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Modulation of haematopoiesis by protozoal and helminth parasites

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Abstract

During inflammation, haematopoietic stem cells (HSCs) in the bone marrow (BM) and periphery rapidly expand and preferentially differentiate into myeloid cells that mediate innate immune responses. HSCs can be directed into quiescence or differentiation by sensing alterations to the haematopoietic niche, including cytokines, chemokines, and pathogen-derived products. Most studies attempting to identify the mechanisms of haematopoiesis have focused on bacterial and viral infections. From intracellular protozoan infections to large multicellular worms, parasites are a global health burden and represent major immunological challenges that remain poorly defined in the context of haematopoiesis. Immune responses to parasites vary drastically, and parasites have developed sophisticated immunomodulatory mechanisms that allow development of chronic infections. Recent advances in imaging, genomic sequencing, and mouse models have shed new light on how parasites induce unique forms of emergency haematopoiesis. In addition, parasites can modify the haematopoiesis in the BM and periphery to improve their survival in the host. Parasites can also induce long-lasting modifications to HSCs, altering future immune responses to infection, inflammation or transplantation, a term sometimes referred to as central trained immunity. In this review, we highlight the current understanding of parasite-induced haematopoiesis and how parasites target this process to promote chronic infections.

KEYWORDS

haematopoiesis, immune modulation, immunological terms, innate immunity, parasite

1 | INTRODUCTION TO HOMEOSTATIC AND INFECTION-INDUCED HAEMATOPOIESIS

Under homeostatic conditions, there is a constant renewal of red and white blood cells. Hundreds of billions of new cells are produced each day in the bone marrow (BM) of humans.¹ This process, known as haematopoiesis, is essential for steady-state function and maintenance. During inflammation, local cells that recognize pathogen-

associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) become activated and either send signals or traffic to the BM to initiate emergency haematopoiesis. This allows for the rapid and efficient production of new immune cells which traffic to the site of inflammation. Haematopoiesis is essential for the robust induction of immune responses. Because of their short half-life, innate immune cells require constant renewal. For example, monocytes, which patrol the periphery and differentiate into effector macrophages and dendritic cells (DCs), have a steady state half-life of

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TABLE 1 HSC subpopulations and lineage potential.

Cell population	Surface markers	Lineage potential
LT-HSC	Lin ⁻ CD45 ⁺ cKit ⁺ Sca ⁻ 1 ⁺ CD135 ⁻ CD48 ⁻ CD150 ⁺	Oligopotent
ST-HSC	Lin ⁻ CD45 ⁺ cKit ⁺ Sca ⁻ 1 ⁺ CD135 ⁻ CD48 ⁺ CD150 ⁺	Oligopotent
MPP	Lin ⁻ CD45 ⁺ cKit ⁺ Sca ⁻ 1 ⁺ CD135 ⁻ CD48 ⁺ CD150 ⁻	Oligopotent
MPP3	Lin ⁻ CD45 ⁺ cKit ⁺ Sca ⁻ 1 ⁺ CD135 ⁻ CD48 ⁺ CD150 ⁻ CD34 ⁺ CD135 ⁻	Oligopotent, myeloid bias
MPP4	Lin ⁻ CD45 ⁺ cKit ⁺ Sca ⁻ 1 ⁺ CD135 ⁻ CD48 ⁺ CD150 ⁻ CD34 ⁺ CD135 ⁺	Oligopotent, lymphoid bias

Note: Lineage negative (Lin⁻): CD11b⁻ CD3⁻ CD19⁻ Ly6G⁻ Siglec-F⁻ Ter119⁻.

Abbreviations: HSCs, haematopoietic stem cells; LT, long-term; MPP, multipotent progenitor; ST, short-term.

approximately 2 days.² Homeostatic and emergency haematopoiesis are dependent on numerous factors, including cell-cell interactions in the haematopoietic niche, cytokines, metabolic changes, and BM-invading pathogens.^{3,4}

Haematopoiesis primarily occurs in the BM, where haematopoietic stem cells (HSCs) differentiate from oligo- and multi-potent progenitor cells into mature effector cells. Notably, this process has also been shown to occur in other organs, including the spleen, gastrointestinal tract, liver and the brain. Haematopoiesis in the BM occurs in a highly specialized compartment. The haematopoietic niche is tightly controlled by a collection of immune cells, stromal cells, mesenchymal stem cells, neuronal synapses, and a small number of blood vessels. This niche provides a buffer for the HSCs from the environment, inhibiting the induction of aberrant haematopoiesis during steady state, while promoting controlled emergency haematopoiesis in response to inflammation.⁵

