Resistance to parasites

Macrophage regulation & function in helminth infection

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Highlights:

- Alternatively activated macrophages (AAM) mediate host defense and tissue repair during helminth infection
- Metabolic reprogramming enables AAM activation and effector functions
- Macrophages produce a diverse set of effector molecules driving host defense, tissue repair and immune regulation during helminth infection
- Helminth molecules are powerful regulators of macrophage effector functions

Abstract

Macrophages are innate immune cells with essential roles in host defense, inflammation, immune regulation and repair. During infection with multicellular helminth parasites, macrophages contribute to pathogen trapping and killing as well as to tissue repair and the resolution of type 2 inflammation. Macrophages produce a broad repertoire of effector molecules, including enzymes, cytokines, chemokines and growth factors that govern anti-helminth immunity and repair of parasite-induced tissue damage. Helminth infection and the associated type 2 immune response induces an alternatively activated macrophage (AAM)

phenotype that – beyond driving host defense - prevents aberrant Th2 cell activation and type 2 immunopathology. The immune regulatory potential of macrophages is exploited by helminth parasites that induce the production of anti-inflammatory mediators such as interleukin 10 or prostaglandin E_2 to evade host immunity. Here, we summarize current insights into the mechanisms of macrophage-mediated host defense and repair during helminth infection and highlight recent progress on the immune regulatory crosstalk between macrophages and helminth parasites. We also point out important remaining questions such as the translation of findings from murine models to human settings of helminth infection as well as long-term consequences of helminth-induced macrophage reprogramming for subsequent host immunity.

Keywords: alternatively activated macrophages, helminth infection, immune regulation, immunometabolism, inflammation, tissue repair, type 2 immunity,

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1. Introduction

Macrophages are plastic and versatile cells of the innate immune system that play essential roles in homeostasis, host defense, tissue repair and the resolution of inflammation [1]. Helminths are large extracellular pathogens that - in contrast to bacterial or protozoan pathogens - cannot be eliminated by phagocytosis. However, based on their exceptional plasticity, macrophages have evolved multiple strategies to efficiently combat helminth parasites and to limit parasite-induced tissue damage (Figure 1). Macrophage-mediated host

defense against helminth parasites largely relies on the activation of an alternatively activated macrophage (AAM) phenotype, which can trap and/ or kill helminth larvae or stimulate the expulsion of adult parasites [2–7]. While AAM-mediated helminth trapping prevents extensive injury of infected tissues [2,8], AAM also actively contribute to tissue repair by producing growth factors, chemokines and building blocks for collagen synthesis [9–12]. In addition, key AAM effector molecules, such as Arginase-1 (Arg1) or Resistin-like protein alpha (RELMα) regulate the activation of Th2 cells and thus limit type 2 immunopathology during helminth infection [13–15].

Besides triggering type 2 immune responses and AAM activation, helminth parasites exhibit potent immune regulatory capacities, which are based on the production of a multitude of immunomodulatory molecules that can regulate type 2 immunity (Figure 2) [16–19]. The induction of regulatory macrophages producing anti-inflammatory mediators such as IL-10 or PGE_2 by helminth proteins is of potential therapeutic relevance as it contributes to the suppression of pathologic type 2 immune responses, e.g. in allergic asthma [16,20].

In addition, macrophage effector functions are regulated by host factors from the tissue microenvironment, that e.g. promote tissue repair following helminth infection [9]. Thus, macrophages are central players in helminth infection and their effector functions need to be tightly regulated to prevent pathological type 2 responses that may e.g. trigger fibrosis or increased susceptibility to infections or cancer. However, the mechanisms underlying macrophage-mediated host defense, tissue repair and immune regulation during helminth infection have only partially been defined. In particular, long-term effects of helminth infection on macrophage activation and effector functions are in need of further investigation. This is particularly relevant in human settings of helminth infection, in which macrophage functions are poorly understood, partially as a result of distinct AAM activation programs in humans and mice [21].

In this review, we summarize the current state of knowledge on macrophage-mediated host defense against helminth parasites with particular emphasis on the mechanisms that induce

and regulate macrophage activation in type 2 immunity. We highlight gaps in our current understanding of macrophage functions in helminth infection and propose avenues for future investigations that will hopefully foster our mechanistic understanding of macrophage-helminth crosstalk and its translation into therapeutic approaches.

2. Macrophage functions in resistance to parasites

Data from various experimental infection models, including *Schistosoma mansoni* [22], *Nippostrongylus brasiliensis* [8,23], *Heligmosomoides polygyrus* [2,24] and *Litomosoides sigmodontis* [25], has highlighted the importance of macrophages in anti-helminth immunity and tissue repair following helminth infection. Specific parameters of the infection, including the species of helminth and host as well as repeated or chronic infections need to be considered when deciphering the unique and versatile roles of macrophages in helminth infection.

2.1 Macrophage mediated host defense against helminth parasites

2.1.1 Induction of anti-helminth effector functions in macrophages

IL-4-/ IL-13-induced macrophage effector functions in helminth infection

Multiple studies have shown crucial roles for host-derived IL-4 and IL-13 in AAM-mediated anti-helminth immunity [3,5,9,24,26]. During infection with helminths that trigger a rapid innate type 2 immune response, e.g. the rat parasite *N. brasiliensis (Nb),* type 2 activated granulocytes [3,4] and innate lymphoid cells (ILC2s) [5] can drive early AAM activation, thus enabling rapid parasite control. In addition, during re-infection with *Nb*, macrophages from previously infected mice could trap larvae more efficiently as compared to macrophages from naïve mice [3]. This was linked to IL-13 production by neutrophils, which triggered the IL-4Rα-dependent induction of a long-lived AAM phenotype [3]. Thus, in addition to priming

macrophages for the direct trapping or damage of helminth larvae, the induction of a long-lived AAM phenotype may provide protection against reinfection independently of memory T cells and B cells [7]. This suggests that macrophage-driven host defense against helminth parasites may have features of trained immunity, which can provide protection against bacterial or viral infection via reprogramming of myeloid cells [27]. It remains to be determined as to whether the memory phenotype of macrophages that is induced during *N. brasiliensis* infection requires a persistent type 2 cytokine milieu and how it may affect host defense to distinct helminth parasites.

In addition to innate type 2 immunity, the adaptive immune response plays a crucial role in inducing AAMs with anti-helminthic effector functions. IL-4 derived from Th2 cells has been reported to induce Arg1 and CD206 expressing macrophages, which provide protection against challenge infection with the murine parasite *H. polygyrus bakeri* (*Hpb*) [24]. Further studies have confirmed a crucial role for type 2 cytokine production by T-cells and subsequent AAM activation during *N. brasiliensis* infection [5]. However, while T-cell and ILC-2-derived IL-13 was crucial for AAM-mediated larval killing in the lung [5], IL-4 and IL-13 production by CD4 T-cells was dispensable for parasite expulsion from the gut despite promoting AAM differentiation [28]. These studies suggest that AAM are particularly involved in larval trapping and killing within the tissue (e.g. intestine for *Hpb* or lung for *Nb*), while being largely dispensable for the expulsion of adult parasites from the intestine. However, another study has implicated AAM in IL4/IL-13-driven intestinal smooth muscle constriction, which depended on Arg1 activity and correlated with parasite clearance during infection with *Nb* [29]. Thus, IL-4/IL-13-induced AAM contribute to multiple crucial events of anti-helminth immunity and the relative contribution of each of these host defense mechanisms likely depends on the parasite and its specific lifecycle as well as the time point assessed after infection. In addition, AAM induced during helminth infection can be of distinct origin (e.g. resident or monocyte-derived), which may differentially affect parasite- and tissue-specific effector functions [30,31].

