

Diversity and dialogue in immunity to helminths

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Abstract | The vertebrate immune system has evolved in concert with a broad range of infectious agents, including ubiquitous helminth (worm) parasites. The constant pressure of helminth infections has been a powerful force in shaping not only how immunity is initiated and maintained, but also how the body self-regulates and controls untoward immune responses to minimize overall harm. In this Review, we discuss recent advances in defining the immune cell types and molecules that are mobilized in response to helminth infection. Finally, we more broadly consider how these immunological players are blended and regulated in order to accommodate persistent infection or to mount a vigorous protective response and achieve sterile immunity.

Innate helper cell

A lymphoid cell that lacks antigen-specific receptors (such as B or T cell receptors) but that has the capacity to make cytokines associated with T helper (T_H) cells (for example, the T_H2 -type cytokines interleukin-4 (IL-4), IL-5 and IL-13) in response to innate 'alarm' cytokines, such as IL-25 and IL-33.

The immune system has evolved to defend us from the full spectrum of pathogens, including microorganisms, such as viruses, bacteria, fungi and protozoal parasites, and macropathogens, such as multicellular helminths and ectoparasites. Each of these pathogens poses a very different problem for the immune system to resolve and, correspondingly, we have evolved specialized mechanisms and cell populations to best address the challenge encountered in each setting. When operating optimally, the immune system interweaves the innate and adaptive arms of immunity, at both sensitization and effector levels, in a continuous dialogue that selects, calibrates and terminates the response in the most appropriate manner. Many pathogens, however, have developed complex evasion strategies and, when the immune response falls short, it may be necessary for the host to enter a damage limitation state, accommodating infection in order to minimize pathology. Moreover, most parasite immune evasion mechanisms themselves depend on a form of molecular dialogue between pathogen and host and, in turn, many parasites depend on host molecular signals for their development.

The variety of parasite life histories, and the finely evolved evasion strategies of different pathogens (which target the full range of host immune pathways), are likely to have driven diversification and redundancy within the immune system to generate alternative mechanisms and duplicate key functions that are essential to survive infection. For example, the adaptive T helper 2 (T_H2) cell response that is typical of helminth infections is mirrored by a range of innate helper cell responses^{1,2}. Thus, multiple cell types contribute crucial cytokines to enhance T_H2 -type immunity^{3,4}, and overlapping

populations of regulatory cells can execute similar functions⁵, guided by the overall stimulatory milieu. These topics are discussed in detail in this Review.

Type 2 immunity

Unlike bacteria, protozoa, fungi and viruses, most helminths do not replicate in the mammalian host. The infective stages must establish infection and then grow to sexual maturity, producing eggs or live offspring for transmission to the next host. The adult stages of these parasites can live for decades inured to immune-mediated attack. These distinct features, as well as the multicellular nature of these pathogens, may explain why helminths induce an entirely distinct immune response profile from microbial pathogens. In both humans and animals, this canonical response is of the T_H2 type and involves the cytokines interleukin-3 (IL-3), IL-4, IL-5, IL-9, IL-10 and IL-13, the antibody isotypes IgG1, IgG4 and IgE, and expanded populations of eosinophils, basophils, mast cells and alternatively activated macrophages^{6–8}. The innate immune system not only anticipates and initiates the adaptive T_H2 cell response but, importantly, continues to provide accompanying and mutually reinforcing pathways of T_H2 -type immunity throughout infection^{1,2,9}. This parallelism no doubt reflects both the ancient evolutionary origin of T_H2 -type immunity and the imperative to mount this mode of response in many different circumstances, not least of which is infection with helminth parasites. As many non-T cells, especially innate cells, are important contributors to the T_H2 cell-dominated response, we refer in this Review to a global 'type 2 immunity' that encompasses all of these players.

