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Review

Mast Cell Response to Parasites: from Recognition and Activation to Host Defense Modulation

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Abstract
Parasites represent a diverse and widely distributed group of pathogens that cause diseases with significant global health implications. The interaction between parasite and host is characterized by a high degree of complexity, with both parties continuously adapting to changes in the other. The successful host invasion is largely attributable to the evasion strategies employed by parasites to ensure their survival in immunocompetent individuals. In turn, the host's defense mechanisms utilize a variety of structures and processes, ranging from primary barriers to the most sophisticated ones, to counter the parasite attack. Acting as an early line of defense, the immune system includes a variety of cell types that are capable of recognizing, destroying, and eliminating infectious agents. Undoubtedly, the orchestration of first-line innate immune responses but also adaptive immunity processes during infection depends to a large extent on the involvement of tissue-resident mast cells (MCs). MCs are capable of supporting immune reactions to parasites through a broad spectrum of processes, including degranulation, synthesis and release of cytokines/chemokines and other mediators, and the generation of reactive oxygen species (ROS). They may also be involved in immune cell recruitment, phagocytosis, and the provision of extracellular DNA traps. Despite the well-documented association of MCs with antibacterial and antiviral defense, their role in host protection against parasites remains incompletely identified. This article provides an overview of the engagement of MCs in host defense mechanisms developed during parasitic infections. Furthermore, it considers the impact of parasites or parasite-derived molecules on the various aspects of MC activity.

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Introduction

Parasitic infections caused by protozoa or helminths are distributed virtually worldwide, but predominantly they constitute a significant health problem in tropical developing countries where they are often neglected. Among the parasitic diseases with important mortality or morbidity rates, are malaria, leishmaniasis, amoebiasis, trypanosomiasis, and schistosomiasis. Furthermore, toxoplasmosis, ascariasis, and taeniasis represent common human parasitic illnesses. The widespread prevalence of parasites is due to their diverse anatomical, physiological, and behavioral adaptations, which allow them to survive even in extreme conditions [1]. Despite the global influence of parasites, effective antiparasitic therapeutics are limited, and malaria is currently the only parasitic disease for which two vaccines are available for humans and recommended by the World Health Organization (WHO) [2]. Depending on the species, parasites may be transmitted to their suitable hosts in several ways, both vertically and horizontally. For example, protozoa and helminths can be spread orally by ingesting water or food contaminated with invasive forms. A defining characteristic of certain parasitic nematodes is their capacity to autoinfect and, as a consequence, self-replicate within their host. Other modes of parasitic infection include active penetration through the skin or mucous membranes or direct contact between hosts. Finally, many blood parasites are transmitted by arthropod representatives that serve as disease vectors [3]. Infection with parasites may result in a spectrum of symptoms, ranging from mild discomfort to severe illness. In some individuals, infection progresses to a chronic phase, which, depending on the type and quantity of parasites, can lead to weakness, severe anemia, and malnutrition with weight loss. It is important to note that asymptomatic carriers of parasites constitute a great challenge for public health, meaning they have a silent infection. Nevertheless, they contribute to the transmission of the infection to the others.

Despite the large number and diversity of antigens presented by the parasite to the host immune system and the response initiated against them, parasites try to survive within the body host by using multiple evasion strategies that have been acquired over millions of years of evolution [4]. In turn, the host's defense mechanisms range from primary barriers to more complex responses involving diverse immune cells and mediators capable of identifying and eliminating infectious agents [5]. Undoubtedly, the orchestration of first-line innate immune responses and adaptive immunity during infection relies on the coordinated activity of various immune cells, including macrophages, granulocytes, dendritic cells, natural killer (NK) cells, B lymphocytes, and T lymphocytes [6]. Among these, tissue-resident mast cells (MCs) occupy a strategic position at the host-environment interface, especially in barrier tissues such as skin, and the gastrointestinal and genitourinary mucosa, which are common entry sites for parasites. Due to their location and rapid response capacity, MCs are well positioned to act as important responders during parasitic infections. These cells recognize pathogen-associated molecular patterns (PAMPs)/microbe-associated molecular patterns (MAMPs), release preformed and newly synthesized bioactive mediators, recruit and activate other immune cells, and participate in processes such as phagocytosis and extracellular DNA trap (MCETs) formation [7, 8]. Although numerous studies have addressed the role of MCs in anti-parasitic defense, their involvement remains incompletely characterized. Therefore, the aim of the present article is to provide an overview of MC engagement in host defense mechanisms developed during parasitic infections. Furthermore, the article considers the impact of parasites or parasite-derived molecules on the various aspects of MC activity.

Hallmarks of the host immune response to parasites

To survive until parasites reach maturity and complete their life cycle, these organisms have evolved a variety of complex strategies. Frequently, these strategies are stage-specific, allowing parasites to use, avoid, or modulate the host's immune response and metabolism [9, 10]. Conversely, physical and chemical barriers, as well as numerous innate and adaptive

components of the host immune system, have been identified as either less or more crucial during a parasite attack. However, the direction of the host immune response, reflecting differences in infection strategies, tissue localization, and interactions with the immune system, is primarily determined by the type of parasitic invader.

The primary line of host defense against parasites, as in the case of bacteria, viruses, or fungi, consists of anatomical and structural barriers, particularly the skin and mucosal surfaces, which are further supported by chemical defenses. Nevertheless, as the common site of infection or route of access for the parasites, mucosal barriers are frequently unable to repel the attack. This phenomenon has been well-described in the context of gut protozoa, such as *Entamoeba histolytica* [11] and *Giardia duodenalis* [12] or *Toxoplasma gondii* [13], which may lead to the opening of intercellular tight junctions and the subsequent breakdown of the intestinal mucosal barrier. Mucins, as integral components of the mucus layer, can either block parasite colonization or facilitate their expulsion. Conversely, data indicate that *G. duodenalis* [14], *E. histolytica* [15], and *Trichuris muris* [16] can proteolytically cleave the major structural component of the mucus gel, i.e., mucin 2 (MUC2), and disrupt the host colonic mucus by breaking down the macromolecular structure and invading the underlying epithelium. Another crucial element of mucosal defense is secretory immunoglobulin A (sIgA), which neutralizes pathogens and prevents their adhesion to the epithelium. sIgA antibodies are important for the clearance of *E. histolytica* [17], *Giardia* sp [18, 19], and *Clonorchis sinensis* [20]. In addition, some authors have proposed that IgA could function as a biomarker for worm infections [21, 22].