Antibody-mediated macrophage functions in host defense and repair during helminth infection

In addition to producing IL-4 and IL-13 Th2 cells provide help to B-cells, thus driving the production of helminth-specific antibodies, which represent an important component of anti-helminth immunity [4,32,33]. Indeed, antibodies are commonly associated with low worm burdens in humans and livestock [34–36] and they mediate host resistance in some (but not all) settings of experimental helminth infection [37]. Multiple studies have shown that the activation of macrophages via FcR- and/ or complement-dependent mechanisms represents an integral component of antibody-mediated host defense against helminth parasites (Figure 1). For instance, helminth-specific IgG or IgE antibodies drive the activation of AAMs that trap *H. polygyrus* or *N. brasiliensis* larvae in the gut or skin, respectively [2,4,38]. Of note, the induction of Arg1-expressing AAMs by *H. polygyrus* specific antibodies was independent of IL-4Rα signaling [2], but depended on complement and IgG2a binding to the high-affinity Fc receptor CD64, which mediated adherence of macrophages to L3/L4 stage larvae and induction of an AAM-like phenotype, respectively [38]. In contrast, Arg1-mediated trapping of *N. brasiliensis* larvae by macrophages required the IgE/ FcεR-driven activation of IL-4-producing basophils [4]. Recently, an important role for antibody-activated macrophages in larval trapping has also been shown for the human parasite *Ascaris lumbricoides* [6]. However, in contrast to macrophage-mediated immunity to the rodent parasite *H. polygyrus,* antibody-mediated trapping of *Ascaris* larvae was greatly enhanced in the presence of eosinophils, which were recruited by immune serum-activated human macrophages [2,6]. Similarly, IL-4Rα–STAT6-activated AAMs attracted eosinophils during infection with *N. brasiliensis* [39]. AAM further work in concert with neutrophils to trap and kill larvae of *Strongyloides stercoralis* or *N. brasiliensis* [3,40]*,* suggesting highly coordinated and synergistic functions between AAMs and granulocytes during infection with parasitic nematodes. On this note, parasite infections can induce organized tissue structures (granulomas) that are largely composed of eosinophils, neutrophils, AAM and Th2 cells, acting in concert to halt the development of larval and/or egg stages of different helminths [41–43]. Antibody-activated macrophages drive the

recruitment of myofibroblasts to these granulomas, thus mediating tissue repair in the intestine of helminth infected mice [44]. A similar reparative function could be shown in a human model of scratch wound closure, where macrophages activated by *Ascaris* larvae and immune serum from *A. suum*-infected pigs triggered chemokine-driven myofibroblast recruitment [44]. Thus, in addition to mediating parasite trapping, antibody-activated macrophages serve as important mediators of tissue repair during helminth infection. The diverse contribution of different isotypes and FcR pathways to antibody-induced effector functions of macrophages is likely instrumental in meeting the specific requirements of trapping and repair in different tissues.

Helminth/C-type lectin-driven induction of anti-helminth effector functions

Besides lymphocyte-derived immune components such as IL-4, IL-13 and antibodies, multiple macrophage intrinsic proteins can sense parasite molecules, leading to the induction of anti-helminthic and reparative effector functions. Recognition of parasite glycoconjugates via surfactant proteins A and D or galactose-type lectin was reported to drive macrophage activation and parasite killing during infection with *N. brasiliensis* or *Trypanosoma cruzi*, respectively [45,46]. Macrophages can further participate in the response to chitin, a widespread environmental biopolymer of N-acetylglucosamine that is abundant in the eggs and cuticle of helminth parasites. Recognition of chitin has been implicated in the induction of an AAM phenotype that produces high levels of leukotriene B_4, thus driving eosinophil recruitment in the context of helminth infection [47]. In turn, chitin-induced chemotactic macrophage functions can be negatively regulated by host-derived chitinases, which are induced by type 2 cytokines [47].

Metabolic programs driving AAM effector functions

Upon type 2 activation macrophages undergo a specific metabolic switch that enables AAM effector functions, e.g. in parasite trapping or tissue repair. While proinflammatory

macrophages fighting bacterial or viral pathogens need high amounts of energy very quickly, tissue remodeling and wound healing as typical functions of AAM require longer time frames and thus depend on highly economic and effective cellular energy generation [48,49].

In contrast to M1 macrophages, AAM favor mitochondrial respiration and oxidative phosphorylation to generate energy [48,50]. The AAM program is further fueled by multiple metabolic pathways including glutaminolysis, lipolysis, mitohormesis and initially increased glucose consumption [12,50–54]. In skin wound healing, time-dependent metabolic reprogramming induces macrophage phenotypes with distinct functionalities adapted to the different stages of the repair process [12]. Whether similar time-dependent metabolic programs govern AAM activation and functions during helminth infection remains to be investigated. Indeed, alternative activation and proliferation of resident peritoneal macrophages during *H. polygyrus* infection is hampered when glycolysis is inhibited [54]. However, as 2-desoxyglucose (2-DG), a commonly used inhibitor of glycolysis, may also impact cellular respiration [55], results from experiments using 2-DG should be interpreted with caution. Inhibition of fatty acid oxidation (by etomoxir) or the electron transport chain (by oligomycin) impacts several - but not all - aspects of the AAM polarization: For example, RELMα and PD-L2 expression are reduced while CD36 induction remains intact [55]. Thus, the exact AAM phenotype and function depends on metabolite availability in a given immunological setting or tissue microenvironment. How helminth infection affects metabolite availability and metabolic reprogramming to modulate macrophage effector functions remains incompletely understood.

Importantly, the source and availability of fuels for macrophage respiration may vary [56] depending on the tissue localization, which is particularly relevant during infection with helminth parasites that migrate through multiple tissues. Indeed, during *N. brasiliensis* passage through the lung, alveolar macrophages exhibit less AAM activation in comparison to interstitial pulmonary macrophages due to reduced responsiveness to IL-4 [57]. This exemplifies the relevance of the tissue environment and its specific metabolite supply in driving

the metabolic programs that determine resident macrophage functions. However, the functional consequences of tissue-specific bioenergetic macrophage reprogramming in helminth infection remain to be elucidated.

Efficient bioenergetic reprogramming and its translation into anti-helminthic effector functions requires kinase pathways, including AMP-activated protein kinase (AMPK), that sense the macrophage metabolic state and drive energy supply. Mice lacking AMPKα in macrophages (and myeloid DCs) show impaired type 2 immunity and increased lung damage during *N. brasiliensis* infection, suggesting an integral role for AMPK in AAM-mediated host defense and restriction of tissue injury [58].

In addition to energy (in the form of ATP), metabolism supplies building blocks for protein modifications such as N-glycosylation, which contributes to enhanced generation of highly glycosylated AAM effector molecules such as Relmα, CD206 and CD301 [52]. Another AAM effector molecule, Arg1 (see 2.1.2 and 2.2 for details on antiparasitic functions), produces ornithine, which AAM metabolize to hypusine used to post-transcriptionally modify a translation initiation factor, eIF5A [59]. Hypusinated eIF5A is necessary for mitochondrial function and OXPHOS in AAM, and inhibition of hypusination led to reduced AAM polarisation of peritoneal macrophages and increased worm burdens during *H. polygyrus* infection. This suggested an important role for Arg1 in the metabolic and transcriptional activation of AAM effector functions during helminth infection. An effect of hypusination on AAM was also shown in human monocyte-derived macrophages *in vitro* [59], arguing that downstream metabolites of Arg1 may contribute to AAM activation in humans although the role of macrophage-derived Arg1 in host defense against human parasites is unclear.