Differentiation of HSCs follows a loose hierarchical structure, with long-lived oligopotent HSCs becoming multipotent progenitors, followed by lineage-committed progenitor cells, and finally mature immune cells. In mammals, the long-term HSC (LT-HSC) resides at the top of this haematopoiesis hierarchy (Table 1). LT-HSC are primarily quiescent, long-lived cells defined by their ability to self-renew and differentiate into every cell of the haematopoietic cell system.⁶⁻⁹ To respond to the haematopoietic needs of the body, LT-HSCs express multiple receptors, including receptors for interleukin (IL)-1, IL-6, tumour necrosis factor (TNF), interferons (IFNs), and colony-stimulating factors (CSFs).^{9,10} Upon activation, LT-HSCs differentiate into short-term (ST)-HSCs and multipotent progenitors (MPPs). During steady state and emergency haematopoiesis, MPPs are responsible for the majority of haematopoiesis.^{9,11} However, both LT- and ST-HSCs have been shown to promote haematopoiesis in homeostatic conditions, highlighting the complexity of this process.¹²⁻¹⁴

Although initially described as a homogenous collection of multipotent cells, single-cell transcriptomic, and epigenomic sequencing

has revealed that MPPs are a heterogeneous population of four small subtypes (MPP1-4).^{15,16} Each of these MPP subtypes can differentiate into every haematopoietic cell, however, each MPP subset has a defined transcriptional bias towards a preferred lineage. For example, MPP4, also known as lymphoid MPPs, display a higher probability of differentiating into lymphoid lineage cells, whereas MPP2 and MPP3 are significantly more likely to develop into myeloid cells.¹¹ This transcriptional bias is shown in the expression of various lineage-specific gene transcripts, however, there is significant overlap in expression between subtypes. After activation with various inflammatory factors, MPPs further differentiate into the lineage-committed progenitors, the common myeloid progenitor (CMP), and the common lymphoid progenitor (CLP). In turn, these lineage-committed progenitors differentiate into increasingly cell-specific precursors, before finally developing into mature immune cells.

Despite their sequestration in the BM niche, HSCs and progenitor cells express receptors for cytokines, growth factors, neurotransmitters, and chemokines. Interestingly, these oligopotent progenitors also express pattern recognition receptors (PRRs) and can respond to PAMPs, such as lipopolysaccharide (LPS) binding to toll-like receptor (TLR) 4.¹⁷ TLR agonists have been shown to directly activate HSCs and induce their proliferation and differentiation *in vitro* and *in vivo*. Zhang et al. demonstrated that a single intraperitoneal injection of mice with flagellin, a TLR5 and NLR4 agonist, induced proliferation of HSCs.¹⁸ HSCs from flagellin-injected mice showed improved engraftment when transferred to irradiated mice, with a preference for myelopoiesis.

During infection, these signals coalesce to induce adaptive responses in the BM niche that direct appropriate differentiation of mature immune cells. For example, infection with the bacterial pathogen *Listeria monocytogenes* induces signals in the HSC niche that induce the proliferation and expansion of monocytes.¹⁹ In addition, recent research into emergency haematopoiesis has found that IFNs play a key role in activating and modulating HSCs in the control of bacterial infections. For example, in mice infected with *Mycobacterium avium*, HSCs respond to IFN- γ signalling to proliferate and increase myelopoiesis.²⁰ In contrast, type I IFNs have a negative influence on myelopoiesis, whereas type II IFNs provide protection in mice infected with *Mycobacterium tuberculosis*. IFN can include long-lasting modifications to HSCs, with altered phenotypes persisting for up to 1-year.²¹

Parasites infect hundreds of millions of people and are a major health burden across the world. Parasites represent a diverse group, ranging from unicellular protozoan parasites, such as the *Plasmodium* species responsible for malaria, to multi-cellular parasitic worms, also known as helminths, such as *Fasciola hepatica* or liver fluke. In general, infection with intracellular parasites induces type 1 immune responses, whereas helminths induce type 2 immune responses. However, parasites, especially helminths also actively modulate these immune responses. The induction and modulation of peripheral immune responses by parasites have been extensively studied and reviewed in the context of both protozoan and helminth parasites.²²⁻²⁶ Parasite infections are typically chronic and can alter

the host in a myriad of ways. During acute infections with bacterial and viral agents, HSCs respond via transient activation and differentiation, followed by a return to quiescence. However, chronic infections with parasites, and the corresponding long-lasting cytokine stimulation can lead to HSC exhaustion and dysfunction. Haematopoiesis in response to acute and chronic bacterial, viral, and fungal infections has been well characterized and documented.²⁷⁻²⁹ There is more limited knowledge on the influence of parasitic infections on haematopoiesis. In this review, we highlight the emerging evidence of a role for haematopoiesis in expanding anti-parasite immune responses, and how parasites have evolved to promote dysfunctional haematopoiesis to promote their survival in the host.