Recently there has been renewed interest in the interaction between the host gut microbiota and invading parasites. It is well established that intestinal parasites have a profound impact on the composition and diversity of the host microbiota, which in turn has significant implications for the efficacy of host defense mechanisms [23, 24]. Conversely, an increasing body of evidence suggests that the intestinal microbiota may be firmly involved in the defense against parasites [25, 26]. Nevertheless, the precise function of the gut microbiota in this process is still not well understood. Some reports indicate that the expulsion of parasites may be strongly dependent on the composition of the microbiota. For example, Li and colleagues [27] demonstrated that early *Trichinella spiralis* infection reduces gut microbiota diversity and alters its composition, leading to a predominance of bacteria that produce pro-inflammatory metabolites, such as ceramides. In the subsequent phase of the infection, the same authors observed an increase in the number of representatives belonging to the *Lactobacillaceae* family that have anti-inflammatory properties through the production of short-chain fatty acids (SCFAs). The presence of *G. duodenalis* was found to be reduced by *Lactobacillus* sp., while the bacteriocins produced prevented parasite adhesion [28–30]. It has been demonstrated that SCFAs, the principal microbiota-derived metabolites, exhibit inhibitory activities against protozoa [31, 32]. Microbiota-derived SCFAs are well-known anti-inflammatory mediators and regulatory T cell (Treg) inducers for host intestinal immunity, as was documented in the case of *Echinococcus multilocularis*-infected mice [33].

Following the breach of anatomical and chemical barriers by invaders, the host immune system must first recognize the threat, after which most, if not all, immune cell types are mobilized in antiparasitic defense. The identification of pathogens is achieved by expressing a set of pattern-recognition receptors (PRRs) by host immune cells. PRRs are able to recognize PAMPs/ MAMPs derived from microbes or parasites, including proteins, lipoproteins, lipids, and nucleic acids. PRRs also detect endogenous danger-associated molecular patterns (DAMPs) released upon cellular stress or tissue injury. These receptors include Toll-like receptors (TLRs), NOD-like receptors (NLRs), RIG-I-like receptors (RLRs), and C-type lectin receptors (CLRs) [34]. Some of these have been documented to detect components derived from parasites (Fig. 1). For instance, TLR1/2 and TLR2/6 heterodimers are capable of recognizing glycosylphosphatidylinositol (GPI) anchors of *Plasmodium* sp. [35] and/or *Trypanosoma* sp. [36]. Lipopeptidophosphoglycan (LPPG) of *E. histolytica* and *Taenia crassiceps* carbohydrates are the most common ligands for TLR4 [37, 38]. TLR11 and TLR12 are localized to endosomes to recognize *T. gondii*-derived profilin [39]. Other significant

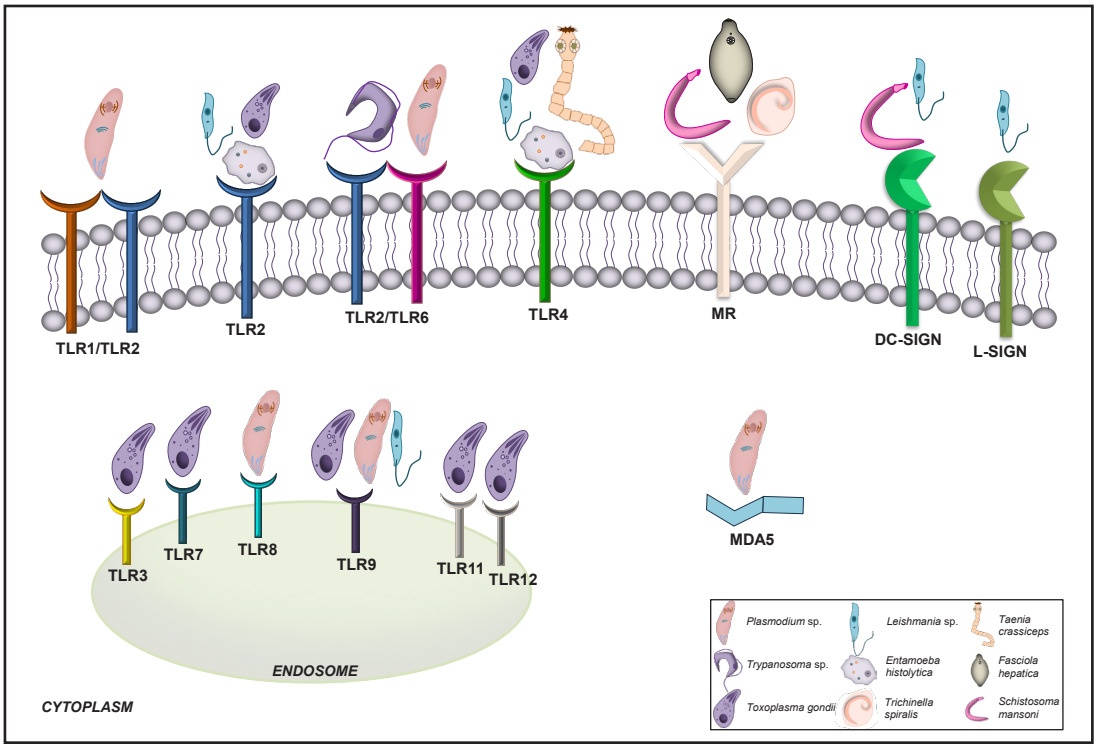

Fig. 1. PRRs representatives involved in the recognition of parasites. DC-SIGN, dendritic cell-specific intercellular adhesion molecule-3-grabbing nonintegrin; L-SIGN, liver/lymph node- specific intercellular adhesion molecule-3-grabbing nonintegrin; MDA5, melanoma differentiation-associated protein 5; MR, mannose receptor; TLR, Toll-like receptor.