Together, these studies suggest that parasite-derived molecules directly or indirectly induce the metabolic programs that enable AAM activation and effector functions during helminth infection.

2.1.2 AAM effector molecules enabling host defense against helminths

Chitinases and chitinase-like proteins - macrophage-derived initiators of type 2 immunity

Several studies have shown that AAM can produce large amounts of chitinases, such as acidic mammalian chitinase (AMCase) and the chitinase-like proteins (CLPs) BRP-39, Chil3 (Ym1) and Ym2 and that these proteins represent key macrophage effector molecules in type 2 immunity [47,60–62]. AMCase, which is induced in epithelial cells and macrophages in response to IL-13 has been associated with allergic airway inflammation (AAI) [63]. Inhibition of AMCase during OVA-induced AAI attenuated Th2 mediated, eosinophilic allergic airway inflammation, but lead to an enhanced pathological neutrophil response [64]. In contrast, during helminth infection AMCase is not required for type 2 immunity in the lung, while it contributes to the initiation of host defense against *H. polygyrus* and *N. brasiliensis* in the intestine. This suggests a tissue-dependent role of AMCase in helminth infection [60]. Importantly, increased expression of AMCase has been demonstrated in PBMCs from patients infected with intestinal parasites, suggesting that AMCase may represent a conserved mechanism of anti-helminth immunity between mice and humans [65]. In addition to the enzymatically active AMCase, murine AAMs express high levels of chitinase-like proteins (CLPs), which lack enzymatic activities, but show biological function. Of note, despite being amongst the most highly expressed molecules in murine AAMs and neutrophils [62], no human orthologs have been found for the murine chitinase-like proteins Chil3 (encoded by chitinase 3) and Ym2 (encoded by chitinase 4). In contrast, BRP-39 has a genetic orthologue in humans named YKL-40, which seems to exert similar effects as those described for Chil3 [61]. In *Schistosoma haematobium* infected children, serum levels of YKL-40 are increased [66], suggesting a role for this CLP in human helminth infection. In murine models, Chil3 has been implicated in the recruitment of eosinophils [67], which contribute to parasite killing in some helminth infections [26]. In addition to their roles in eosinophil recruitment, CLPs may promote the IL-17A-mediated chemotaxis of neutrophils, thus driving early type 2 inflammation in the lung of *N. brasiliensis*-infected mice [61,68]. The wide occurrence of chitinases and CLPs in

mammals suggests that they represent a conserved mechanism of resistance to chitin-rich pathogens.

Arginase-1 enables trapping of helminth larvae and limits aberrant Th2 activation

The activation of AAMs with anti-helminthic effector functions depends on the activation of multiple metabolic pathways, including increased oxidative phosphorylation (OXPHOS), fatty acid oxidation (FAO), lipolysis and glycolysis [54,69,70]. However, in addition to this general bioenergetic reprogramming, specific enzymatic pathways are required for macrophage-mediated host defense against helminth parasites. A prime example of an enzyme involved in macrophage-dependent anti-helminth immunity is Arg1. Arg1 converts L-arginine to L-ornithine, polyamines and urea. Indeed, L-ornithine and the polyamines spermidine, spermine and putrescine were shown to directly limit the motility of *H. polygyrus* larvae *in vitro* [2]. This suggests that release of Arg1 metabolites by macrophages directly reduces larval fitness and helminth-driven tissue disruption at the site of infection. Furthermore, Arg1 activity - presumably in intestinal macrophages - contributed to parasite expulsion during *N. brasiliensis* infection by increasing smooth muscle constriction [29], however the exact metabolite mediating this effect remains to be identified. In addition to their roles in host defense, Arg1 expressing macrophages exert important immune regulatory functions during infection with helminth parasites. During infection with *S. mansoni*, a parasite that can cause severe type 2 immunopathology, macrophage Arg1 activity limits inflammation and fibrosis by depleting Arginine from $CD4^+$ T-cells. In contrast to murine AAMs, human monocyte derived AAMs express low levels of Arg1 [71] and inhibition of Arg1 did not affect the immobilization of *Ascaris suum* larvae by human macrophages [6]. Thus, control of human helminth parasites appears to be largely independent of macrophage-derived Arg1.

Resistin like protein alpha (RELMα) – a pleiotropic regulator of host defense and type 2 immunopathology

Resistin like molecules (RELMs) represent hallmark IL-4-induced genes [72], but their functions in macrophage-mediated anti-helminth immunity have only partially been elucidated. RELMs (resistin, RELMα, RELMβ and RELMγ) are a family of cysteine-rich proteins secreted by many effector cells ranging from macrophages, dendritic cells and eosinophils to specialized epithelial cells. During helminth infection, RELMα expression in macrophages is induced in an IL-4Rα and STAT6 dependent manner [72] and RELMα-expressing AAMs contribute to host defense against challenge infection with *N. brasiliensis* [7]. However, while macrophage-expressed RELMα appeared to promote larval trapping in the skin [7], RELMα deficient lung macrophages exhibited an enhanced capacity to trap *N. brasiliensis* larvae *in vitro* [73]. This may suggest that the function of RELMα-expressing macrophages depends on the tissue microenvironment and the developmental stage of the parasite. While the exact roles of RELMα in parasite trapping and killing remain to be resolved, immune regulatory functions of RELMα-expressing AAMs are relatively well-understood and appear to be conserved between different parasite species. Thus, mice with a global deficiency in RELMα exhibit exaggerated Th2-cytokine responses and consequently develop liver, intestinal and lung pathology after *S. mansoni* or *N. brasiliensis* infection [14,15,74]. In contrast, transgenic mice expressing human resistin developed increased airway inflammation and exhibited increased egg and worm burdens during infection with *N. brasiliensis*. Furthermore, in humans infected with STHs or filarial nematodes, resistin levels correlated positively with parasite burden [75]. In combination with recently reported antibacterial activities of RELMα [76] this may suggest that the upregulation of resistin during helminth infection modulates immune responses in order to prepare for possible co-infections that are common in real-life settings [77].

Taken together, previous studies have revealed an elementary role for macrophage effector molecules in mediating protective immunity against helminths; however, the molecular mechanisms underlying macrophage-mediated parasite trapping, killing and expulsion are only beginning to be understood. Taking the differences in AAM activation programs in

humans and mice into account, future studies should close the current gap in our understanding of macrophage-mediated host defense in human helminth infection.

2.2 Mechanisms and functions of AAM-mediated repair of helminth-induced damage

Induction of tissue reparative macrophages during helminth infection

Migration of parasites trough epithelial barriers and multiple organs can cause tissue disruption and thus hemorrhage or translocation of microbiota. Therefore, the rapid and efficient induction of repair mechanisms is essential to prevent inflammation, loss of tissue function and bacterial dissemination. Indeed, several of the AAM effector molecules involved in trapping and killing of helminth parasites (see 2.1) also play essential roles in tissue repair. In addition, macrophages release a variety of growth factors (e.g. platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), insulin-like growth factor 1 (IGF-1)) that promote the recruitment, proliferation and activation of fibroblasts and endothelial cells, thus facilitating repair of helminth-induced tissue damage [78].

