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Review Article

Mast cells: new therapeutic target in helminth immune modulation

K. V. VUKMAN,[1,2] R. LALOR,[2] A. ALDRIDGE[2] & S. M. O'NEILL[2]

[1]Department of Genetics, Cell- and Immunobiology, Semmelweis University, Nagyvarad ter 4., H-1089, Budapest, Hungry, [2]Parasite Immune Modulation Group, School of Biotechnology, Faculty of Science and Health, Dublin City University, Glasnevin, Dublin, Ireland

SUMMARY

Helminth infection and their secreted antigens have a protective role in many immune-mediated inflammatory disorders such as inflammatory bowel disease, rheumatoid arthritis and multiple sclerosis. However, studies have focused primarily on identifying immune protective mechanisms of helminth infection and their secreted molecules on dendritic cells and macrophages. Given that mast cells have been shown to be implicated in the pathogenesis and progression of many inflammatory disorders, their role should also be examined and considered as cellular target for helminth-based therapies. As there is a dearth of studies examining the interaction of helminth-derived antigens and mast cells, this review will focus on the role of mast cells during helminth infection and examine our current understanding of the involvement of mast cells in T_H1/T_H17-mediated immune disorders. In this context, potential mechanisms by which helminths could target the T_H1/T_H17 promoting properties of mast cells can be identified to unveil novel therapeutic mast cell driven targets in combating these inflammatory disorders.

Keywords *autoimmunity < disease, immune modulation < immunological terms, inflammation < disease, mast cell < cell, parasite*

INTRODUCTION

Parasitic worms or helminths are highly successful metazoans that infect an estimated third of the world's population, causing chronic infections (1). While helminth infection is not associated with high mortality rates, high degrees of morbidity are associated with affected populations. The disability-adjusted life years (DALYs) of individuals is generally used as a measure of the burden of helminth infection (2) and a report in 2010 estimated that approximately 15 million DALYs were a direct result of helminth infection (3–5). Helminths have developed immunomodulatory strategies to evade host immune responses enabling them to persist within their host for prolonged periods of time. While studies have shown that the immunomodulatory effects of helminth infection can increase the susceptibility of a host to a number of secondary infections (6,7), they also have been demonstrated to have a protective role in many noncommunicable immune-mediated inflammatory disorders (8,9).

Helminth therapy is being explored as a viable treatment of T_H1/T_H17-mediated inflammatory disorders such as multiple sclerosis (10) and inflammatory bowel diseases, including ulcerative colitis (11,12) and Crohn's disease (13). Human clinical trials to date have demonstrated that this therapy is both safe and effective (10,11,14–16). Furthermore, studies in mouse models such as experimental autoimmune encephalomyelitis (EAE) (17,18), type 1 diabetes (19), rheumatoid arthritis (20) and colitis (21) have suggested that helminth infection and the molecules it secretes are also protective in these disease models. Therefore, understanding the immune protective properties of helminths could offer potential therapeutic targets for a wide range of diseases.

Mastocytosis is a pathological infiltration of mast cells that is a common feature of helminth infection and a major component of protective immunity against helminth infection in the intestinal tract (22,23). Moreover, mast cells are associated with many T_H1/T_H17 immune-mediated disorders including multiple sclerosis, inflammatory bowel disease and rheumatoid arthritis (24). While studies have established the impact of helminth infection on the ability of innate immune cells such as dendritic cell and macrophages to drive inflammatory responses (25),

Correspondence: Dr. Sandra O'Neill, Parasite Immune Modulation Group, Biotechnology, Faculty of Science and Health, Dublin City University, Glasnevin, Dublin 9, Ireland (e-mail: Sandra.ONeill@dcu.ie).
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relatively few studies have examined the role of mast cells in this context. This review will examine the role of mast cells in helminth infection and inflammatory disorders with a view to highlight mast cells as an important cellular target in the development of helminth-derived therapies.

