut involves a robust type 2 host response, and an acute mastocytosis is often generated at the site of infection. However, the role of mast cells in resistance to worm infections appears to be parasite specific. Mast cells are also involved in tissue repair, but the long-term contribution of mast cell activation after worm expulsion has not been definitively studied. In this issue of *European Journal of Immunology*, Sorobetea et al. [Eur. J. Immunol. 2017. 47: 257–268] demonstrate that activated mast cells persist in the large intestinal lamina propria and intraepithelial compartment long after worm expulsion, resulting in continued local and systemic presence of the mast cell protease mast cell protease 1 (MCPt-1) and enhanced intestinal permeability. In this commentary, we discuss these findings in the wider context of mast cell function in health and disease.

Keywords: Intestinal immunity · Mast cells · Mucosal immunity · Parasitology

See accompanying article by Sorobetea et al.

Cells of the innate immune system are essential first responders to immune challenge from parasites and pathogens, but their long-term roles in resolution of inflammation and repair of tissue following inflammation are not well understood. Within the innate cell cohort, mast cells appear to be an essential component of the immune system: no human devoid of mast cells has been documented (though that does not preclude the existence of such individuals) [1]. Yet despite this, most of our understanding of mast cell function revolves around their potentially fatal roles in allergy and anaphylaxis [2]. Mast cells were initially described by Paul Ehrlich as "*Mastzellen*" due to their abundant granular contents, giving them the appearance of well-fed cells ("*Mast*" is the German term for the fattening of farm animals) [3]. Mast cells are broadly distributed and function as immune sentinels, being particularly prevalent in mucosal tissues and skin, where they can respond rapidly to infection if barrier integrity is compromised. Mast cells are activated after binding immunoglobulin E (IgE) to the high-affinity IgE receptor FcεRI, but can also recognize pathogen-associated or damage-associated molecular patterns through various pattern recognition receptors and act as antigen-presenting cells [4]. Mast cell granules contain a diverse cocktail of compounds including histamine, heparin, proteoglycans, and proteases, the combined and rapid release of which can result in fatal anaphylaxis within minutes of exposure to allergen [5]. Mast cells produce numerous cytokines and chemokines, and are capable of influencing polarization toward type-1, type-2, or regulatory immune responses via production of IL-12, IL-4, and IL-10, respectively [6–8].

During exposure to parasitic worms, type 2 cytokine-mediated immune responses (including IL-4, IL-13, and IL-9) result in production of B-cell derived IgE, which in turn causes mast cell degranulation during late-stage helminth infection [9, 10]. However, the contribution of mast cell degranulation on worm expulsion is dependent on the species of parasite in question and the