TLRs include TLR3, TLR7, and TLR9, which may collaborate with TLR11 and TLR12 in the host response to *T. gondii* [40, 41]. In turn, dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN), a known CLR, has been demonstrated to bind to *Leishmania* sp. or *Schistosoma mansoni* egg antigens [42, 43].

Each type of innate immune cell occupies a specific role within the host's defense system, collaborating with others to form interconnected networks regulated by cytokines and other molecules. Macrophages and neutrophils are among the most crucial players in the immune response due to their multifaceted functions. Concerning their capacity to phagocytose parasites, these cells can do so with some protozoa, smaller helminth larvae, and eggs. However, the adult forms are typically too large to be engulfed. Instead, macrophages and neutrophils contribute to the immune response against helminths by migrating to the infection site, secreting effector molecules such as reactive oxygen species (ROS), and recruiting other immune cells to attack the parasite. Of note is the observation that macrophages and neutrophils release extracellular DNA traps in response to protozoa and helminths [44–46]. Regarding antiparasitic properties of eosinophils, they are primarily based on their increase in the circulation and affected tissues during helminth infection. Eosinophils bind to the worm larvae through antibodies or complement, after which they release intracellular granules containing toxic substances for parasites, such as major basic protein (MBP), eosinophil cationic protein (ECP), and many others. Also, NK cells control parasitic infections by contributing to parasite lysis and producing significant amounts of interferon (IFN)-γ, a cytokine that is vital in the context of infection with intracellular protozoan parasites [47]. Nevertheless, the most characteristic feature of the immune response to parasite attack is the binding of immunoglobulin E (IgE) to the high-affinity IgE Fc receptor (FcεRI) on basophil and MC surfaces, which triggers degranulation and the release of numerous mediators, including interleukin (IL)-4 and IL-13. These, in turn, trigger

a T-helper type 2 (Th2) response [48].

The innate immune defense system is supported by its specific soluble components. Among these, the complement system plays a pivotal role in the elimination of pathogens by forming the membrane attack complex (MAC) and promoting an inflammatory reaction on the surface of invaders. The available data regarding the effectiveness of the complement system in host defense against parasites appears to be largely ambiguous. Although the host complement system has been demonstrated to play a beneficial role during malaria infection [49], an increasing number of studies point to the effective evasion of this mechanism by many other parasites, such as *Leishmania* sp. [50], *Trypanosoma* sp. [51], and *Fasciola hepatica* [52]. Parasites avoid complement attacks using strategies including the expression of proteins that are homologous to host regulators to inhibit complement activation or the expression of proteins that target different complement components, to inhibit complement function and final formation of the MAC [53].

The role of numerous other effector molecules produced by the host organism for the elimination of parasites has been documented. Substances with a recognized role in anti-parasitic defense are antimicrobial peptides (AMPs). Among the AMPs, the defensins are the most extensively researched family, with several members demonstrating antiparasitic activities. The direct parasiticidal activity of β-defensin 130 (DEFB130) against *Plasmodium falciparum* [54], defensin α-1 against *Trypanosoma cruzi* [55], α-defensin-5 against *T. gondii* [56], and β-defensin-1 and -2 against *Cryptosporidium parvum* [57] has been observed. Furthermore, the potential of cathelicidins to damage *E. histolytica* or *Leishmania* sp. has also been revealed [58, 59].

The ability of parasites to evade innate immune mechanisms highlights the importance of adaptive immunity, which exhibits certain general patterns in its response. Typically, extracellular parasites (mainly helminths) induce a Th2-type response. The main drivers of this response are $CD4^+$ Th2 cells, which release type-2 cytokines such as IL-4, IL-5, and IL-13, with contributions from group 2 innate lymphoid cells (ILC2s) that serve as an additional source of these cytokines [60]. Type 2 immune responses can be accompanied by IL-10, produced by Th2 cells as well as other T cell subsets and innate immune cells, which primarily exerts regulatory and immunosuppressive functions [61]. In turn, IL-4, mainly produced by Th2 cells, is important for Th2 cell differentiation, as well as for the activation of the class switching mechanism in B cells that enables IgE synthesis [62]. Conversely, intracellular protozoan infections rely on a Th1-type response to resolve infection and results in a significant increase of Th1 cytokines, including IL-1β, IL-12, tumor necrosis factor (TNF), and most importantly, IFN-γ. Some data suggests that IFN-γ-producing $CD4^+$ Th1 cells are important for the infection caused by *Leishmania* sp. [63] and *Plasmodium* sp. [64]. However, it should be stressed that many intracellular protozoa have evolved sophisticated egress mechanisms that allow them to evade immune detection and destruction [65].

Although the aforementioned mechanisms and components each contribute in a parasite-specific manner, one of the central characteristics of anti-parasitic immunity is the activation of IgE-mediated type 2 responses. In this context, MCs emerge as pivotal effector cells acting at barrier sites, capable of bridging innate and adaptive immunity, and shaping the outcome of parasitic infections.

MCs and their role in host defense

The presence of MCs at surfaces in contact with the external environment, a common site of microbe attack, indicates that these cells constitute a potent arm of the immune response against external invaders. MCs are typically located in the subepithelial layers of the skin, the respiratory system, or the gastrointestinal and genitourinary tracts, but they are also found in the adipose tissue or around the blood vessels or nerves [66]. Furthermore, a number of additional factors contribute to the crucial role of MCs in host defense. MCs represent a dominant source of bioactive compounds that may affect all stages of microbial-induced inflammation, from its initiation, maintenance, and modulation, to resolution [67]. They include pre-formed mediators present within cytoplasmic granules (for example, histamine

and proteases), lipid-derived molecules synthesized from arachidonic acids (for example, prostaglandins (PGs) and leukotrienes (LTs)), and a wide array of cytokines and chemokines [68]. The direct antimicrobial activity of MCs may be mediated through the release of antimicrobial peptides (AMPs) with multidirectional mechanisms of action [69]. Also, the formation of ROS or reactive nitrogen species (RNS), such as nitric oxide (NO), represents an important approach of MCs that contributes to pathogen eradication [70]. Crucial to the MC involvement in the host defense is their capacity to efficiently destroy microorganisms through phagocytosis and kill them through oxidative and non-oxidative pathways. Following phagocytosis, MCs can process pathogen-derived antigens for presentation mediated by class I and II major histocompatibility complex (MHC) molecules, thereby initiating adaptive antimicrobial immunity [71]. Also, MCs are able to release their nuclear DNA to become MCETs, which consequently trap and eliminate a variety of pathogens [72, 73]. Additionally, MCs may indirectly regulate host defense mechanisms through the activation of other immune cells and the release of chemoattractants, which recruit, for example, other phagocytic cells to the site of infection [74].