THE ROLE OF MAST CELLS IN HELMINTH INFECTION

Helminth infections are associated with increased mast cell numbers which are primarily redistributed to the site of infection (26). Activated mast cells secrete serine proteases, chymase and tryptase that have a direct cytotoxic effect on the helminth (27,28). In addition, mast cell-derived mouse mast cell protease 1 has been shown to loosen tight junction spaces in epithelial barrier, increases intestinal permeability resulting in increased luminal flow, leading to the expulsion of the parasite (29). However, the importance of mast cells in clearance is species specific (8). While the ablation of mast cells in murine models of *Trichuris muris* is not critical to its expulsion (30), there is strong evidence to support the involvement of mast cells in intestinal nematode infection (29). *In vivo* studies of *Heligmosomoides polygyrus* infection with mast cell-deficient Kit^{W}/Kit^{W-v} mice show higher rates of nematode fecundity, compared to wild-type controls, highlighting their importance in intestinal helminth immunity (31). Enhanced mast cell number were associated with the clearance of *Strongloides ratti*, *Trichinella spiralis*, *Nippostrongylus brasiliensis* and *Strongyloides ratti* in rodent models, further implicating their importance (29,32,33).

The role of mast cells in tissue dwelling helminth infection, such as *Schistosomais or Fasciolosis* is not clearly understood, despite mast cells being implicated with both the acute and chronic stages of the infection (34). The early stages of *Schistosoma* infection are predominately skewed towards T_H1 immune responses (35). Given that mast cells are an important source of T_H1 inflammatory cytokines, their relative contributions to the development of T_H1 immune responses at this stage remains unclear. Similarly, mast cells are observed in the chronic stages of *Schistosoma* infection, when T_H2/T_{reg} immune responses are predominant (36), again implicating an important role for mast cells in shaping the adaptive immune response. Increased mast cell infiltration in the liver remains a key feature of *Fasciola hepatica* infection (37,38), and in rodent models, this is dominated by T_H2/T_{reg} responses within hours of infection.

Extensive migration is a common feature with tissue dwelling helminths, *F. hepatica* for example, migrates from the intestine to the peritoneal cavity, finally residing in the bile ducts of the liver (39). This migration is correlated with increased mast cell infiltration in the gut mucosa, peritoneal cavity and liver (40–42). This increased mast cell population may be involved in promoting the balance between inflammation and wound healing as mast cells secrete mediators, such as histamine, serotonin, enzymes and cytokines that are important in inducing fibroblast proliferation; a marker for wound healing responses, while also increasing vascular permeability and recruiting neutrophils (43,44). In mast cell-deficient mice, wound closure is significantly impaired compared to normal or mast cell reconstructed mice (44).

During helminth infection, the activation of mast cells is mainly studied in the context of adaptive T_H2 immune responses. Protective immunity to helminths is thought to be mediated by the T_H2 subset of $CD4^+$ T cells; however, mast cells are observed in the early stages of infection suggesting that these cells may have an important role to play in shaping the T_H2 immune response. Cytokines, namely IL-4 and IL-13, secreted by T_H2 cells direct B-cells to produce helminth-specific IgE antibody (8,45). Mast cells express the high affinity FcεRI receptor, which in the presence of helminth-specific antigens and IgE antibody induce mast cell degranulation, resulting in the release of inflammatory mediators such as histamine, cytokines and chemokines (46,47).

The release of these mediators by mast cells was shown to contribute to the development of T_H2 immune responses towards gastrointestinal helminths by activating other cells involved in T_H2 immunity, (48). A recent study demonstrated the importance of mast cell crosstalk in the early stages of *H. polygyrus* infection. T_H2 immune responses and the clearance of the helminth was associated with mast cell released IL-25, IL-33 and thymic stromal lymphopoietins (TSLP) (49). Wild-type mice were characterized by high expression levels of T_H2 cytokines, namely IL-4, IL-5, IL-9, IL-10 and IL-13. However mast cell-deficient Kit^{W}/Kit^{W-v} mice showed a significantly impaired T_H2 response. Mast cell-derived IL-25, IL-33 and TSLP was shown to be crucial for driving T_H2 cell priming through the activation of dendritic cells (48). Other studies have demonstrated that mast cells can indirectly modulate T-cell responses by crosstalking with dendritic cells, influencing their maturation (50). In contact hypersensitivity mouse models, activated dendritic cells bind to mast cells, promoting Ca^{2+} influx and the induction of tumour necrosis factor alpha (TNF-α) production. Activated mast cell-derived TNF-α was also shown to induce the *in vivo* migration of DCs (51).