To enable tissue repair following *Nippostrongylus* or *Taenia* infection, macrophages undergo a switch from a pro-inflammatory (M1-like) to an anti-inflammatory AAM state [79,80]. This is exemplified by the IL-4Rα-dependent induction of IGF-1-, Arg1-, metalloproteinase 13- (Mmp13) and IL-10-expressing macrophages that were essential for controlling lung damage during *N. brasiliensis* infection [8]. While in line with reprogramming of wound macrophages following skin wounding [12], such plastic temporal adaptations of macrophage polarization have not been described for other helminthiases.

In addition to IL-4 (or IL-13) produced by recruited type 2 activated lymphocytes or basophils, local tissue-derived signals may govern reparative functions of macrophages during helminth infection. In the lung, SP-A derived from type II pneumocytes promoted AAM polarization and proliferation, resulting in the control of *N. brasiliensis*-induced inflammation, hemorrhage and tissue damage [9]. In particular, lung-derived SP-A enhanced the induction of the AAM effector

molecules RELMα and Chil3, which have both been implicated in the regulation of helminth-induced inflammation and damage. Indeed, a significant amount of the damage found in helminth-infected tissues can be attributed to the pro-inflammatory and tissue-disruptive functions of infiltrating granulocytes. Thus, immune regulatory and anti-inflammatory effects of AAM effector molecules are likely integral to their regenerative capacities in helminth infection.

The functions of key AAM effector molecules in repairing helminth-induced tissue damage are summarized below.

Chil3 as a mediator of lung repair during helminth infection

Several studies support a role for Chil3 in regulating tissue damage and repair during *N. brasiliensis* infection [8,61,68], particularly at later time points following lung migration of *N. brasiliensis* [81]. In keeping with these studies, the activation of Chil3, Arg1 and RELMα-expressing AAMs correlated with lung repair in mice infected with *Toxocara canis* [82]. Although the Chil3-mediated induction of RELMα in epithelial cells has been implicated in these reparative effects [81], the mechanisms underlying Chil3-induced repair during helminth infection remain to be fully elucidated.

RELMα – a pleiotropic mediator of tissue repair and fibrosis

Besides its roles in helminth trapping, AAM-derived RELMα has been implicated in wound healing responses based on its capacity to induce lysyl hydroxylase 2 in fibroblasts and thus crosslinking of collagen fibrils [11]. In addition, while promoting rapid and homeostatic tissue repair following nematode infection [7], RELMα negatively regulates type 2 immunopathology and liver fibrosis triggered by *S. mansoni* eggs [14,15], further supporting its role as a key regulator of tissue repair and remodeling during helminth infection. However, the precise roles and molecular mechanisms of RELMα-mediated repair in different settings of helminth-induced tissue damage remain to be investigated.

Tissue reparative functions of Arg1

In addition to RELMα and Chil3, both Arg1 and IGF-1 were reported to contribute to the prevention of hemorrhage and inflammation in the lung of *N. brasiliensis* infected mice [8]. As discussed above, Arg1 converts arginine into ornithine which in turn can be converted into proline and hydroxyproline, essential building blocks for collagen synthesis [78,83]. Similar to RELMα, AAM- specific expression of Arg1 functions as an inhibitor of inflammation and fibrosis following infection with *S. mansoni* [13].

Thus, key AAM effector molecules have likely evolved to both prevent and repair parasite-induced tissue damage by enabling larval trapping, reducing helminth fitness and stimulating collagen synthesis while simultaneously preventing aberrant fibrotic remodeling.

Macrophage-derived chemokines as mediators of intestinal repair

While hallmark IL-4-induced AAM effector molecules such as RELMα, Ym-1 and Arg1 appear to be particularly important for tissue repair during a rapid (full-blown) type 2 immune response such as during infection with *N. brasiliensis*, alternative mechanisms may contribute to repair in distinct settings of helminth infection. For example, macrophages activated by immune complexes during challenge infection with *H. polygyrus* upregulate CXCR2 ligands (CXCL2/3) that attract alpha smooth muscle actin (αSMA)-expressing myofibroblasts, thus promoting intestinal repair [44]. A similar CXCR2-dependent repair mechanisms could be confirmed in a human model of scratch wound closure, in which supernatant of helminth/ immune complex-stimulated human macrophages accelerated myofibroblast migration [44]. Future studies should thus investigate how chemokines that are typically associated with type 2 immune responses (e.g. CCL17, CCL24) may affect macrophage-driven repair or fibrotic remodeling during helminth infection.

Pathological consequences of AAM repair functions

While the formation of AAM-rich granulomas likely contributes to helminth trapping and to restoring tissue architecture following parasite-induced damage [14,15,41,84], they may also cause liver fibrosis and subsequent portal hypertension or even death, e.g. in hosts chronically infected with *S. mansoni* [85]. In addition, AAMs expressing high levels of MMP-12 have been associated with the development of emphysema following infection with *N. brasiliensis* [86], suggesting dual roles for AAMs in damage and repair even during infection with the same parasite. As the aberrant activation of AAMs can lead to loss of tissue integrity, fibrosis and impaired organ function, effector mechanisms of AAM must be tightly regulated.

3. Regulation of macrophage effector functions in type 2 immunity

As discussed above, macrophages exhibit potent effector functions that allow them to restrict parasite burdens and tissue damage during infection with helminth parasites (Figure 1). To ensure proper control of these functions and avoid pathology, a number of host-derived regulatory factors are induced during helminth infection (Table 1). In turn, helminths have developed a multitude of molecular tools to hijack these immune regulatory mechanisms and evade host immunity (Table 1, Figure 2).

3.1 Macrophage-intrinsic regulation of anti-helminthic effector functions

Innate sensing pathways as negative regulators of AAM functions

While some helminth molecules induce type 2 cytokines and AAM effector functions, innate sensing pathways that are typically associated with bacterial or viral infection often counter-regulate AAM activation. This includes TLRs and C-type lectin receptors, which mediate the induction of multiple type 2 suppressive mediators (e.g. IL-10, TGFβ, PGE_2, IL-12, IL-1β) during helminth infection or during treatment with helminth molecules (see below) [87–90].

A recent study further identified the NLRP3 inflammasome, typically associated with M1 polarization, as a negative regulator of neutrophil recruitment and anti-helminthic immunity during *N. brasiliensis* infection. NLRP3 deficient mice exhibited enhanced host defense against the lung stage of *N. brasiliensis*, suggesting that inflammasome activation may represent a macrophage-intrinsic mechanism that restricts type 2 immunity [91]. However, the signaling and mediator pathways underlying the NLRP3-mediated regulation of AAM effector functions remain to be defined. In addition, it will be important to define effects of PRR-driven activation by bacteria or viruses on macrophage host defense and repair functions during helminth infection.

Kinase pathways mediating immune regulatory effects in macrophages

Once macrophages have sensed external cues via a multitude of pattern recognition- and cytokine receptors, these signals are integrated via an intricate network of intracellular signaling pathways. These include MAP kinases (e.g. p38) and ERK, that have broad implications in macrophage activation, host defense and immune regulation in diverse settings of infection and inflammation. In the context of helminth infection, p38 and ERK appear to participate in the modulation of type 2 immunity and immune evasion [16,89,92] .

P21-activated kinase 1 (PAK1), which is activated downstream of AMPK signaling in macrophages [93], is another pleiotropic kinase that has been implicated in inflammation. PAK1 was shown to trigger the activation of inflammatory macrophages, thus inducing IL-6-dependent T_H17 differentiation and liver pathology in *Schistosoma japonicum* infection [94]. PAK1 also downregulated *Arg1* expression, suggesting a suppressive effect on AAM activation and type 2 immunity.