As mediators of host defense, MCs express multiple classes of PRRs that detect various MAMPs/PAMPs or endogenous DAMPs. Expression of TLRs, RLRs, NLRs, and CLRs has been confirmed in a wide range of MC types and MC cell lines [75, 76]. The selective activation of PRRs represents an essential mechanism in regulating the type of MC antimicrobial response. For example, PAMPs associated with bacteria are mainly recognized by TLR or NLR representatives. RLRs and some TLRs can detect viral double-stranded RNA (dsRNA), single-stranded RNA (ssRNA), or envelope proteins. In turn, MCs express CLRs, which are essential for the sensing of fungal antigens [75]. However, limited data are available concerning the detection of parasite components by MCs. In a study conducted by Furuta and colleagues [77], it was demonstrated that MCs can produce TNF in response to the binding of TLR4 or FcεRI/IgE to malaria parasite-derived peroxiredoxin. A recent report indicates that 5'-methylthioinosine, a *P. falciparum*-specific intermediate of the purine salvage pathway, is an agonist for TLR8, which has been documented to be expressed in MCs [78]. Besides, some studies suggest that parasites or parasite-derived constituents may influence the expression of certain PRRs in MCs. For example, stimulation of a hybrid rat mast cell line (HRMC) with either F2 or the total soluble extract of *G. duodenalis* resulted in an increase (but non-significant) in TLR2 and TLR4 expression in these cells [79]. Further, lipophosphoglycan (LPG) from *Leishmania mexicana* was observed to enhance the expression of TLR2 in bone marrow-derived MCs (BMMCs) [80].

Parasites affect MC activity

Modes of MC response to Protozoa

Evidence indicates that various species of parasitic protozoa may directly affect MC activity *in vitro*. Many available data concern their impact on the generation and/or release of bioactive molecules from MCs. Firstly, it has been documented that protozoa have different effects on the MC degranulation and the secretion of preformed mediators, including those known for their potent proinflammatory properties. The trophozoites of *G. duodenalis* and their total soluble extract have been observed to increase the expression of tryptase and the secretion of histamine from rat peritoneal MCs (PMCs) [79, 81]. Conversely, it has been demonstrated that the stimulation of BMMCs with an extract containing soluble proteins of *Giardia* activates those cells, resulting in the release of tryptase, but not degranulation [82]. A more pronounced stimulatory effect observed with whole *Giardia* trophozoites compared to the extract alone indicates the presence of additional factors that enhance MC degranulation and preformed mediator release. In turn, unambiguous data indicate that another common flagellated protozoan parasite, i.e., *Trichomonas vaginalis*, is capable of triggering MC degranulation. It has been reported that *T. vaginalis*-derived excretory-secretory product (ESP) or live trichomonads activate rat PMCs and human MC (HMC-1) line to degranulate

[83–85]. It is worthy of note that when HMC-1 cells were exposed to live trichomonads, there was a notable increase in β-hexosaminidase release in proportion to the number of trichomonads present. Moreover, the addition of supernatants derived from human vaginal epithelial cells incubated with live *T. vaginalis* to HMC-1 cell cultures led to an increase in β-hexosaminidase secretion [86]. Also, parasites belonging to the *Trypanosoma* genus, i.e., *Leishmania donovani* and *Leishmania tropica* as well as *Leishmania major* and *Leishmania infantum* have been observed to activate the rat-derived basophilic leukemia cell (RBL-2H3) line or murine BMMCs, thus resulting in degranulation and β-hexosaminidase release [87, 88]. More detailed studies have confirmed that LPG, a surface protein derived from *L. mexicana* stimulates BMMCs from BALB/c but not C57BL/6 mice to degranulate, suggesting that susceptibility to LPG-induced MC activation is strain-dependent and may be attributed to the genetic background of the experimental model [80]. In addition, the exposure of primary MC types, such as BMMCs or rat PMCs to tachyzoites of the Apicomplexa protozoan *T. gondii* has been demonstrated to stimulate the secretion of histamine and serotonin by these cells [89, 90]. On the other hand, Smith and co-workers [91] documented that *T. gondii* inhibits RBL-2H3 cell degranulation and β-hexosaminidase release by suppressing the mobilization of intracellular Ca^{2+} by phospholipase C (PLC), a pivotal and well-known aspect of IgE/FcεRI-mediated signal transduction in MCs.