Further work is required to define the phenotype of mast cells that promotes early T_H2 immune responses in the absence of antigen-specific IgE. The definition of these

subsets could be based on analogy to dendritic cells and macrophages in helminth infection. Helminths alternatively activate innate immune cells, which display unique phenotypical and functional properties. Alternatively activated dendritic cells have been shown to display partial maturation (52,53) characterized by low expression of the co-stimulatory, major histocompatibility complex (MHC) molecules and a restricted cytokine and chemokine secretion profile compared to bacterial activated dendritic cells. Alternatively activated macrophages have also been shown to exhibit an M2-phenotype characterized by the expression of ARG1, YM1/2, RELMα genes and secretion of TGF-β, PGE2 and IL-10. The alternate activation of these cell populations contributes to the induction of T_H2 responses (54,55).

While there is strong evidence to support the influence mast cells can have in inducing T_H1, T_H17 and T_H2 immune responses (50), a subset of mast cells that drive T_{reg} immune responses has yet to be defined. However, considering mast cells secrete IL-10 and TGF-β, two cytokines important in the induction and maintenance of T_{reg} cells, further work is required to examine whether mast cells contribute to tolerogenic immune response (56,57).

POSITIVE BYSTANDER EFFECTS OF HELMINTHS UPON T_H1/T_H17 INFLAMMATORY DISORDERS

Numerous studies in helminth endemic regions reported a reduced risk of individuals developing T_H1/T_H17-mediated autoimmunity or inflammatory bowel disease (IBD) at the population level (58–60) and this led to the hypothesis that helminths conferred protection against inflammatory disorders. Leading on from these initial observations and overwhelming evidence from experimental models, helminth therapy is currently being used in phase I clinical trials as a novel approach for the treatment of a range of inflammatory disorders. Initial reports from these clinical trials have demonstrated that treatments are safe (10). While helminth therapy was shown as a good therapeutic candidate in individuals with multiple sclerosis; results were less promising for allergic rhinitis (61). There is also still debate to the effectiveness of helminth therapy on treating IBD. Despite positive results in initial studies using *Trichuris suis ova* to treat Ulcerative colitis or Crohn's disease (62), a more recent study in a large clinical trial of patients with Crohn's disease, showed no signs of improving disease activity index or remission rates and was subsequently stopped due to a lack of efficacy (63,64).

While human trials with worm therapy are a new development, there is overwhelming evidence in experimental models that helminth infection and the products they release exert immune-suppressive effects that prevent the initiation and perpetuation of inflammatory disorders. Infection with *Schistosoma mansoni* reduces the incidence of autoimmune disease in mice by 50% (65) while gastrointestinal nematodes can suppress innate and adaptive pro-inflammatory immune responses, which are linked to the suppression of inflammation associated with IBD (66). *Hymenolepsis diminuta* was shown to have beneficial effect in a murine model of colitis while *T. spiralis* infection was observed to have a protective effect in the same model, reviewed elsewhere (60,67).

Similar to infection, helminth-derived excretory–secretory (ES) products and extracts have been shown to have a protective effect in the treatment of a range of inflammatory disorders such as murine arthritis, allergy and diabetes which have also been extensively reviewed elsewhere (68-71). The use of these parasitic antigens or synthetic analogues may allow for the development of specific and or more effective drugs to cure inflammatory disorders.

MAST CELLS, T_H1/T_H17 AND INFLAMMATORY DISORDERS

Similar to dendritic cells and macrophages, upon activation mast cells can elicit immune responses, by interacting with other cells through adhesion molecules, co-stimulatory/co-inhibitory molecules and the secretion of cytokines (72). MHC class I and II play central roles in antigen presentation. Mast cells express high levels of MHCI but very low levels of MHCII, although this can be up-regulated by LPS or IFN-γ stimulation, or during bacterial infection (73). Expression of ICAM-1, VCAM-1, OX40L, CD40L, LFA-1 and many other molecules by mast cells would suggest a broad ability to directly mediate T-cell activation, although the mechanism is yet unclear (74,75).