A better definition of the specific kinase pathways that regulate macrophage activation and function in type 2 immunity may identify amenable drug targets as multiple approved kinase inhibitors are in clinical use.

438 Immune regulatory functions of macrophage-derived IL-10 in helminth infection

439 IL-10 is the prototypic IL-10 family cytokine and IL-10 expression in macrophages is induced
440 upon PRR ligation (TLR2, 3, 4, 9, dectin-1, DC-SIGN) by activation of ERK and p38 and
441 transcription factors C/EBPβ and NFκb, among others (reviewed by Ouyang and O'Garra
442 [95]). During helminth infection, IL-10 is a widely studied mediator of parasite-induced
443 tolerance.

444 Notably, IL-10 antagonizes the proinflammatory metabolic activation of macrophages via
445 inhibition of glycolysis to the advantage of oxidative phosphorylation and by upregulating an
446 inhibitor of mTOR signaling, DDIT4, and inducing autophagy [96]. However, whether IL-10-
447 induced metabolic reprogramming may similarly affect AAM activation and functions during
448 helminth infection remains to be investigated. While IL-13-induced alternative activation is
449 lost upon IL-10 exposure [97], *in vitro* stimulation of IL-4-induced AAM with IL-10 rather
450 enhanced type 2-inflammatory functions such as eosinophil chemotaxis [98]. Furthermore, IL-
451 10 shifts splenic AAM towards a regulatory phenotype in *Brugia malayi*-infected mice over
452 time [99], while peritoneal macrophages require IL-10 exposure to upregulate AAM markers
453 *Mrc1* and *Chil3l3* upon Schistosome egg exposure [100], suggesting that IL-10 has complex
454 effects on AAM functions, which still need to be fully resolved.

455 In addition to regulating inflammatory effector functions of macrophages, IL-10 acts as an
456 autocrine mediator of repair in the lungs and livers of helminth-infected mice [8,101]. The
457 reparative roles of IL-10-producing and IL-10-stimulated macrophages may translate to
458 human settings of helminth infection as IL-10 stimulated human macrophages (also termed
459 "M2c") upregulate multiple genes related to extracellular matrix remodeling, angiogenesis,
460 blood clotting and phagocytosis, which are integral to tissue repair [102].

461 Given the conserved anti-inflammatory and reparative roles of IL-10 in helminth infection, it is
462 not surprising that IL-10 represents a key immune regulatory mechanism employed by
463 helminth parasites. Indeed, a multitude of helminth molecules induce IL-10 production in

464 different subsets of immune cells (Tregs, Bregs, dendritic cells (DCs) and macrophages)
465 [16,20,87,103–107] (see also 3.2). Of particular importance, helminth products have recently
466 been shown to induce a persistent anti-inflammatory epigenetic imprint, resulting in increased
467 macrophage IL-10 responses and suppression of auto-immunity [107]. It will be important to
468 further decipher the complex roles of IL-10 in helminth-induced immune regulation and innate
469 immune training and determine its contribution to macrophage-dependent tissue repair and
470 immune evasion during helminth infection.

471 Regulatory roles of macrophage-derived prostaglandin E_2 in type 2 immunity

472 Bioactive metabolites of arachidonic acid (eicosanoids), are upregulated in tissues as well as
473 in macrophages of helminth-infected mice [50,108,109]. This includes the cyclooxygenase
474 (COX)-derived mediator prostaglandin (PG)E_2, which is upregulated in macrophages from
475 humans infected with *Onchocerca volvulus*, [110] or from mice infected with *B. malayi* [50]. In
476 addition to (helminth-) activated macrophages and epithelial cells, certain helminth parasites
477 themselves can produce PGE_2 [111]. Thus, during helminth infection *in vivo,* host cell- and
478 parasite-derived PGE_2 will likely act in concert to regulate inflammation, host defense and
479 repair. Indeed, helminth-induced PGE_2 produced by macrophages and DCs acts as a
480 regulator of type 2 immune responses both during helminth infection and in allergic airway
481 inflammation [16,112]. PGE_2 production is also necessary for AAM-mediated protection from
482 colitis following *Taenia crassiceps* infection in mice [113]. In addition, PGE_2 has been
483 implicated in immune evasion and liver fibrosis during infection with *S. mansoni* and *S.*
484 *japonicum* [114,115]. While immunosuppressive effects of PGE_2 during helminth infection are
485 largely in line with findings in allergy, viral infection and cancer (for review see [116]), its effects
486 on helminth-induced fibrosis remain controversial as PGE_2 is usually considered as a potent
487 anti-fibrotic mediator [117]. However discrepant findings related to PGE_2-mediated effects
488 may be explained by the existence of four different PGE_2 receptors (EP1-4) [116], which trigger
489 distinct downstream signaling events. Thus, depending on the EP receptor profiles of
490 individual cell types and tissues, PGE_2 can have diverse effects. For example, while EP2 and

491 EP4 signaling suppresses inflammation in diverse models of airway disease [118], EP4 drives
492 joint inflammation [119]. In contrast, EP1 and EP3-signaling are predominantly involved in the
493 induction of pain or fever, e.g. during systemic inflammation [120].

494 However, the PGE_2 receptors mediating helminth-induced immunosuppression and immune
495 evasion remain to be defined. In addition, it will be important to decipher the roles of PGE_2 and
496 other macrophage-derived COX metabolites (e.g. thromboxane, 12-HHT) in host defense,
497 tissue repair and immune regulation during helminth infection, e.g. by studying mice with a
498 myeloid deletion of individual prostanoid receptors.

499

500 Type 2 suppressive effects of pro-inflammatory cytokines

501 In addition to IL-10 and PGE_2, which exert broadly immunosuppressive effects during
502 infection, the PRR-mediated activation of macrophages triggers the induction of type-1
503 associated mediators, which can have suppressive effects on AAM activation. The TLR-driven
504 induction of IL-12 in macrophages and DCs promotes T_H1 differentiation and IFNγ production
505 in T cells, thus reducing type 2 immune responses [121]. In a model of *H. polygyrus/*
506 *Plasmodium*-co-infection, a *Plasmodium*-induced switch from T_H2 to T_H1 led to IL-12 secretion
507 which antagonized antiparasitic immunity and AAM activation [122]. While early infection with
508 some species (e.g. *Taenia*, *Schistosoma*) may result in the activation of classically activated,
509 IL-12 producing macrophages, pro-longed or chronic helminth infection elicits alternatively
510 activated macrophages [123]. The efficient induction of a T_H2 response and subsequent
511 parasite clearance indeed requires the downregulation of macrophage-intrinsic IL-12
512 production, e.g. during infection with *Trichuris muris* [124]. The type 2 suppressive potential of
513 IL-12 is also harnessed by helminth parasites, which induce IL-12 production by macrophages
514 or DCs to evade host immunity (see below). Together this suggests a key role for IL-12 in
515 limiting AAM activation and functions during helminth infection.

Further macrophage-derived pro-inflammatory cytokines with suppressive effects on type 2 immunity include IL-6 and IL-1β [125,126], although mast cell-derived IL-6 has been implicated in AAM activation by upregulating IL4Rα on macrophages [127]. Surprisingly, TNFα has been described to promote anti-helminth immunity [128] despite suppressive effects on AAM differentiation [129]. Thus, future studies should clarify macrophage-intrinsic roles of key pro-inflammatory cytokines in different settings of helminth infection and helminth-driven immune regulation in inflammatory disease models.