Correspondence: Prof. Colby Zaph
e-mail: colby.zaph@monash.edu

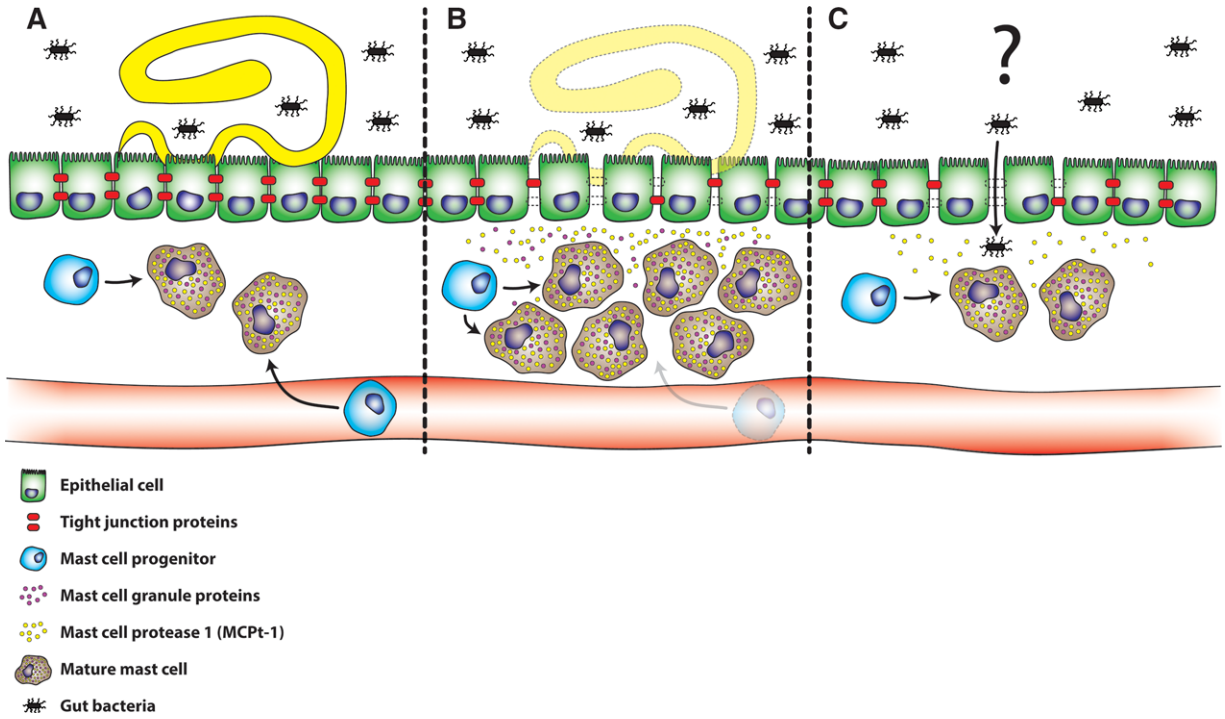

Figure 1. Activated mast cells remain much longer than previously thought at the site of infection following expulsion of *T. muris*. (A) During helminth infection, local mast cells are activated at the site of infection and populations of mast cells expand via maturation of local progenitors and influx of circulating mast cell progenitors. (B) Development of mastocytosis and rapid degranulation of activated mast cells assists in the expulsion of helminths by increasing gut "leakiness." Mast cell granule proteins including MCPt-1 contribute to enzymatic digestion of tight junction proteins. (C) New data now show prolonged survival and maturation of local mast cells and their progenitors following worm expulsion. Continued production of MCPt-1 in the absence of any ongoing immune challenge may have profound effects on gut barrier integrity, potentially allowing gut bacteria entry into the lamina propria.

dynamics of the host immune response. Where mast cells do not contribute to parasite expulsion, ILCs and T cells are likely to be the primary source of type 2 polarizing cytokines [11]. The use of parasitic worm infection models in genetically modified animals that have depleted mast cells (e.g. $Kit^{W/W\text{-}v}$ mice, or more recently $Kit^{W\text{-}sh/W\text{-}sh}$ "sash" mice), demonstrate mast cell functionality in worm expulsion. Mast cells are integral to the expulsion of *Trichinella spiralis* [12] and *Strongyloides ratti* [13], and contribute, although they are not essential, in the expulsion of *Nippostrongylus brasiliensis*, *Trichuris muris*, and *Heligmosomoides polygyrus bakeri* [14–16]. Importantly, one specific mast cell derived product, mast cell protease 1 (MCPt-1), is a key factor in the immune response against *T. spiralis* [17, 18].

What do mast cells do after successful clearance of helminth parasites? The long-term effects of mast cells accumulation at mucosal sites are not well understood. While mast cells have positive roles in wound healing and repair [19], activated mast cells continue to release potentially damaging proinflammatory mediators and enzymes that disrupt the tight junctions of the gut. The process by which a mast cell may transition phenotypically from proinflammatory to mediating repair is unknown [20]. The timing of mastocytosis development after *T. muris* infection is dependent on the strain of mouse, with NIH mice developing accumulation of mast cells 10 days after worm expulsion, for example [21]. Previous studies have shown that mast cells persisting after parasite infection are less sensitive to activation upon secondary infection [22, 23], which suggests they may remain to assist in wound healing and repair.