2 | PROTOZOAN PARASITE INFECTION AND HAEMATOPOIESIS

Protozoa are a large family of unicellular organisms, which includes *Plasmodium*, *Leishmania*, *Toxoplasma*, and *Trypanosoma* species. Protozoan infections are typically spread through the faecal-oral route or by arthropod vectors, such as sand flies or mosquitos. There are different treatment approaches for different species, however, persistent, or recurrent infections are common. A robust immune response is essential for survival after infection with a protozoan parasite, which is often lethal in the immunocompromised individuals. Early responding immune cells, in particular neutrophils, monocytes, and macrophages, migrate to the site of infection and mediate characteristic type 1 immune responses. This includes classical activation of macrophages, and production of pro-inflammatory mediators, such as IFN- γ , IL-1 β , IL-12, and nitric oxide.^{23,30} To maintain effective immune responses, innate immune cells, both tissue-resident and infiltrating, require constant renewal from HSCs. This can occur centrally in the BM, or in the periphery at the site of inflammation, otherwise known as in situ haematopoiesis. For example, Osorio et al. show that *Leishmania* infection enhances local proliferation of infiltrating monocytes in the spleens of infected hamsters.³¹ However, much like viral and bacterial pathogens, protozoan species have adapted to manipulate this emergency haematopoiesis to benefit their own survival. Locally proliferating monocytes, which contribute to the characteristic splenomegaly of leishmaniasis, were found to be preferred targets for infiltrating parasites. Targeting the in situ haematopoiesis with STAT3 inhibitors decreased monocyte proliferation and parasite burden.³¹

2.1 | *Leishmania*

In contrast to large parasitic worms, single-celled parasites are uniquely capable of directly altering haematopoiesis in the BM. Indeed, many protozoan parasites, including *Leishmania* species can invade the BM or act on peripheral HSCs. *Leishmania* parasites are spread via sandflies and are found throughout the world, the two dominant species being *Leishmania donovani* and *L. chagasi*.³² Once inside the mammalian hosts, the *Leishmania* parasites primarily reside

in monocyte-derived macrophages and DCs in the liver and spleen. However, it has also been widely reported that *Leishmania* can be found in the BM of infected individuals.³² Indeed, a study of Brazilian patients suffering from visceral leishmaniasis, found that an increased number of amastigotes in the BM correlated with increased parasite load in the periphery.³³ Furthermore, patients who died from the infection had high parasite burdens in the BM. *Leishmania* activate the HSC compartment in the BM to promote the expansion of select immune cells. For example, infection of mice with *L. donovani* induces IFN- γ -secreting CD4⁺ T cells in the BM, which direct development and activation of monocytes.³⁴

BM-resident macrophages can act as a reservoir of *Leishmania* parasites. During infection with *L. donovani* BM-resident macrophages are susceptible to infection and promote the expansion of HSC and myelopoiesis through secretion of granulocyte-macrophage CSF (GM-CSF) and TNF.^{35,36} *L. donovani* has also been shown to specifically direct HSCs to differentiate into monocytes that are more permissible to infection.³⁷ Monocytes found in the BM of infected mice had a regulatory phenotype and a reduced capacity to differentiate into macrophages capable of initiating pro-inflammatory anti-leishmania responses. Moreover, this was mediated by cytokines, such as IL-1 β and IFN- γ , and various growth factors in the BM. In support of these findings, it was demonstrated that BM extracellular fluid from infected mice directly expanded HSCs and generated suppressive monocytes seen during experimental infections.³⁷ In a separate study, HSCs from *L. donovani*-infected mice were found to have defective self-renewal and engraftment abilities. This coincided with increased proliferation of LT-HSCs, mediated by TNF-induced expansion and maintenance of IFN- γ -secreting BM-resident CD4⁺ T cells.³⁸ Mice lacking T and B cells showed no changes to their HSC populations following infection with *L. donovani*, despite displaying an increase in parasite burden. Modulation of HSCs appears to occur across multiple *Leishmania* species, as experimental cutaneous infection of mice with *L. major* induces the expansion of LT-HSC in BM, and myeloid-biased MPP2/3 in the BM and spleen.³⁹

Despite the evidence that mature immune cells and stromal cells are the predominant hosts for *Leishmania* in the BM, it has recently been reported that HSC harboured the parasites in Syrian hamsters infected with *L. donovani*.^{36,40,41} Using bioluminescent live imaging, *Leishmania* were found in the BM during infection, as well as post-treatment with anti-leishmanial drugs. After treatment, *Leishmania* in the BM were found to repopulate the spleen and liver, therefore identifying the BM as an essential niche for parasite persistence. Crucially, while *Leishmania* have previously been shown to reside in BM-resident mature immune cells, this study demonstrated that long-lived LT-HSC also provides a key sanctuary for the parasite during leishmania infection.