Epigenetic reprogramming of macrophages in type 2 immunity

In addition to the acute regulation of macrophage activation during helminth infection, recent studies have highlighted potential anti-inflammatory long-term effects of helminth-induced macrophage reprogramming. Strikingly, subcutaneous treatment of mice with *Fasciola hepatica* excretory-secretory products leads to long-term (>1.5 years) anti-inflammatory reprogramming of hematopoietic precursors which commit to differentiation into hyporesponsive, anti-inflammatory monocytes by mTOR-mediated metabolic and epigenetic imprinting [130]. The *F. hepatica*-induced anti-inflammatory imprinting in monocytes enabled protection from autoimmune encephalitis, an experimental model of multiple sclerosis, which could be transferred to naïve animals by adoptive transfer of HSC from *F. hepatica* extract-treated mice. Similarly, *S. mansoni* infection of mice induces metabolically reprogrammed macrophages which are hyporesponsive to LPS stimulation and can protect *Apoe*$^{-/-}$ mice from high fat-diet (HFD)-induced metabolic disease [131]. The effect of reprogrammed macrophages was communicable via adoptive bone marrow transfer and lasted for 10 weeks. Interestingly, the protective effect was not recapitulated by IL-4 complex injection, indicating that additional factors beyond stereotypical type 2 activation confer helminth-induced anti-inflammatory myeloid reprogramming. A similar myeloid reprogramming may occur in humans as patients previously infected with *Necator americanus* developed monocytosis and exhibited increased CD206 and IL-10 expression in monocytes [132].

Thus, helminth infection may have profound effects on hematopoiesis, which can be long-lasting as anti-inflammatory reprogramming may extend to macrophage progenitors. In addition to having central effects on bone marrow (BM) progenitors, helminth infection may impact on resident macrophage populations, which can self-renew, particularly in settings of type 2 immunity [25,133]. As different types of infections elicit distinct types of macrophage pools consisting of resident and/ or recruited populations [31], the functional capacities of BM-derived vs. resident macrophages will differ depending on the pathogen(s) and the associated immune response. In addition to macrophage origin, the site and duration of helminth infection will determine macrophage reprogramming and its functional consequences [31]. Thus, epigenetic reprogramming of BM-derived, recruited and resident proliferating macrophages may result in diverse, persistent alterations of macrophage effector functions, particularly following chronic helminth infection.

The exact epigenetic mechanisms and associated chromatin landscapes underlying helminth-induced regulatory macrophage reprogramming remain to be defined. Histone demethylase JMJD3 (KDM6B), implicated in macrophage differentiation, mediates AAM activation during *N. brasiliensis* infection by removing methyl groups from H2K27, thus enabling expression of AAM-related genes during helminth infection [134]. Of note, the contribution of individual histone modifications to AAM gene expression may differ depending on the mouse strain and the specific locus, exemplified by IL-4-triggered H3K27ac at enhancer regions of AAM genes (e.g. *Arg1*, *Mmp12*) [135]. Another study implicated HDAC3 in the negative regulation of AAM polarization [136], supporting a central role for H3K27 modifications in macrophage polarization and functions during helminth infection.

Given the potent immune regulatory, reparative and anti-helminthic capacities of macrophages, it will be important to decipher the mechanisms and consequences of long-term helminth-induced epigenetic reprogramming, e.g. in the context of inflammatory disease or susceptibility to subsequent infections with distinct pathogens.

3.2 Regulation of macrophage effector functions by parasite molecules

To survive and thrive within the host organism, parasites have evolved a variety of successful strategies to modulate the host immune response [19]. Chronic helminth infection frequently results in clinically silent disease, but enhanced susceptibility to other infections and blunted vaccine responses [137,138]. While many studies have identified immunosuppressive effects of helminth infection, infections with some helminths can enhance anti-viral immunity or exacerbate chronic inflammation, e.g. in asthma [139,140]. Thus, helminth infections are not per se immunosuppressive and it is of utmost importance to identify the individual immunomodulatory molecules in order to utilise their therapeutic potential in different settings of infection and inflammation.

Several helminthic immunomodulatory molecules have been isolated and purified, some of which are homologues of human signaling factors, while others are unrelated to human molecules in regard to sequence or function. Macrophages and DCs are major targets of helminthic immunomodulators and commonly mediate suppressive effects on type 2 immunity [18,141]. In addition to soluble factors, helminth parasites release extracellular vesicles containing immune regulatory miRNAs, which efficiently target macrophages potentially due to the phagocytic potential of these cells.

<u>Helminth-derived extracellular vesicles carrying immune regulatory miRNAs</u>

Exosomes are small (30-100 nm) membrane-enclosed structures that shuttle sensitive cargo such as proteins, metabolites or microRNAs (miRNA) between cells. Helminths release a mixture of exosomes and microvesicles (EMVs) which can be taken up by host cells, including epithelial cells and macrophages and function as means of communication [18,142,143]. In particular, exosome-delivered helminthic miRNAs modify host cell gene expression by targeting mRNAs involved in antiparasitic and proinflammatory actions. *F. hepatica* larvae-derived miRNA fhe-miR-125b was identified to target and inhibit *Traf* in murine macrophages

596 and thereby downregulate macrophage classical activation [144]. Based on their stability and
597 long-range actions helminth-derived exosomes may be particularly well suited to create an
598 environment permissive to infection, e.g. by modulating the early proinflammatory response
599 of macrophages towards the parasite. Macrophage classical activation is also suppressed by
600 *Taenia pisiformis* exosomes, which deliver miRNA let7-5p to inhibit macrophage *Cebpd*
601 mRNA and thus reduce *Il12* and *Nos2* gene expression [145]. Interestingly, exosomes
602 containing M1-suppressive miRNA were derived from cysticerci of *T. pisiformis*, suggesting
603 that it is indeed advantageous for early parasite stages to target classical activation of
604 macrophages. Correspondingly, suppression of classical proinflammatory mediators *Nos2*
605 and *Tnf* by exosomes from adult *S. japonicum* was described [146], although the mechanism
606 remains to be defined. Similarly, deactivation of AAM and reduction of IL-10 is mediated by
607 adult *H. polygyrus*-derived exosomes [18]. The specific cargo and immune regulatory effects
608 of exosomes from different parasite stages likely reflect the specific conditions that these
609 stages require in order to thrive in different tissues and settings of immune attack.

610 Cystatins interfere with antigen processing and induce IL-10 production in macrophages

611 Cystatins are cysteine protease inhibitors which have been described as immunomodulatory
612 molecules from multiple parasites, including *A. viteae*, *S. japonicum*, *B. malayi*, *A.*
613 *lumbricoides* and *T. spiralis* [104,147–151]. Cystatins appear to modulate multiple
614 macrophage effector functions, thus regulating host immunity and inflammation in
615 experimental models of allergic airway inflammation or colitis [20,152,153].

616 Similar to the role of endogenous human cystatins in antigen-presenting cells (APC) [154],
617 helminth-derived cystatins have been shown to interfere with APC functionality by inhibiting
618 invariant chain cleavage and antigen pre-processing prior to MHC II complexation in
619 macrophages and dendritic cells [150,155]. To be effective in MHC II regulation, parasitic
620 molecules must reach the endosomal pathway and it seems evolutionarily favorable to target
621 macrophages by harnessing their potent capacities for endocytosis. Uptake of cystatins was
622 indeed demonstrated for murine peritoneal macrophages *in vivo* and goat monocytes *in vitro*

[17,156]. Moreover, cystatin-induced upregulation of IL-10 in macrophages is mediated by MyD88 (via TLR2 and TLR4) [89] and computational modeling has suggested that cystatins may bind to TLR4 [157]. This may suggest that TLR-signaling is likely involved in the cystatin-triggered induction of IL-10 producing macrophages [17,103,147,151,158], which suppress inflammation in experimental models of allergy and colitis [20].