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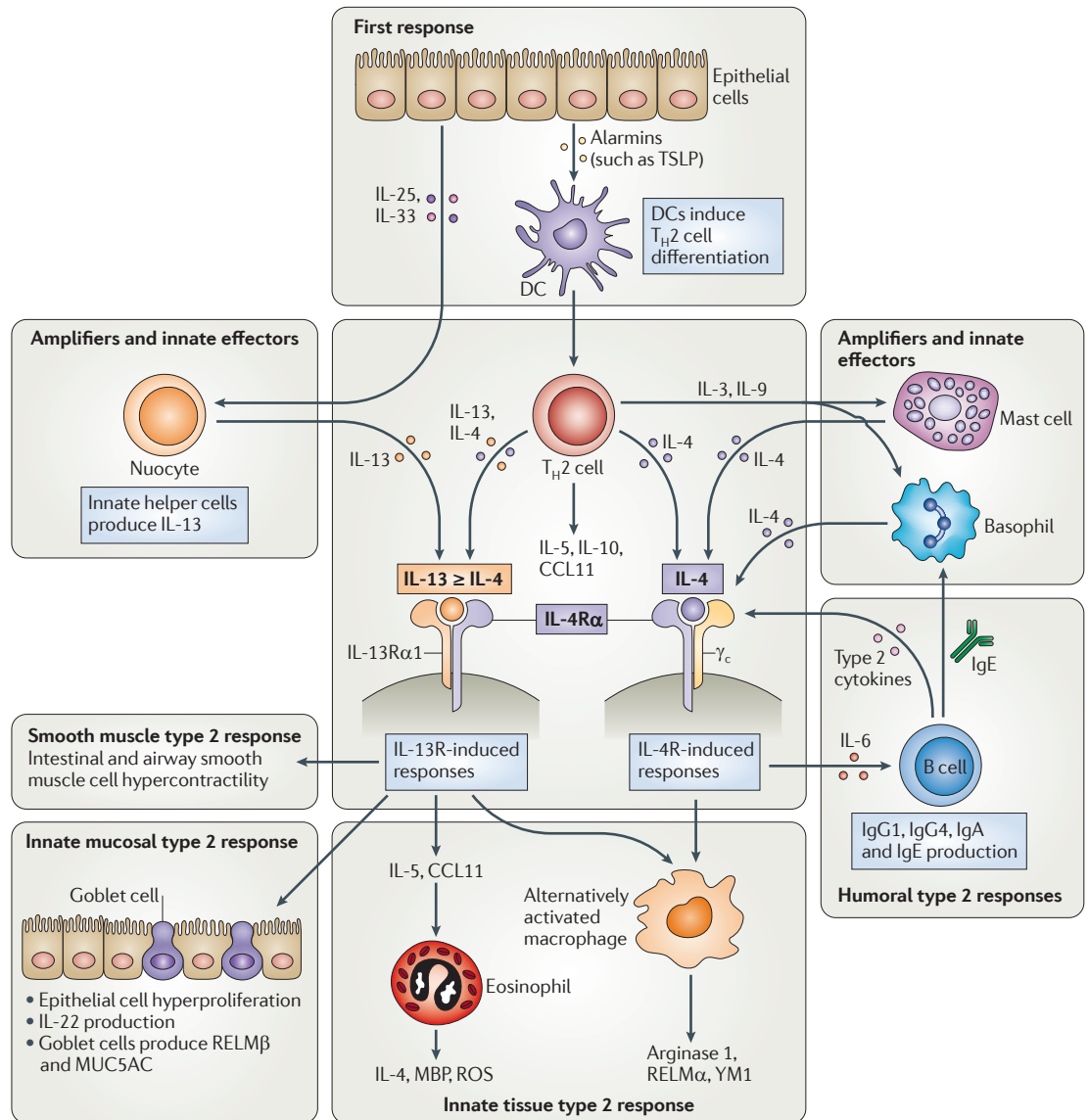


Figure 1 | IL-4R α is at the centre of type 2 immunity. The central role of the interleukin-4 receptor α -chain (IL-4R α) for type 2 immunity is illustrated. IL-4R α may combine with the common γ -chain (γ_c) or IL-13R α 1 to bind IL-4 alone, or both IL-4 and IL-13, respectively. The relative potency of IL-4 and IL-13 in signalling through the type II receptor (IL-4R α –IL-13R α 1) may depend on the surface concentrations of each receptor subunit, with IL-13 being more effective than IL-4 at inducing receptor signalling when the levels of IL-13R α are low¹⁶⁹. CCL11, CC-chemokine ligand 11; DC, dendritic cell; MBP, eosinophil granule major basic protein; MUC5AC, mucin 5AC; RELM, resistin-like molecule; ROS, reactive oxygen species; TSLP, thymic stromal lymphopoietin; T_H2, T helper 2.