2.2 | *Plasmodium*

In humans, malaria is primarily caused by *Plasmodium falciparum* and *P. vivax*.⁴² Like *Leishmania*, *Plasmodium* species have been shown to

reside in the BM.^{43–45} Interestingly, a recent study of patients found that total parasite biomass in the BM, rather than in the blood, correlated strongly with poor prognosis.⁴⁶ Histological and genetic screening of samples collected from children who died from *P. falciparum* in Malawi found that the BM contained a large reservoir of parasites.⁴⁷ Further histological analyses revealed that the parasites were located primarily extravascularly, with many residing in BM macrophages, and some found directly adjacent to erythroid progenitors.

A number of studies have attempted to decipher the mechanisms of *Plasmodium*-induced alterations to haematopoiesis. Belyaev et al. found that mice infected with *P. chabaudi* had increased numbers of IL-7 receptor-expressing lymphoid-biased MPPs in the BM by day 11 post-infection, and this was dependent on IFN- γ signalling in haematopoietic progenitors.⁴⁸ Upon isolation and culture *ex vivo*, these malaria-induced lymphoid-biased MPPs lacked erythroid potential and preferentially differentiated into lymphoid and myeloid cells. Similarly, *P. berghei* infection of mice expands the oligopotent HSC populations in the BM via a mechanism that involved IFN- γ and IL-27.⁴⁹ These cytokines aided in expanding HSCs in the BM, followed by HSC mobilization to the spleen and induction of rapid myelopoiesis to resolve the infection.

As *Plasmodium* is found beyond the BM, extramedullary, or non-BM, haematopoiesis is essential to fight the infection. Like *P. berghei*, mice infected with *P. yoelii* display a rapid and sustained increase of progenitor populations in the spleen.^{50,51} Interestingly, these progenitor cells were essential for establishing splenic immune responses to the parasite through secretion of IL-17 and activation of local stromal cell populations. The activated stromal cells promoted B-cell differentiation *in vitro* when co-cultured with the expanded splenic progenitors. Further studies have demonstrated the importance of extramedullary haematopoiesis in plasmodium infections. During infection with *P. chabaudi*, mice have fewer myeloid-committed progenitors, CMP and GMP, in the BM, while the number of these progenitors increase in the spleen.⁵² This was dependent on IFN- γ -induced increases in serum CXCL10 and CCL2, which caused mobilization of the CCR2⁺ CMP and GMP to the spleen.

2.3 | Toxoplasma

Toxoplasma gondii is a protozoan parasite that infects millions of people around the world. Toxoplasmosis induces a strong type 1 response, which is essential for pathogen elimination and host survival. Indeed, mice lacking IFN- γ or IL-12 are highly susceptible to *Toxoplasma* infections.^{23,30,53} However, unlike *Leishmania* and *Plasmodium* infections, many people are undiagnosed and live asymptotically with the *Toxoplasma* parasite. In a study of patients with chronic *T. gondii*, peripheral blood monocytes had significantly altered surface expression of various markers, including immunoglobulin receptors and MHC molecules.⁵⁴ Furthermore, IL-12 mRNA expression was enhanced in monocytes from patients following *ex vivo* stimulation with *Toxoplasma*. Since monocytes have a short lifespan, these alterations could potentially be due to infection-associated modifications

to the HSC population. *Toxoplasma* can invade haematopoietic and non-haematopoietic cells in the BM. However, due to its global range, and often asymptomatic disease, toxoplasma can go undiagnosed and present potentially fatal risks for patients, in particular those receiving BM transplants.^{55–59} Lopes et al., have shown that infection of BM donor mice with two different strains of *T. gondii* resulted in decreased survival of recipient mice.⁶⁰ *T. gondii* drastically alters erythropoiesis and skews HSCs towards granulopoiesis which expands effector immune cells that fight infection.^{23,30} This was recently found to be mediated by the induction of systemic IL-6 signalling, leading to a reduction in erythrocyte progenitors and a subsequent increase in the GMP population in the BM of infected mice.⁶¹ Importantly, this shift away from erythropoiesis was found to be exclusive to the BM; splenic erythropoiesis was unaffected, highlighting the role of extramedullary haematopoiesis in response to infection.