Mast cells indirectly activate the adaptive T_H1 immune system by secreted cytokines, chemokines and also acting as antigen presenting cells. These mast cells are characterized by the lack of degranulation and the production of pro-inflammatory mediators, such as TNF-α. These cells have been shown to also contribute to pathology in inflammatory disorders (26,76). Mast cells are therefore thought to be a potential novel cellular target in the treatment of a range of T_H1/T_H17 immune-mediated diseases where mast cells contribute to pathology (26). Studies using mast cell knockout mice show a critical role for mast cells in many inflammatory disorders such as multiple sclerosis (MS), rheumatoid arthritis (RA) and inflammatory bowel disease (IBD) (77,78).

In experimental autoimmune encephalitis (EAE), the murine model for MS, the release of pro-inflammatory mediators by mast cells was shown to contribute to the severity of disease (79), while others have implicated mast cells in the induction of the disease rather than as effector cells contributing to disease severity (80). Studies in mast cell-deficient mice showed mast cell-derived pro-inflammatory cytokines, such as TNF-α, are integral to the development of EAE (81,82).

In collagen-induced murine RA models, mast cells were shown to accumulate and de-granulate in the affected joints (83). Mast cell-deficient mice are resistant to anti-glucose-6-phosphate isomerize (GPI) antibody-induced RA, while wild type and mast cell reconstituted mice retain their sensitivity (84). The precise pathogenesis of RA is still unclear. T_H1/T_H17 cells are currently considered to be the key participants in the pathophysiology of this disease (85–87), and mast cells may have a critical role in skewing lymphocytes towards T_H1/T_H17 responses and in the development of these pathological processes (88–90).

Enhanced mast cell numbers have been observed in animal models of IBD at the site of inflammation, where mast cell associated inflammatory mediators are found in abundance and are positively linked with pathogenesis and disease progression. In these studies, mast cells were shown to undergo degranulation, release histamine and pro-inflammatory cytokines, such as IL-6 and TNF-α (91). Considering the longevity of these cells, mast cells could exert influence in IBD development and progression at multiple checkpoints. In contrast, studies based on IL-10-deficient mice that are highly susceptible to developing IBD, demonstrated that mast cell depletion enhanced susceptibility suggesting that mast cells may have a protective role (92).

Studies have shown that mast cell inhibitors have therapeutic potential in the treatment of IBD (93). While there still remains conflicting data on the involvement and distribution of mast cells in the intestine of patients presenting with ulcerative colitis (94–96), it was demonstrated by Kurosawa and Nagai that ulcerative colitis patients were successfully treated with anti-allergic drugs which targeted mast cell activation and T_H2-polarized immune responses (97). The role of mast cells is alluded to, by the elevation of UC severity in patients treated with drugs which directly target mast cell activation. Mast cells play a prominent role in inflammatory disorders, and yet there is a dearth of studies examining the potential of helminths