The central player in type 2 immunity is certainly the CD4⁺ T_H2 cell, which expresses some or most of the cytokines listed above, as well as key chemokines, such as the CC-chemokine receptor 3 (CCR3) ligand CC-chemokine ligand 11 (CCL11; also known as eotaxin 1). In classic studies, mice depleted of CD4⁺ cells did not mount a protective immune response following vaccination with *Schistosoma mansoni*¹⁰ and lacked the ability to expel the intestinal helminth *Nippostrongylus brasiliensis*¹¹. However, transfer of IL-4-expressing CD4⁺ cells led to worm expulsion in T cell-deficient mice¹². Furthermore, deficiencies in key signalling molecules associated with type 2 immune cells increase the

susceptibility of mice to infection with helminths, and mice lacking the IL-4 receptor α -chain (IL-4R α), signal transducer and activator of transcription 6 (STAT6)¹³ or the transcription factor GATA-binding protein 3 (GATA3)¹⁴ show highly compromised anti-helminth immunity.

IL-4R α , which is a component of both the IL-4 and IL-13 receptors, is in fact the nexus of type 2 immunity (FIG. 1), as shown by the suite of effector mechanisms driven by IL-4 and/or IL-13. These two key inducer cytokines can be produced by innate as well as adaptive immune cells, with innate IL-4 and IL-13 being required for timely expulsion of *N. brasiliensis*¹⁵. Recent

studies of IL-4 and IL-13 expression patterns in mice have shown that significant numbers of cytokine-producing non-B, non-T cells (NBNT cells) are found during helminth infection^{16–19}. In particular, this work has highlighted the contribution of a new type of innate helper cell (also termed a ‘nuocyte’ or ‘natural helper’ cell) that is among the first to produce type 2 cytokines following helminth infection. These cells create conditions that favour T_H2 cell induction and, after receiving signals from differentiated T_H2 cells, they continue to release IL-13 and promote type 2 immunity. In the absence of these innate helper cells (for example, in IL-25-deficient mice, as discussed in detail below), T_H2 cell immune responses during helminth infection are greatly impaired.

Irrespective of their cellular source, type 2 cytokines mobilize a broad range of downstream effector mechanisms⁸ (FIG. 2). In the gut, epithelial cells express IL-4R α and act both as key sentinels²⁰ and as responders to promote goblet cell differentiation, the enhancement of mucus secretion²¹ and the production of resistin-like molecule- β (RELM β), which is an innate protein with direct anti-helminth activity^{22,23}. In addition, IL-4R α ligation stimulates intestinal muscle hypercontractility²⁴ and accelerated epithelial turnover²⁵ to promote the ‘epithelial escalator’, which functions together with epithelial secretions to dislodge resident parasites. Mucosal mast cells multiply in the infected gut in response to IL-9 (REF. 26) and IL-18 (REF. 27) and release mast cell proteases that can degrade tight junctions, thereby increasing fluid flow as part of the ‘weep and sweep’ response. IL-4 and IL-13 also drive the alternative activation of macrophages, and this is implicated in trapping *Heligmosomoides polygyrus* in the gut wall²⁸. As the helminth worm is several orders of magnitude larger than any host cell, macrophage-mediated killing of helminths may be a protracted affair, in which these cells impose a slow death by compromising worm vitality rather than providing an immediate lethal hit.

In non-mucosal tissues, parasites must be destroyed rather than excluded, and the type 2 response is consequently very different. In the tissues, effector mechanisms can involve the full panoply of innate immune cells in different settings⁸, with antibody also acting to ‘arm’ Fc receptor (FcR)-expressing effector cells. Basophils produce high levels of IL-4 to drive T_H2 -type responses during both mouse²⁹ and human³⁰ helminthiasis, and act as effectors to promote parasite killing during challenge infections of immunized animals^{31,32}. However, basophils are not essential for the clearance of primary *N. brasiliensis* infection³³, perhaps as they are not sufficiently armed with parasite-specific antibody at that point. Although eosinophils can prove crucial in producing early IL-4 (REF. 34), they are generally participants and amplifiers of immunity rather than indispensable players^{15,35,36}. Similarly, neutrophils can also attack helminth larvae in response to IL-4 and IL-5 (REFS 37,38), but the relative importance of each host cell type depends on both the tissue in question and the differential susceptibilities of individual helminth species to attack. Often, the most important tissue site in