In contrast to the well-defined effects of helminthic cystatins in inflammatory disease models, their roles in macrophage-mediated host defense, repair and immune regulation during helminth infection remain to be characterized.

TGF-β and MIF homologues – molecular mimicry of host immune regulators

Similar to the homologous function of helminthic cystatins in host immunomodulation, parasites exhibit molecular mimicry of TGF-β, a potent immunosuppressive cytokine in both humans and mice [159]. TGF-β mimics of *H. polygyrus* and *F. hepatica* act by inducing Tregs and modulating macrophage responses [160–162].

Macrophage inhibitory factor (MIF), a pleiotropic cytokine with tissue- and cell-specific effects in immunity, represents another example of helminthic molecular mimicry [163]. Host-derived MIF contributes to protective immunity during *H. polygyrus* infection by inducing STAT3-dependent alternative macrophage activation [164] and endogenous MIF provided control of worm burdens in *S. japonicum*-infected mice [165]. Similar effects have been described for helminth-derived MIF homologues (MIF-1 and -2), which promote the transcription of AAM genes (*Arg1*, *Retnla*, *Chil3*) and synergized with endogenous MIF in inducing AAM activation *in vitro* and *in vivo* [166,167].

Thus, helminth-derived immunomodulators that act as homologues of macrophage cytokines can either suppress or promote AAM functions and type 2 immunity and it will be important to determine whether different helminths employ specific or conserved molecular mimicry to regulate macrophage functions according to their specific needs.

Hpb glutamate dehydrogenase

The simultaneous induction of multiple immune regulatory factors such as IL-10 and PGE_2 (3.1) and the suppression of type 2 inducing mediators can be expected to efficiently suppress type 2 immune responses, thus enabling efficient parasite evasion. The enzyme glutamate dehydrogenase (*Hpb* GDH), which has recently been identified as a major immune regulatory component of *Hpb* L3 stage larvae, targets several key mechanisms of type 2 immunity [16]. While suppressing the production of leukotrienes (LTs), which play important roles in allergy and helminth expulsion [168,169], *Hpb* GDH induces IL-10, PGE_2 and IL-1β production, thus inducing a type 2 suppressive phenotype in both murine and human macrophages. When administered to house dust mite-sensitized mice, recombinant *Hpb* GDH reduced allergic airway inflammation (AAI), indicative of a type 2 suppressive potential *in vivo* [16]. However, whether *Hpb* GDH predominantly exerts its immune regulatory functions by interfering with macrophage metabolism or by activating surface receptors such as C-type lectins is currently unclear. In addition, effects of *Hpb* GDH and related helminthic GDHs on host defense and tissue repair during helminth infection remain to be investigated.

Neutralization of DAMPs and PAMPs

A broadly exploited mechanism of helminth-mediated host immunomodulation is neutralization of danger signals related to tissue damage (DAMPs) or pathogen intrusion (PAMPs). This is exemplified by *H. polygyrus* secretion of HpARI which binds the epithelial alarmin IL-33, thus either preventing IL-33 secretion or activation of the IL-33 receptor ST2 [170]. Due to a similar structure as the human antimicrobial peptide LL-37, processed *F.hepatica* helminth defense molecule 1 (FhHDM1) binds and deactivates LPS, thereby preventing TLR4 activation in macrophages. In addition, FhHDM1 impairs antigen processing and presentation in macrophages by inhibiting lysosomal acidification [171,172]. Similarly, *A. vitea* ES-62 was reported to interfere with IL-33 and TLR4 signaling [173], which depended on the phosphorylcholine moiety of the molecule [174]. TLR4 signaling is also targeted by *F. hepatica* fatty acid binding protein Fh12, in part by downregulating the coreceptor CD14, thus

675 dampening LPS-induced IL-1β and IL-12 production by macrophages [175]. In summary,
676 multiple helminth molecules have been shown to neutralize DAMPs and PAMPs in order to
677 modulate host immune responses and it will be important to further characterize the role of
678 macrophages in this immune regulatory strategy of helminths parasites.

679 Together, these studies highlight macrophages as prime targets and mediators of helminth-
680 induced immune regulation. The broad immune regulatory functions of macrophages during
681 helminth infection have likely evolved to prevent aberrant type 2 inflammation and fibrosis and
682 they rely on the unique plasticity, phagocytic capacity and broad expression of immune
683 regulatory molecules of macrophages. However, the mechanisms and functions of helminth-
684 driven macrophage regulation are incompletely understood, particularly in human settings,
685 thus limiting the therapeutic exploitation of this fascinating, evolutionary matured host-parasite
686 crosstalk.

687

688 **Conclusions and future directions**

689 A multitude of studies have shown key roles for macrophage effector- and regulatory functions
690 in helminth infection. However, most of the studies examining pathways involved in
691 macrophage-mediated host resistance and repair have been conducted in mice. In
692 comparison to commonly studied rodent models, anti-helminth immunity in humans often fails
693 or develops slower, potentially as a result of efficient immune evasion of human parasites.
694 Thus, it will be important to translate insights from mouse models into settings of human
695 helminth infection and to identify conserved mechanisms of macrophage-mediated chronicity,
696 host defense and repair.

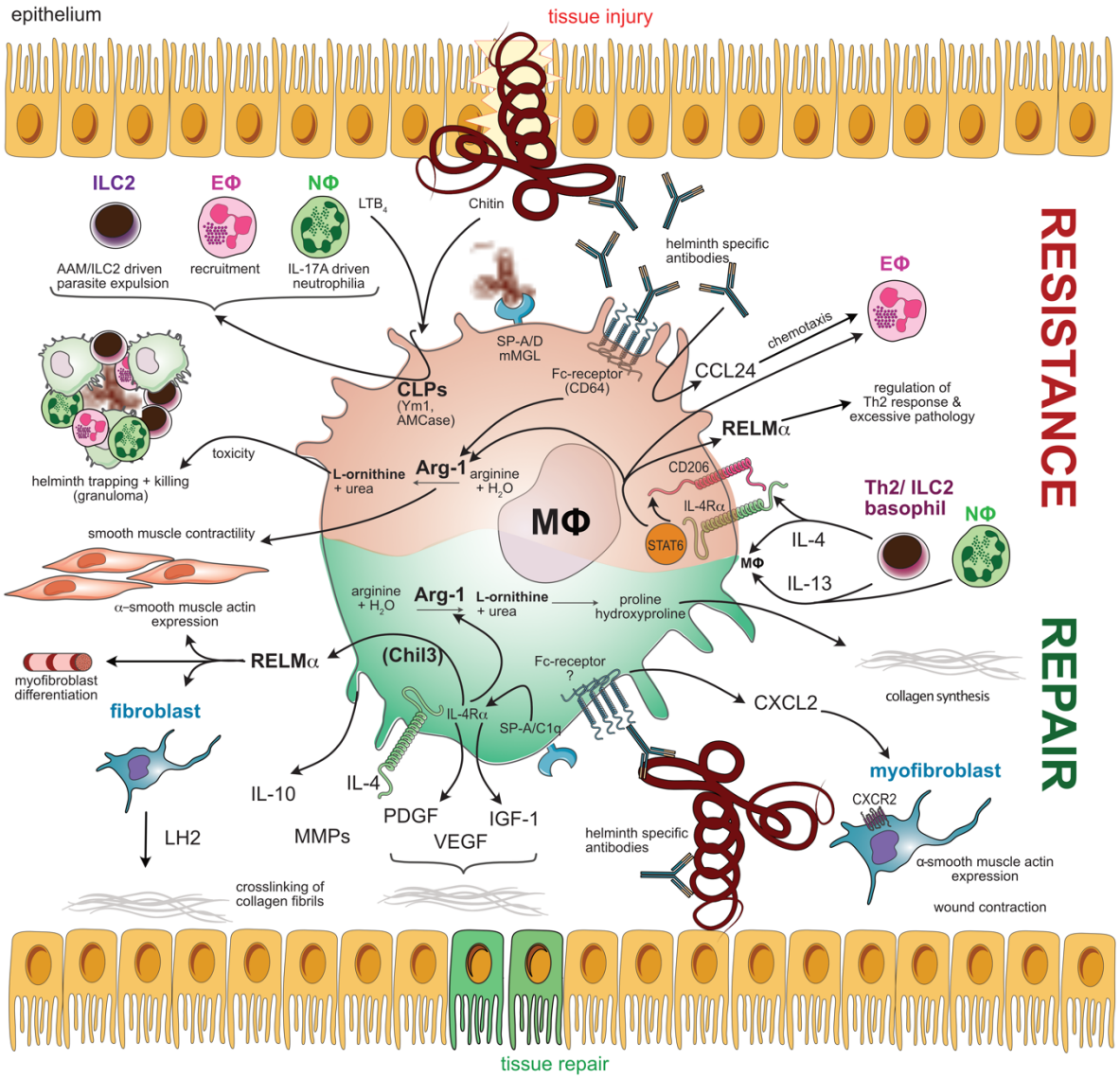
697 While macrophages are key initiators of innate and adaptive immunity, e.g. by triggering the
698 recruitment and activation of granulocytes and T cells, they are also essential regulators of
699 inflammation and aberrant tissue remodeling during helminth infection. Future research should
700 thus define the heterogeneity underlying the functional diversity of macrophages in helminth