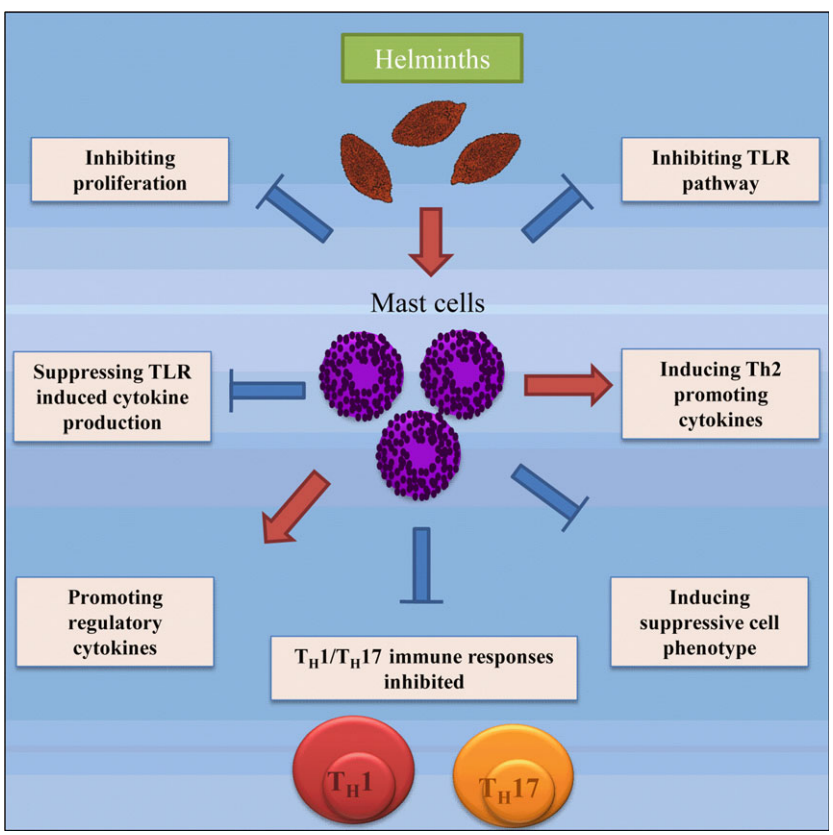

Figure 1 Potential mechanisms of action of Helminth-treated mast cells: evidence in the literature would suggest that helminths could have the potential modes of action on mast cells that would lead to the suppression of Th1/Th17 immune response. **1.** Inhibiting mast cell proliferation (42). **2.** Suppressing TLR-induced cytokine production (18,53). **3.** Promoting regulatory cytokines (19,25,54). **4.** Inhibiting TLR pathway (52,53). **5.** Inducing Th2 promoting cytokines (18,19). **6.** Inducing suppressive phenotypes (104).

to modulate these cells as targets for helminth-derived therapies. This highlights the need of further studies.

MAST CELLS AS THERAPEUTIC TARGETS FOR HELMINTH THERAPY

A strong rationale exists to analyse mast cells as cellular targets for helminth-based therapies. We have shown that helminth-derived molecules namely *F. hepatica* tegumental coat antigens (FhTeg) target mast cells inhibiting their ability to drive T_H1 immune responses. FhTeg suppress LPS-induced NF-κB and MAPK pathway (ERK) activation in mast cells (98). NF-κB and MAPKs are important signalling molecules leading to the expression of ICAM1 (99) and the secretion of pro-inflammatory cytokines. We demonstrated that the expression of ICAM1 was important in mast cell-T-cell communication, as inhibiting its expression in conjunction with the release of pro-inflammatory cytokines blocked the induction of T_H1 responses (98). This inhibition of T_H1 immune responses is thought to be due in part by the expression of suppressor of cytokine signalling-3 (SOCS3) (a pathway not previously described in mast cells) (98), a negative regulator of T_H1/T_H17 inflammatory processes (100). We also demonstrated that FhTeg does not induce mast cell proliferation while promoting migration of mast cells *in vitro* suggesting that the increase in mast cell numbers observed in the peritoneal cavity and liver of mice may be the result of mast cell migration and not proliferation (42).

Some other studies on *T. spiralis* have also demonstrated the immunomodulatory effects of helminths on mast cells. The *T. spiralis*-secreted molecule ES-62 was shown to block calcium mobilization and bind toll-like receptor 4, inhibiting downstream signalling of NF-κB, antagonizing mast cell degranulation (47). *T. spiralis*-secreted molecules have also been shown to selectively modulate the secretion profiles of activated mast cells while *T. spiralis* muscle larval antigens were demonstrated to induce the release of histamine but inhibit β-hexosaminidase in mast cells (101,102). *T. spiralis*-secreted enzymes were also shown to inhibit mouse mast cell protease 1 (103).

There is strong evidence in the literature demonstrating the mechanisms by which helminth infection and their secreted molecules target innate immune cells. These mechanisms are well described for macrophages and dendritic cells, many of which we have discussed are shared by mast cells. While there are relatively few studies, we can hypothesise the potential modulatory interaction (Figure 1). Given the prominent role mast cells play during inflammatory disorders and the interest in using parasitic helminths to treat these disorders, future studies should be focused on the mechanisms used by helminths to suppress mast cell responses for the potential discovery of novel therapies.

SUMMARY

In summary, mast cells are involved in multiple inflammatory and autoimmune disorders (26), where TNF-α secretion from these cells is critical to disease pathology (81,82). It is therefore possible that the protective effect of helminths against immune disorders may be the result of its molecules directly blocking the release of pro-inflammatory mediators from mast cells. These findings might lead to the development of a therapeutic inhibitors for pathogenic mast cell phenotypes.

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