2.4 | Trypanosoma

Trypanosoma species are found throughout the world, although the two most common species *Trypanosoma cruzi* and *T. brucei*, the causative agents of Chagas disease and African sleeping sickness, respectively, are found in South America and Africa. Similar to other single-cell parasites, trypanosomes can infiltrate the BM. Indeed, stromal cells infected with the parasite are found 2 weeks post-challenge in mice infected with *T. cruzi*.⁶² Parasite infiltration of the BM coincided with an increase in HSC populations, including MPP3/4 and CMPs, with an accompanying decrease in lymphoid-biased MPPs and CLP. Interestingly, the authors also found a concomitant increase in HSCs in the spleens of infected mice, highlighting again the importance of extramedullary haematopoiesis in counteracting impairments in the BM.

Infection of mice with experimental and field isolates of Trypanosome strains, *T. brucei* and *T. congolense*, can rapidly deplete B cells in the BM and spleen.^{63–65} Infection of mice with *T. cruzi* has been shown to infect BM stromal cells, leading to a reduction in IL-7, an essential cytokine for the differentiation of B cells from progenitor cells.⁶⁶ Indeed, reduction in mature B cells has been shown to coincide with severe depletion of up to 95% of CLP, pre- and pro-B cell precursors, and immature B cells in the BM of mice infected with *T. brucei*.⁶³ This depletion coincided with an increase in compensatory B-cell lymphopoiesis in spleens, as indicated by increased numbers of B-cell precursors and HSCs. In addition to impaired B-cell lymphopoiesis, whole BM from *T. cruzi*-infected mice have a significantly reduced ability to differentiate across many lineages, including myeloid and erythroid, an effect that was transferrable to naïve mice via BM transplantation.⁶⁷ However, this is effectively prevented by treatment with anti-trypanosome therapeutics. Furthermore, a recent study demonstrated that treatment with commercially available anti-trypanosome drugs increased the total number of B-cell precursors in the BM of *T. congolense*-infected mice.⁶³

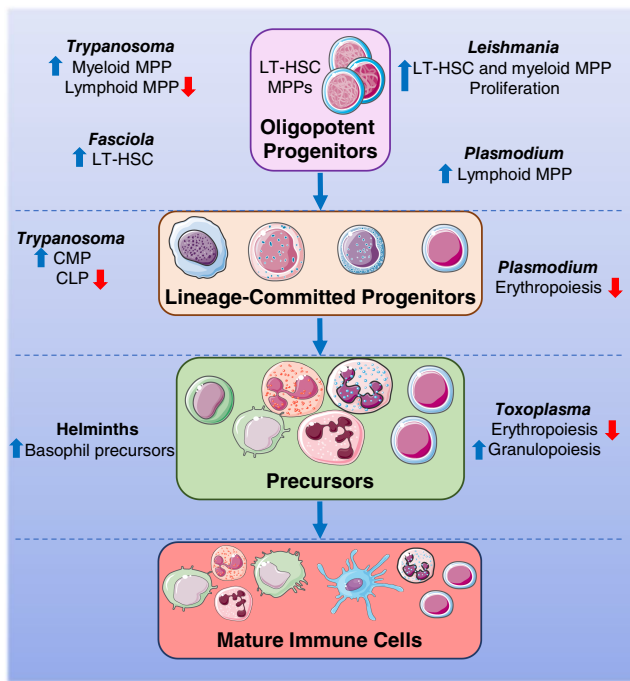


FIGURE 1 Parasites target HSCs throughout haematopoiesis. Simplified hierarchical view of haematopoiesis, beginning with oligopotent progenitors (LT-HSC, MPP), followed by lineage-committed progenitors (CMP, CLP, MEP), then direct precursors (e.g., basophil precursor, MDP, cMoP), and finally mature immune cells. Many parasites modulate this pathway directly and indirectly to improve their survival in the host. This includes, increasing proliferation, enhanced differentiation, or inhibition of development of specific lineages. CLP, common lymphoid progenitor; cMoP, common monocyte precursor; CMP, common myeloid progenitor; HSCs, haematopoietic stem cells; LT-HSC, long-term HSC; MDP, macrophage/dendritic cell precursor; MEP, megakaryocyte/erythrocyte progenitor; MPP, multipotent progenitor.