terms of helminth immunity is the lung: this is the focal point traversed by schistosome, hookworm and other migrating larvae, and CD4⁺ T cell-dependent immunity can be initiated here³⁹. In addition, the lung is a potent locale for the IL-4R α -dependent alternative activation of macrophages, which then produce arginase 1, chitinase 3-like proteins 3 and 4 (also known as YM1 and YM2, respectively) and RELM α (rather than RELM β , which is a product of epithelial cells in the gut)^{40,41}.

The humoral profile of T_H2 -type immunity centres on the elevation of the levels of IgG1, IgE and (in humans) IgG4 isotype antibodies. Although these isotypes are dependent on cytokines that can be derived from both innate and adaptive sources (namely, IL-4 and (in the case of IgG4) IL-10 (REF. 42)), innate helper cells cannot substitute for T cells in providing CD40-mediated co-stimulation of B cells. Antibodies are particularly important for mediating protection against the extraintestinal stages of helminth infections, including the encysted stages of intestinal parasites⁴³. On the other hand, B cell- or immunoglobulin-deficient mice show only minor differences in susceptibility to most primary helminth infections compared with control mice, although antibodies act to reduce the ‘fitness’ of *H. polygyrus*⁴⁴. In humans⁴⁵ and sheep⁴⁶, there is a good association between IgE production and acquired immunity to helminth infections, but evidence in mice is more limited, perhaps owing to poor expression of the high-affinity IgE receptor on mouse eosinophils⁴⁷. Nonetheless, there is *in vitro* evidence that IgE can kill helminth larval stages through antibody-dependent cellular cytotoxicity mechanisms⁴⁸, and both eosinophils and IgE are required for vaccine-mediated protection against larval *Onchocerca volvulus* in mice⁴⁹. Thus, IgE may be a crucial means by which incoming larvae are killed during concomitant or secondary infection.

There are important subtleties, in both antibody and cytokine responses, in the mix and balance of the T_H2 -type response. High IgG4 levels, and depressed IgE levels, are seen both in chronic human helminth infections, in which effector immunity is muted⁵⁰, and in desensitized allergy patients, in whom a modified IgG4-dominated T_H2 -type response is associated with the resolution of symptoms⁵¹. Moreover, in some specific instances immunity to helminths does not require the T_H2 cell pathway at all, being more T_H1 cell dependent^{52–54}.

Why did type 2 immunity evolve?

The crucial role for T_H2 cells in protection against helminths suggests that type 2 immunity is the evolutionarily appropriate response to worms. Indeed, exposure to any large metazoan, including ectoparasites, can trigger a T_H2 -type immune response and its downstream consequences⁵⁵, but how did a distinct pathway for multicellular pathogens evolve? Classical T_H1 cell-induced inflammatory mediators certainly damage worms⁵⁶, but at a substantial cost in collateral damage to host tissue. Clearly, macroparasites cause extensive tissue disruption while migrating through the host. Thus, in evolutionary terms, type 2 immunity may have

Non-B, non-T cells

(NBNT cells). Cells that are distinct from immunoglobulin- or T cell receptor-bearing lymphocytes, basophils, eosinophils, mast cells and natural killer T cells and can produce T helper 2 (T_H2)-type cytokines.

Tight junctions

A tight junction is a belt-like region of adhesion between adjacent epithelial or endothelial cells that regulates paracellular flux. Tight-junction proteins include the integral membrane proteins occludin and claudin, in association with cytoplasmic zonula occludens proteins.