Same as central indicators of MC degranulation (histamine, β-hexosaminidase), other MC-derived mediators are synthesized in response to protozoa *in vitro*. Mounting evidence indicates that these organisms promote the production of a variety of factors, cytokines, and chemokines, including those with potent pro-inflammatory and antiparasitic properties. It was observed that the RH strain of *T. gondii* activates rat PMCs to release LTs, an important group of robust pro-inflammatory mediators known for their antiparasitic activities [90, 92]. Also, *T. gondii* lysates trigger the release of certain cytokines (TNF and IL-4) and chemokines (CCL2 and CXCL8) from HMC-1 cells, but not from murine BMMCs [89, 93]. Both *G. duodenalis* live trophozoites and total soluble extract (TSE) of trophozoites induce mRNA expression and production of the pro-inflammatory cytokines IL-6 and TNF by the hybrid rat MC line (HRMC) [81]. Further detailed studies demonstrated that distinct protein fractions derived from *Giardia* trophozoites and designated as F1-F3 exhibited slight variations in their impact on cytokine synthesis by MCs. The findings of this study showed that fraction F2, which contains molecules with important biological activities such as enolase and arginine deiminase (ADI), has the greatest capacity to activate HRMC cells to produce TNF and IL-6 [79]. Also, *G. duodenalis* has been observed to induce the release of IL-6 from murine BMMCs [82]. The stimulation of HMC-1 cells with the secretory products of another intestinal protozoan, namely *E. histolytica*, resulted in an increase in CXCL8 mRNA and protein expression in these cells [94]. Living *L. major* or *L. infantum* promastigotes enhance the release of TNF from BMMCs [88], whereas LPG from *L. mexicana* activates those cells to synthesize pro-inflammatory cytokines, including TNF and CCL3, but also anti-inflammatory IL-10 [80]. The ESP and/or live trichomonads of *T. vaginalis* stimulate rat PMCs and HMC-1 cells to produce, for example, TNF, CXCL8, and CCL2 [83, 85, 86]. Notwithstanding the observed disparities in cytokine and chemokine release, likely attributable to the various parasite species and distinct characteristics of the MC source, the aforementioned data strongly indicate that MCs function as regulators or even initiators of inflammation during protozoan infections. Additional support for this hypothesis comes from some *in vivo* studies. The idea that MC-derived IL-6 plays an important role in the control of *Giardia* infection was confirmed by a study conducted by Li *et al.* [95], which demonstrated that intestinal tissue IL-6 mRNA levels are reduced in infected mice treated with MC blocking antibody compared to infected mice treated with control IgG or not treated with antibody. It was also noted that PMCs obtained from *Plasmodium berghei* ANKA-infected C57BL/6 mice released elevated amounts of TNF in comparison to MCs derived from control mice [96].

Furthermore, a substantial body of evidence from *in vivo* and *in situ* studies substantiates the influence of protozoa on the accumulation of MCs in tissues and/or their local degranulation. One of the initial findings in this context was performed by Im and co-

workers [97]. They observed a higher number of MCs and their degranulation in murine mesenteric tissues of the *E. histolytica*-infected group than the control mice [97]. Further, Rose and colleagues [98] reported an augmented number of MCs in the intestinal lamina propria of chickens after *Eimeria* sp. oocyst inoculation; however, there was no evidence of MC degranulation.

Infections with other enteric protozoa, such as *C. parvum* and *G. duodenalis*, further underscore this trend. The increase in the number of MCs within the intestinal mucosa and histamine level in the serum and intestinal contents of calves following an oral challenge with *C. parvum* oocysts compared to the animals from the control group was documented [99]. Likewise, *G. duodenalis* infection in mice was associated not only with higher MC counts in the small intestine but also with degranulation [100].

Malaria parasites induce similarly responses. Elevated MC number in ileal tissues and plasma histamine levels were noted in *Rhesus macaques* infected with the malaria parasite *Plasmodium fragile* in comparison to control animals [101]. Wilainam and colleagues [102] present an interesting *in vivo* study dealing with MCs in patients with *Plasmodium* infection. They showed that MC degranulation was significantly higher in the skin of patients with the complicated *P. falciparum* group in comparison to the uncomplicated *P. falciparum* and control groups. In that case, it has also been proposed that the percentage of MC degranulation correlates significantly with the degree of parasitaemia [102]. An additional study found that MCs promote *Plasmodium* spreading and that *P. berghei* infection of mice caused massive MC degranulation in the skin and draining of lymph nodes [103]. Also, a higher number of MCs and degree of MC degranulation were observed in the skin, cervical lymph node, and brain of mice with experimental cerebral malaria induced by the *P. berghei* ANKA strain than in uninfected mice [104]. It was also shown that MCs are recruited to the ileum in mice infected with *Plasmodium yoelii*, accompanied by elevated plasma histamine levels in that animal model [105]. It has recently been demonstrated that the activation of MCs and the subsequent release of MC protease-4 (MCPT-4) serve to suppress the host immune response to *P. yoelii* [106]. Although the aforementioned data suggest that *Plasmodium* species may induce MC degranulation *in vivo*, a recent study has demonstrated that the different stages of malarial infection exert varying effects on the murine PMC degranulation mechanism [107].

In vivo studies have also indicated the potential for MCs to play a significant role in the immune response to toxoplasmosis. The use of toluidine blue staining and immunofluorescence staining of tryptase revealed a high number of degranulated/total MCs in the spleen and mesentery tissues from mice infected with tachyzoites of the highly pathogenic *T. gondii* RH strain [108]. Similar findings were obtained by Ferreira *et al.* [109] who performed a morphological analysis of rodent PMCs following intraperitoneal injection with the same strain of *T. gondii* and observed a higher number of degranulated MCs obtained from peritoneal cavities compared to uninfected animals. Simultaneously, they showed the changed size and shape of MCs as well as exhibited lower numbers of granules, with a fusion of their membranes and the formation of intracytoplasmic channels [109]. There is also strong evidence that MCs are required for host survival following oral infection with *T. gondii*. In studies using MC-deficient (W/W^v) mice orally infected with a low-virulent ME49 *T. gondii* strain, Cruz and colleagues [110] observed a rapid lethality and decreased serum IFN-γ and IL-12 levels compared to control mice (control +/+ counterparts).

Trypanosoma infections similarly engage MCs, contributing to modulation of host immune responses. In murine experimental trypanosomosis induced by *T. brucei* or *T. cruzi*, there have been descriptions of an increase in the number and/or degranulation of MCs in the jejunum and cardiac lesions. This may be associated with a worse prognosis, possibly implying ongoing inflammation and fibrotic processes involving MCs [111–113]. During the *T. brucei* infection, the levels of histamine in the mucosal tissues of the jejunum of the infected mice were found to be significantly elevated [111]. In an experimental model of Chagas' disease, mice infected with *T. cruzi* show increased histamine levels in the heart tissues compared to control animals [114] and histological examination revealed the presence of MCs in these mice in regions of fibrosis [115]. Martins *et al.* [116] found an elevated numbers

of MCs and elevated tryptase levels in the colons of *Trypanosoma cruzi*-infected patients, suggesting MC activation and a potential role in the recruitment and activation of eosinophils.