Long-lasting disruption to B-cell lymphopoiesis induced by *Trypanosoma* species has serious implications for the generation of immune responses to subsequent infections and vaccinations. A recent study demonstrated that infection with *T. brucei* after immunization with an acellular pertussis vaccine abolished the protective effects of the vaccine against *Bordetella pertussis* infection.⁶⁸ The *T. brucei* infection post-vaccination was cleared with an anti-parasite drug and mice were intranasally challenged with *B. pertussis* 8 weeks. Mice that had been infected with *T. brucei* prior to *B. pertussis* challenge were unable to mount competent B-cell responses to the bacteria and subsequently were unable to clear the infection from the lung. Conversely, a study that assess the efficacy of *T. brucei*-induced killing of B cells in a mouse model of multiple myeloma showed that infected mice survived significantly longer than un-infected mice, in part due to the potent suppression of B-cell lymphopoiesis.⁶⁹ Collectively, these reports demonstrate that protozoan parasites can invade the BM and modulate haematopoiesis, which impacts the host immune responses to other diseases (Figure 1).

3 | PARASITIC WORMS AND HAEMATOPOIESIS

Parasitic worms or helminths, have evolved mechanisms of suppressing host immune responses to prevent their ejection and thereby maintain long-term infections. The host immune response has also co-evolved with parasite to limit infection-associated pathology. Infection with helminths induces a robust type 2 response, characterized by prominent Th2 cells, eosinophils, alternatively activated macrophages, mast cells, basophils, and innate lymphoid type 2 cells (ILC2s).²⁵ Helminths have developed sophisticated methods of immune modulation to promote chronic infection, including induction of regulatory and anti-inflammatory immune responses.^{25,70,71} The size and life cycles of helminths, which often include migration through the body and damage to the host, can result in significant immune activation. This mechanical stress, as well as to excreted/secreted factors (ES) produced by the parasites induce release of type 2 alarmins, including IL-25, IL-33, and TSLP. These cytokines activate local immune cell populations, induce differentiation of HSCs in the BM, and promote in situ haematopoiesis, for example during infection with the blood fluke *Schistosoma mansoni*.^{72,73}

Although not yet fully understood, modifications to BM HSC have been demonstrated during helminth infections. Transplantation of BM from mice susceptible to helminth infection into normally resistant recipient mouse strains can transfer susceptibility to infection.⁷⁴ The transfer of susceptibility was specific to the migratory, rather than the tissue, stage of infection with *Nippostrongylus brasiliensis*, suggesting a role for emergency haematopoiesis and production of new circulating immune cells. Babayan et al. found that infection of mice with the filarial nematode *Litomosomoides sigmodontis* enhanced multipotent progenitor populations in the BM of aged compared with young mice and this correlated with an increase in worm burden.⁷⁵ Furthermore, stimulation of HSCs with the filarial nematode product ES-62 promoted the differentiation of tolerogenic DCs which were hyporesponsive to LPS stimulation and promoted induction of Th2 cells.⁷⁶

Infection with the helminths *Heligmosomoides polygyrus* and *N. brasiliensis*, used extensively as mouse models of helminth infection, is associated with expansion of basophils in the BM and spleen. *H. polygyrus* infection induced the expansion of basophil precursors in the BM through the combined effect of IL-3, IL-4, and immunoglobulins.⁷⁷ IL-33, released upon mechanical stress, has been shown to indirectly promote the expansion and differentiation of basophils through induction of IL-3 and GM-CSF.⁷⁸ During infection with *Trichuris muris*, a mouse model of the human roundworm *Trichuris trichiura*, TSLP acts directly on precursors in the BM to induce basophil expansion.⁷⁹ TSLP can directly induce extramedullary haematopoiesis, expanding splenic GMP-like cells capable of differentiating into macrophages, dendritic cells, and granulocytes.⁸⁰ Transfer of the TSLP-induced GMP-like cells into TSLP receptor deficient mice infected with *T. muris* resulted in improved goblet cell hyperplasia, enhanced type 2 cytokine production and a significantly lower parasite burden. Infections with *T. muris* or *N. brasiliensis* induce IL-25-dependent increases in a type 2 MPP in the gastrointestinal tract-associated lymphoid tissues.⁸¹ Interestingly,

the increased type 2 MPPs generated by the helminth infections were not found in the spleen or BM. Furthermore, lineage mapping studies showed that these cells were able to differentiate into mast cells, basophils, and macrophages in response to type 2 cytokines. Subsequent studies showed that IL-33 and IL-25 were responsible for enhancing ILC2s and the type 2 MPPs in the mesenteric lymph nodes, lungs, and blood.⁸² Moreover, when adoptively transferred into mice lacking the IL-25 receptor, type 2 MPPs differentiated and induced IgE and goblet cell hyperplasia to promote clearance of *T. muris* infection. Although typically expelled quickly via type 2 inflammation in acute infection, chronic infection with *T. muris*, initiated by low-dose infection, induces expansion and proliferation of oligopotent HSCs and neutrophils in the BM.⁸³ Interestingly, no changes occur to the HSC compartment during acute infections, which are cleared rapidly. Instead, chronic *T. muris* induces an ineffective type 1 response and expansion of IFN- γ -secreting CD4⁺ and CD8⁺ T cells in the BM, resulting in proliferation of LT-HSC and MPP, culminating in neutrophil expansion and worm persistence.