In this issue of *European Journal of Immunology*, Sorobetea et al. investigated the presence and role of mast cells following acute infection with *T. muris* [24]. It was previously known that mast cells accumulate in large numbers following worm infection in several animal models, but the subsequent role of these long-lived cells was unknown. Sorobetea et al. show that activated mast cells persist in the gut after an acute infection of *T. muris* has been expelled, and remain there much longer than previously thought (Fig. 1) [24]. Chronic infection, which is associated with a type 1 cytokine response, does not lead to the induction of persistent mast cells, demonstrating a role for type 2 cytokines in promoting mast cell accumulation. These mast cells display an activated phenotype and are shown to continue producing and secreting MCPt-1 both at the site of infection, and systemically. These mast cells appear to be the product of a single founder population established during the course of the *T. muris* infection, and are supplemented only by the maturation of local mast cell progenitors, rather than from an accumulation of circulating progenitors. Physiologically,

the presence of these MCPt-1-producing mast cells in the intestinal tissues leads to increased intestinal permeability, as measured by the absorption of the fluorescent tracer FITC-dextran. Thus, although mast cells are not necessary to immunity to *T. muris*, infection results in their activation, expansion, and persistence following clearance.

There are many potential consequences of this discovery, and further work is needed to investigate the ongoing impact of MCPt-1 production and high mast cell presence in the months following infection and expulsion. The manner by which MCPt-1 contributes to worm expulsion involves degradation of epithelial tight junctions and an increased leakiness of the gut [12, 18]. Continued production of MCPt-1 after expulsion may protect against secondary helminth infection via continued cleavage of cell–cell bonds, and it is likely that maintenance of a larger population of activated mast cells at the epithelium enables a rapid response to any pathogens that are able to gain entry into the lamina propria. Sorobetea et al. also rightly speculate regarding the impact of prolonged mastocytosis on the development of allergic and autoinflammatory conditions [24]. Helminth infection has previously been associated with protection against development of autoimmune diseases such as IBD, but this new data would suggest the opposite may actually be true. Previous studies provide further evidence of this potential role by demonstrating a link between IL-9-mediated mastocytosis and subsequent MCPt-1 release with increased intestinal permeability and oral antigen hypersensitivity [25]. Nevertheless, the precise role of persistent mast cells remains to be determined.

Systemic detection of MCPt-1 in the months following acute *T. muris* infection is particularly interesting in terms of sensitizing the host to an allergic response in the lung. In addition to MCPt-1 being linked to oral hypersensitivity, it has been shown that chronic *T. muris* infection confers systemic protection against allergic airway inflammation via localized production of interferon-γ and IL-10 in the lung [26], suggesting that worm infection may be protective against autoimmunity and allergy up until the point of expulsion; reinforcing the viewpoint that host immunity is conditioned for a chronic low-level infection state. Further implications may arise during deworming programs, where patients may see an increase in barrier dysfunction following anthelmintic treatment regimes. However, the long-term effects of parasitism have negative consequences of their own; children in countries where helminth infections are prevalent have a significant reduction in school absenteeism when deworming programs are implemented [27].

Mast cells clearly play highly context-dependent roles during and after immune challenge by intestinal helminths. Sorobetea et al. provide new insight into the function of mast cells in an acute *T. muris* infection, providing evidence of longevity and activation, and hinting at two potentially conflicting outcomes: strengthening surveillance in the gut to protect against secondary infection, while increasing the risk of allergic responses elsewhere [24]. Latent, systemic effects of seemingly resolved immune responses provide an added layer of detail to an already complex field.

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Abbreviations: **IgE**: immunoglobulin E · **MCPt-1**: mast cell protease 1

Full correspondence: Prof. Colby Zaph, Infection and Immunity Program, Department of Biochemistry and Molecular Biology, Monash Biomedicine Discovery Institute, Monash University, Clayton, VIC, Australia
e-mail: colby.zaph@monash.edu

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