During *Leishmania* infection, alterations in MC numbers and degranulation have been also observed. Cutaneous infection with *L. major* in C57BL/6 and BALB/c mice resulted in a decrease in the number of dermal MCs, but these cells exhibited extensive degranulation [117]. Interestingly, MC degranulation may inhibit leishmaniasis. The intraperitoneal and intrafootpad administration of a well-known MC degranulating agent, compound 48/80, to mice before infection with *L. major* resulted in a reduction in the incidence of infection, an increase in the popliteal lymph nodes' levels of IFN-γ, CCL2, CCL5, iNOS and a decrease in IL-4 levels [118]. Recently, Sánchez-García and co-workers [119] have conducted fascinating studies regarding the effect of male sex hormones on the MC-mediated response to *Leishmania* infection. They found that MCs showed a retarded activation pattern associated with slower degranulation and weaker histamine and tryptase staining in response to the infection with *L. mexicana* combined with vector-salivary proteins, as compared to sham mice in orchiectomized mice [119].

Very little was found in the literature on the question of the exact effects of protozoa on MC proliferation and/or survival. For instance, *L. major* or *L. infantum* notably reduced BMMC viability [88], yet no proliferation of dermal MCs from *L. major*-infected C57BL/6 and BALB/c mice was observed [117]. In turn, analysis of cardiac tissue samples obtained from *T. cruzi*-infected mice revealed enhanced MC proliferation [115]. Other authors revealed that during the *T. cruzi* infection, murine cardiac MCs exhibited increased expression of molecules involved in cell death, namely the $P2X_7$ receptor and Fas [120]. The viability of BM-MMCs remains unchanged in response to soluble *Giardia* proteins (sGPs) [82].

There is also some data regarding the mechanisms of various killing strategies of parasitic protozoa exerted by MCs. Noteworthy, Naqvi *et al.* [87] reported that RBL-2H3 cells phagocytose the promastigotes of *L. tropica* but not of *L. donovani*. This finding may suggest species-specific interactions between the parasites and the MCs, possibly involving distinct surface molecules or immune evasion strategies. The same authors have demonstrated that RBL-2H3 cells release extracellular structures upon stimulation with promastigotes of *L. tropica* and *L. donovani*. These structures are MCETs, which are capable of ensnaring pathogens [87]. Considering that ROS are highly toxic to pathogenic microorganisms, the information that MCs generate free radicals in response to parasites is highly relevant. It has been established that *L. tropica* and *L. donovani* stimulate ROS generation by RBL-2H3 cells [87]. Additionally, *T. vaginalis*-derived ESP has been observed to induce a significant increase in ROS production by HMC-1 cells [84]. HMC-1 cells treated with *T. gondii* lysate produce greater amounts of NO, which is known to be involved in anti-microbicidal activity [93]. In contrast, Henderson and Chi [90] documented that ROS are not implicated in the rat PMC-mediated toxoplasmacidal activity. Similarly, the production of ROS was not observed in HMC-1 cells stimulated with secretory products derived from *E. histolytica* [94].

It is well established that the recruitment of MCs represents a crucial aspect of the immune response to infection. However, up to date, the subject that parasitic protozoa-derived substances promote MC chemotactic activity has received minimal attention. *T. vaginalis*-derived ESP has been demonstrated to function as a potent chemoattractant for rat PMCs and HMC-1 cells [83, 86]. It has been also observed indirect effect on the promotion of MC migration in response to *T. vaginalis*-secreted cysLTs [85].

Activities of MCs regarding Platyhelminthes

The data indicate that the number of MCs increases in host tissues infected with parasitic flatworms, suggesting that MC infiltration is a common immune response across different hosts and plays a role in the host's defense against parasites from this phylum. Birck and colleagues [121] showed that the extent of MC infiltration was higher in the liver tissues of pigs infected with *Schistosoma japonicum* compared to the unexposed control group. In turn, a mild to moderate degree of MC infiltration was observed in the majority of hepatic granulomas. Also, it was documented that the number of MCs increased markedly in the

peritoneal cavity and liver of mice infected with *F. hepatica* metacercariae and mice that had been injected with the tegumental coat antigen of *F. hepatica* [122]. A considerable number of MCs were observed in the cardiac tissues of fish infected with *Ichthyocotylurus erraticus* metacercariae [123]. The number of MCs was found to be higher in the duodenum and bile duct tissues of mice infected with *Hymenolepis microstoma* than in uninfected animals [124]. Interestingly, immunostaining of tissues collected during liver biopsies from children with echinococcosis revealed an abundance of tryptase-positive MCs within the cyst capsules and the portal tracts surrounding the cyst [125]. Likewise, an increased number of MCs was observed in the intestinal mucosa of mice infected with *Echinostoma hortense*, with the most visible rise in the duodenum [126]. Observational studies in individuals vocationally exposed to *S. mansoni* demonstrated a negative correlation between the number of circulating MC precursors and resistance to reinfection. However, there is a lack of mechanistic explanation of this phenomenon [127].

Studies on host immunity to parasitic flatworms also looked at the *in vitro* and *in vivo* processes of MC degranulation. However, the results in this context are ambiguous and dependent on the flatworm species, possibly due to variations in their molecular components and specific mechanisms by which each parasite interacts with MCs. The molecule obtained from the adult worm of *S. mansoni* (i.e., *S. mansoni* incubation product, SIP) strongly inhibited rat MC degranulation in both *in vitro* and *in vivo* contexts [128]. In contrast, Coelho-Castelo and co-workers [129] evaluated rat peritoneal MC degranulation by exposing these cells to *S. mansoni*-derived mannose-binding protein, termed Sm60. They reported a high number of degranulated cells determined by their counting using a Neubauer chamber. Also, the stimulation of rat peritoneal MCs with synthetic peptides based on sequences identified in *F. hepatica* resulted in the degranulation of these cells as evidenced by the release of histamine [130]. In contrast, bone marrow- and peritoneum-derived murine MCs do not degranulate in the presence of *F. hepatica* tegumental coat antigen [122]. It has been also found that *T. crassiceps* metacestode-secreted products from the peritoneal cavity of infected mice inhibit the *in vitro* degranulation of murine and rat MCs, as well as *in vivo* degranulation in rats [131]. Dezfuli *et al.* [123] observed a considerable number of MCs and a high rate of degranulation in regions in close proximity to the site of *Eubothrium crassum* attachment in the caecum of infected fish.