Infection of mice with the nematode parasite *Trichinella spiralis*, the parasite responsible for trichinosis, is characterized by rapid expansion of mast cells and basophils from the BM, which migrate to tertiary lymphoid organs, such as the spleen and mesenteric lymph nodes, and to the site of infection.^{84,85} During early infection with *T. spiralis*, the lineage-committed progenitors CLP and GMP are significantly expanded, while oligopotent LT-HSCs and MPPs are unchanged.⁸⁶ The study utilized intravital microscopy to show that *T. spiralis* infection induced a dramatic mobilization, as well as expansion, of HSC. HSCs in infected mice remain largely in their niche, with approximately 12% undergoing some form of movement, however, *T. spiralis* infection promoted expansion and migration of nearly 60% of HSC from the BM. Furthermore, transplantation of mixed chimera BM from uninfected and infected mice showed that BM from *T. spiralis*-infected mice had short- and long-term advantages in repopulating irradiated recipient mice. The study of *T. spiralis* infection has also led to the discovery of a common erythrocyte-mast cell progenitor population in the HSC compartment.^{87,88} Using single-cell RNA sequencing, Inclan-Rico and colleagues found that erythrocyte and mast cells progenitors exist at steady state in the BM, spleen, and lymph nodes. However, during *T. spiralis* infection, these HSCs are activated and mobilized to leave the BM and expand in the spleen and mesenteric lymph nodes where they differentiate and replenish mast cells at the site of infection.

In addition to haematopoiesis in the BM, stem cells in the intestine can, under the influence of IL-4 and IL-13, expand and differentiate into the secretory tuft and goblet cells required for worm clearance from the gut.⁸⁹⁻⁹¹ Mice lacking transcription factors involved in tuft cell differentiation from resident intestinal stem cells were unable to clear infection with *N. brasiliensis*.⁹⁰ Indeed, during *N. brasiliensis* infection, newly differentiated tuft cells secrete IL-25, which in turn activates local ILC2s, which initiates a feed-forward loop to promote proliferation and expansion of tuft cells and protective type 2 immune responses.^{89,90,92} This pathway has been targeted by helminths to enable them to evade expulsion. *H. polygyrus* infection

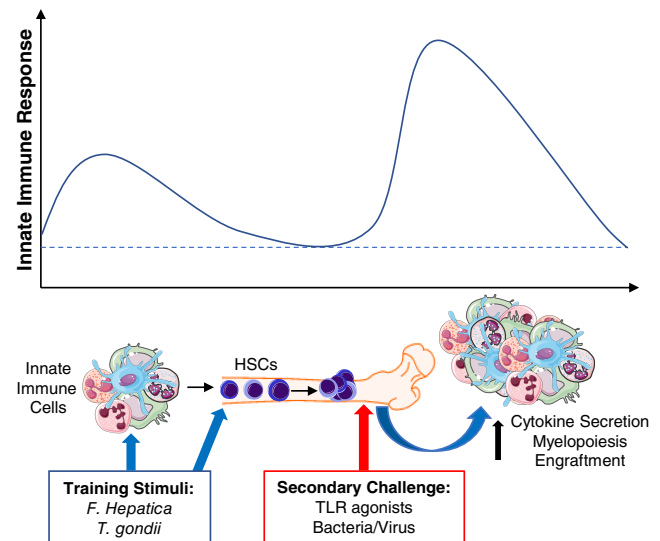


FIGURE 2 Central trained innate immunity and parasitic infections. Infection with parasite or administration of parasite-derived, such as *Fasciola hepatica* ES or *Toxoplasma gondii*, act on peripheral innate immune cells and haematopoietic stem cells (HSCs) to imprint epigenetic modifications that produce trained innate immune cells that respond to secondary stimuli with enhanced responses. Protozoan- and helminth-induced changes to HSCs result in bias towards myelopoiesis and improved engraftment during transplantation. Epigenetic and metabolic reprogramming induces long-term enhanced effector responses in future generations of innate immune cells, that can modulate development of autoimmunity.

induces activation and proliferation of intestinal stem cells, however, they have significantly impaired ability to differentiate into tuft cells.^{93,94} Ex vivo stimulation of intestinal organoids (three-dimensional structures that mimic the murine intestine) with ES from *H. polygyrus* (HES) induces proliferation and expansion of stem cells, creating spheroid-like structures.⁹³ Interestingly, stimulation with HES, or co-culture of with larvae, inhibited IL-4 and IL-13 induced differentiation of stem cells into tuft cells. Furthermore, co-infection with *H. polygyrus* and *N. brasiliensis* significantly reduced *N. brasiliensis*-induced expansion of tuft cells in the gut epithelium. Collectively these studies demonstrate that helminths can modulate haematopoiesis in the BM but also differentiation of stem cells in the intestine (Figure 1).