infection. Such studies will benefit from recent single cell technologies and the availability of new macrophage-specific deleters, which will help to determine the relative contribution of individual macrophage subsets to host defense and immune regulation in type 2 immune responses.

In addition to characterizing macrophage activation and heterogeneity by transcriptomic approaches, macrophage reprogramming during and post helminth infection should be defined by current metabolomic (LC-MS/MS-based) and epigenetic (ATACseq/ ChIPseq) analyses. This will provide important insights into the mechanisms and duration of macrophage-mediated trained immunity in helminth infection, which remains poorly defined. Studying long-term reprogramming of bone marrow (or monocyte)-derived and resident macrophages from helminth infected mice and humans may also aid to predict and prevent pathological responses to subsequent infectious or inflammatory insults. Given that monocyte and macrophage epigenetic reprogramming has been implicated in chronic type 2 airway inflammation [176] and the therapeutic effects of allergen specific immunotherapy [177], it will be interesting to determine whether “trained type 2 immunity” is a common feature of protective and pathological type 2 immune responses.

Ultimately, a better understanding of the mechanisms that govern macrophage functions in host defense and tissue repair during helminth infection may guide the design of new anti-helminthic treatments as well as of therapeutics targeting detrimental AAM functions in asthma, fibrosis or cancer.

Figures and Tables



724

725 **Figure 1: Macrophage functions in helminth resistance and tissue repair.**

726 Abbreviations: Eϕ eosinophil, Nϕ neutrophil granulocyte, Mϕ macrophage

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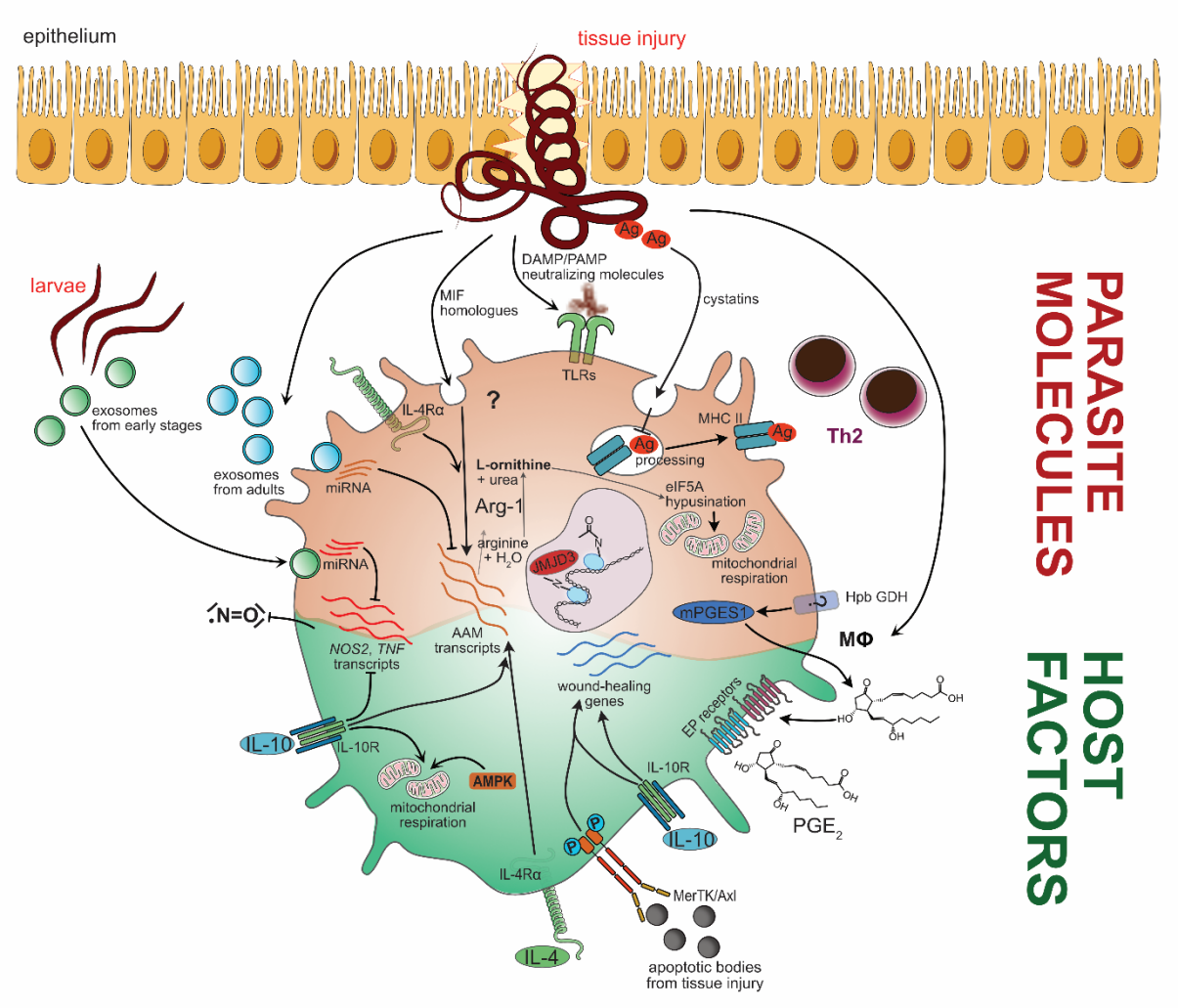

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732 **Figure 2: Macrophage regulation by host factors and helminth molecules.**

733 Abbreviations: Mϕ macrophage, mPGES1 microsomal prostaglandin E synthase 1

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