There is no evidence to suggest that molecules derived from flatworms directly promote the migration of MCs. However, Vukman *et al.* [122] have demonstrated that the tegumental coat antigen of *F. hepatica* indirectly induces BMMC migration through the action of dendritic cell-derived chemokines, including CCL3 and CXCL2. Furthermore, *E. multilocularis*-obtained calreticulin, which is known to regulate the host immune system through binding to complement C1q, was found to suppress the chemotactic effect of C1q on HMC-1 cells [132]. These findings imply that *E. multilocularis* can use calreticulin to interfere with the host immune system's attack mechanisms, potentially representing a strategy of immune evasion.

There is a lack of data concerning the synthesis and function of MC-derived mediators during infection with parasitic flatworms. Only Vukman *et al.* [133] demonstrated that *F. hepatica* tegumental coat antigen suppresses TNF and IL-6 expression in LPS- or *Bordetella pertussis*-stimulated BMMCs and PCMCs. The use of a murine model of *Hymenolepis diminuta* infection has demonstrated that mice lacking MCs require a longer time to expel the invading parasites entirely [134]. Furthermore, it appears that MC-derived proteases play a role in this process [135].

Effect of Nematode species on MC actions

According to available literature, molecules derived from parasitic nematodes may have the capacity to influence MC degranulation *in vitro*, potentially exerting either a stimulatory or an inhibitory effect on this process. Stimulation of rat PMCs with antigens derived from the muscle larval stage of *T. spiralis* (TSL-1 antigens) and a total extract of its adult forms resulted in the release of histamine but not β-hexosaminidase from these cells

[136, 137]. On the contrary, synthetically obtained recombinant nematode galectin reduced the secretion of β-hexosaminidase from RBL-2H3 cells [138]. In addition, ES-62, a molecule secreted by filarial nematodes, has been shown to inhibit human BMMC degranulation and β-hexosaminidase release by forming a complex with TLR4 at the plasma membrane [139]. The process of MC degranulation during nematode infections has also been studied *in vivo*. The earliest study demonstrating that MC numbers in host tissues increase and degranulate during nematode infection was presented by Wells in 1962 [140]. A further report on this phenomenon was presented by Befus and colleagues in 1979 [141]. They observed increased histamine content in the intestinal tissues of rats infected with *Nippostrongylus brasiliensis*, which correlated with the number of intestinal MCs [141]. Additionally, serum levels of mMCPT-1 were higher in *N. brasiliensis*-infected mice than in healthy controls [142]. Increased MC density in the murine thoracic cavity and circulating levels of MC protease-1 (MCPT-1) have also been observed during infection with *Litomosoides sigmodontis*, a parasite that is widely used as a study model for human filarial infections [143]. Furthermore, the accumulation of MCs in infected tissues and/or elevated levels of MC degranulation markers have been reported in animal models infected with *T. spiralis*, *Strongyloides stercoralis*, *Strongyloides venezuelensis*, *Ascaridia galli*, *Toxocara canis*, and *Heligmosomoides polygyrus* [144–151]. The findings obtained by Patrizi *et al.* [152] indicate that infection with *Enterobius vermicularis* may act as a trigger for the onset of general cutaneous mastocytosis symptoms or may exacerbate cutaneous mastocytosis due to massive MC degranulation. Although the degranulation of MCs and the release of preformed mediators are generally regarded as crucial for the host's defense against parasites, some *in vivo* studies indicate that this process may enhance vascular permeability and, consequently, facilitate larval migration. Indeed, it has been demonstrated that the blockade of MC degranulation with MC stabilizers results in a reduction in the burden of *L. sigmodontis* in mice. This suggests that the release of MC-derived mediators during degranulation improves larval migration through the host skin [153, 154]. Conversely, MCs may promote the expulsion of *T. spiralis* by increasing the permeability of the gut *via* mouse MC protease-1 (mMCP-1)-mediated breakdown of epithelial tight junction proteins [144]. The interest of researchers has been also generated in the context of the activity of other MC-derived mediators' in host defense against parasitic nematodes. The stimulation of the rat HRMC-1 line with TSL-1 antigens has been found to increase mRNA expression of TNF and IL-4, while simultaneously reducing the expression of IFN-γ and IL-10 in these cells [155]. It has also been demonstrated that nematode galectin reduces the release of leukotriene C_4 (LTC_4) from RBL-2H3 cells [138]. Conversely, Carlos and colleagues [151] observed elevated circulating LTB_4 levels in rats following *T. canis* infection, which correlated with the accumulation of MCs and eosinophils. Shimokawa *et al.* [156] have pointed out the significance of IL-33 produced by MCs in eradicating *Heligmosomoides polygyrus* in the early stage of infection in mice. It has been established that MC-derived IL-33, following the recognition of tissue damage-derived ATP by the P2X7 receptor, activates ILC2s, which have been shown to contribute to the expulsion of a variety of helminths [156, 157].

There is currently no direct evidence to suggest that parasitic nematodes impact the survival of MCs. However, Knight *et al.* [145] reported that the expression of stem cell factor (SCF), a well-known MC growth factor, was significantly up-regulated in the epithelium of *T. spiralis*-infected mice. Very little is known about MC proliferation in response to parasitic nematodes or their molecules *in vitro*. Only Donskow-Łysoniewska *et al.* [138] demonstrated that synthetically obtained nematode galectin dose-dependently decreases the proliferation of RBL-2H3 cells.