4 | CENTRAL TRAINED INNATE IMMUNITY DURING PARASITE INFECTION

Although initially thought to be exclusive to T and B cells, cells of the innate immune system can undergo training and display features of immunological memory. When primed with certain stimuli, innate immune cells undergo metabolic and epigenetic remodelling before returning to an inactive state. Upon reactivation with PAMPs or cytokines, these primed innate immune cells respond with enhanced

effector capabilities.⁹⁵⁻⁹⁷ This process, termed trained innate immunity, has been demonstrated in NK cells, monocytes, macrophages, and dendritic cells.⁹⁶ Trained innate immunity has primarily been studied with respect to patrolling and tissue-resident mature innate immune cells. However, innate immune cells are largely short-lived, while many studies have reported effects lasting many months, indicating mechanisms of long-lasting modification to pools of innate immune cells or their progenitors. In recent years, certain pathogens, vaccines, and PAMPs have been reported to induce long-term alterations to HSCs. This has been termed central trained immunity, where activation by certain stimuli, such as β -glucan or *Mycobacterium tuberculosis*, induces metabolic and epigenetic rewiring of HSCs.^{98,99} This rewiring, or training, is a type of non-specific memory to inflammatory stimuli, allowing HSCs to respond faster and more acutely to secondary challenge.¹⁰⁰ HSCs, including LT-HSCs and MPPs, have been identified as targets of central trained immunity. For example, vaccination with BCG expands and modifies MPP, imprinting a bias towards myelopoiesis.⁹⁹ Furthermore, macrophages expanded from these MPP have enhanced bacterial killing capacities and increase mRNA expression of pro-inflammatory cytokines. Research on central trained immunity has largely focused on the modulatory effects of bacterial and fungal products, including LPS, β -glucan or flagellin, or on pro-inflammatory cytokines, such as IL-1 β and IFN- γ .^{18,21,99,101-104} However, recent studies have demonstrated that central trained immunity can also be mediated by parasites (Figure 2).

Central trained immunity has been described following infection with the protozoal parasite *T. gondii*. Mice infected with *T. gondii* exhibit rapid expansion of monocytes along with increased pro-inflammatory cytokine production.¹⁰⁵ Askenase et al., found that during infection with *T. gondii*, IL-12-activates BM-resident NK cells to produce IFN- γ , which primes the common monocyte precursor (cMoP) and immature monocytes.¹⁰⁵ These primed monocytes developed a regulatory phenotype following stimulation with various PAMPs, such as LPS and flagellin. Importantly, analysis of *T. gondii*-primed monocyte gene expression via Nanostring revealed increased expression of both anti- and pro-inflammatory genes after LPS stimulation, indicating a non-specific augmentation of innate immune responses rather than selective enhancement of anti-inflammatory response.

We have demonstrated that treatment of mice with ES from the helminth *F. hepatica* (FHES) imprints a long-lasting memory on HSCs.¹⁰⁶ Mice treated with FHES had enhanced proliferation and expansion of LT-HSCs and myeloid-committed precursors, resulting in expansion of anti-inflammatory monocytes. This helminth-induced anti-inflammatory trained innate immunity rendered the mice less susceptible to induction of experimental autoimmune encephalomyelitis, a mouse model of multiple sclerosis. The protection against development of Th1- and Th17-driven autoimmune disease persisted for up to 18 months after treatment with the helminth products and could be transferred to naïve mice via transplantation of LT-HSCs isolated from FHES-treated mice.

5 | CONCLUSIONS

Immune responses to parasitic infections involve a plethora of immune and non-immune cells, which activate and induce local and systemic modifications to aid in parasite expulsion. Most of the work to date has been done on mature immune cells. However, there is emerging evidence of roles for HSCs in combatting infections. HSCs play a fundamental role in shaping, as well as generating, the cells that mediate innate and adaptive immune responses that are mobilized to act at the site of infection. The HSC provide memory or trained cells of the innate, as well as adaptive, immune system also help to fight future infections and inflammation. Understanding how HSCs are activated and differentiated may aid in the discovery of novel therapeutics for various parasitic infections, but may also help to identify new targets for long-lasting disease-modifying treatments for autoimmune and other inflammatory diseases.

AUTHOR CONTRIBUTIONS

Kyle T. Cunningham and Kingston H. G. Mills wrote the review.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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