Conclusion

The current state of knowledge regarding the role of MCs in the host's defense against parasites is not yet clearly defined, due to at least two major reasons. The heterogeneity of MCs employed in *in vitro* studies does not always yield consistent conclusions as

different MC types display various characteristics, including their phenotype, activity, and lifespan. Furthermore, it is important to consider that various parasites possess a vast array of antigens, and there is presently limited information regarding the parasite-derived specific molecules that are responsible for triggering the MC response. Further studies, which consider these variables, will need to be undertaken. Nevertheless, several strong assumptions concerning the role of MCs in anti-parasitic defense mechanisms can be deduced from an analysis of the available research literature. The majority of studies indicate that MCs exert a protective immune response during parasitic infection. The first substantial evidence to support this premise is the observation that MCs accumulate at the site of parasite presence in the host organism. Furthermore, the control of parasitic infections is achieved through the multifaceted actions of MCs (Fig. 2), which range from the elimination of invaders by phagocytosis or MCET formation to the synthesis and/or release of various mediators with direct anti-parasitic activity or which are necessary for the recruitment of other immune cells and their activation. The significance of preformed mediators such as histamine and MC-specific proteases in the context of parasite defense is of particular interest, as evidenced by several *in vivo* studies (Table 1). Finally, crucial to host defense during parasitic infection is the involvement of MCs in triggering a Th2-associated response [158]. The evidence presented above unequivocally indicates that MCs either initiate or modulate the inflammatory response during parasitic infections. Additional support for this hypothesis can be found in studies on human tissue samples from infected individuals and findings in various animal models. Nevertheless, to gain a comprehensive understanding of the role of MCs in defense mechanisms that develop during parasitic infection, additional studies will be invaluable. Further research should focus on the mechanisms by which MCs recognize parasites and how parasite-derived immunomodulatory factors act on these cells. Such an approach may be used in developing strategies to protect the host against infection and/or the pathological consequences of infection.

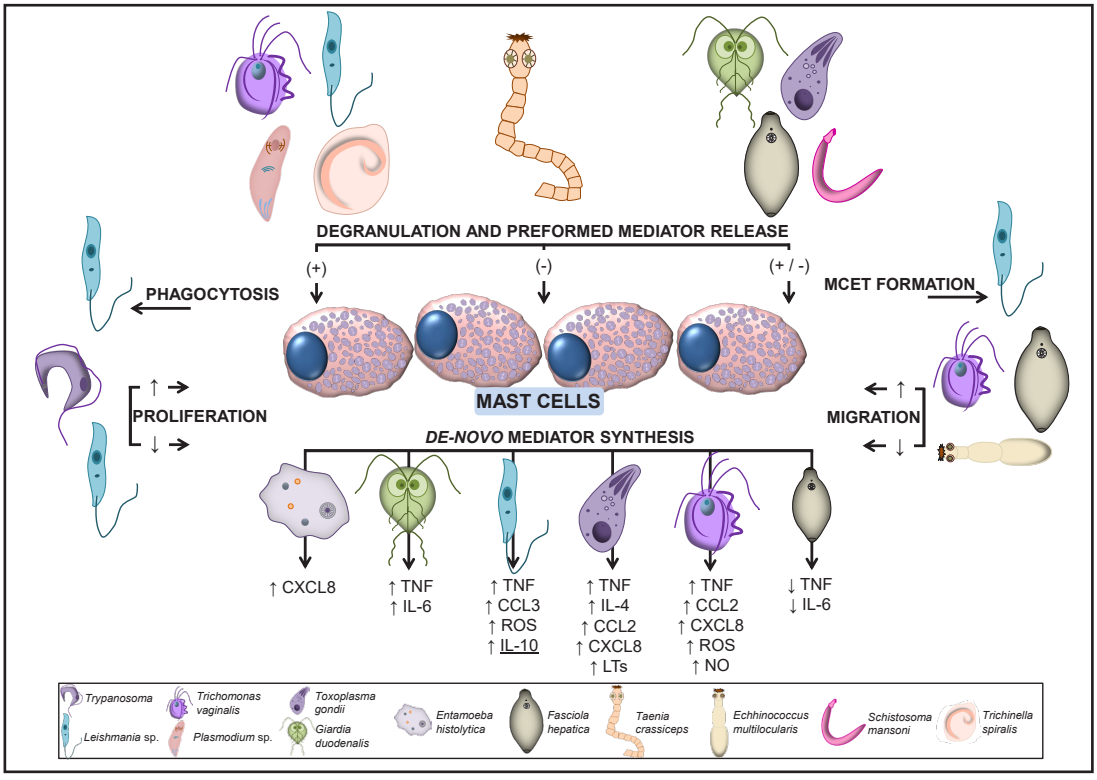

Fig. 2. MC activities in response to different parasite species. CCL, CC chemokine ligand; CXCL, C-X-C motif chemokine ligand; IL, interleukin; LT, leukotriene; NO, nitric oxide; ROS, reactive oxygen species; TNF, tumor necrosis factor.

Table 1. Changes in MC-derived mediators' mRNA/protein expression during parasitic infection. Data from in vivo studies. Note: ↑, increased; ↓, decreased. Abbreviations: CCL2, CC chemokine ligand 2; CXCL1, C-X-C motif chemokine ligand 1; mMCPT-1, mouse mast cell protease-1; MMP-9, matrix metalloproteinase-9; TNF, tumor necrosis factor

Parasite	Model	Material	MC-derived mediators	References
P. berghei ANKA	murine	cervical lymph node, skin	↑ CCL2, CXCL1, MMP-9	94
P. yoelii	murine	plasma	↑ mMCPT-1	97
G. duodenalis	murine	serum	↑ histamine, mMCPT-1	86
L. mexicana	murine	skin	↑ histamine, tryptase, TNF	110
	human	colon	↑ tryptase	107
T. cruzi	murine	stomach, small intestine, colon, heart and skeletal muscle	↑ histamine	105
F. hepatica	murine	peritoneal MCs	↓ TNF	124
Echinococcus sp.	human	liver	↑ tryptase	116
H. diminuta	murine	small intestine	↑ mMCPT-1	125
	murine	bile duct, duodenum	↑ mMCPT-1	126
L. sigmodontis	murine	serum	↑ mMCPT-1	134
T. spiralis	murine	serum, intestine	↑ mMCPT-1	135
		jejunum	↑ mMCPT-1, mMCPT-2	136
S. venezuelensis	murine	serum	↑ mMCPT-1	138
N. brasiliensis	murine	serum	↑ mMCPT-1	133
	rat	intestine, thymic lobes	↑ histamine	132
		mesenteric lymh node	↓/↑ histamine	131
H. polygyrus	murine	serum	↑ mMCPT-1	140

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Author contributions

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Disclosure Statement

The authors have no conflicts of interest to declare.

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