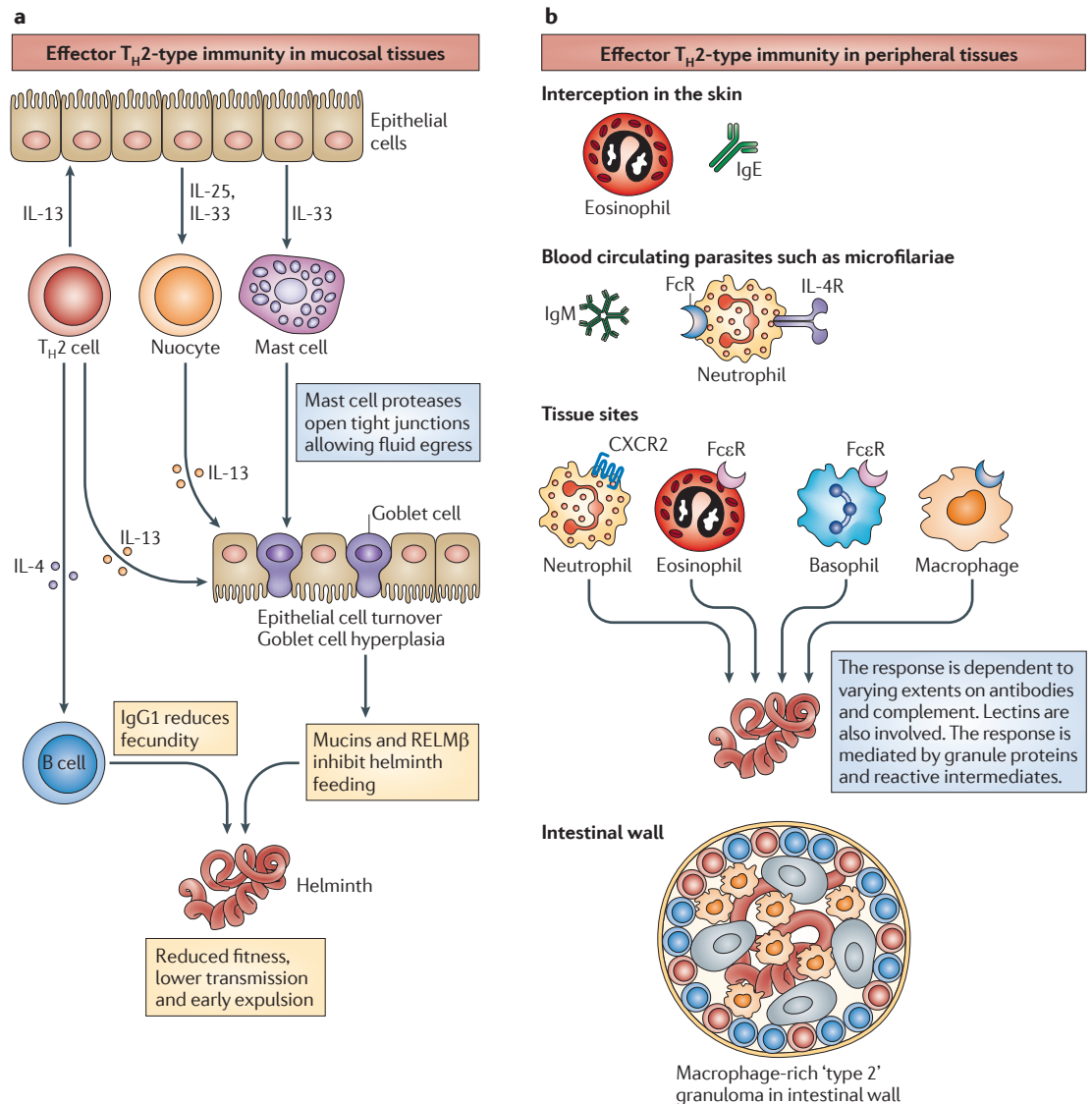


Figure 2 | T_H2 -type effector mechanisms in immunity to helminths. Pathways of immune clearance mediated by T helper 2 (T_H2) cells are more clearly defined in the intestinal setting than in the tissues, but in both instances multiple mechanisms come into play. **a** | In mucosal immunity to helminths, T_H2 -type responses are initiated and sustained by innate populations (including the epithelial cell layer) through interleukin-25 (IL-25) and IL-33 (REF. 19). Epithelial cells are also one of the principal targets of T_H2 -type cytokines, as IL-13 increases cell turnover (resulting in the 'epithelial escalator')²⁵ and induces the differentiation of goblet cells, which produce mucins and the anti-nematode protein resistin-like molecule- β (RELM β)^{21,22}. Fluid transfer into the gut is raised by the action of mast cell proteases, which degrade tight junctions in the epithelial cell layer²⁶, adding to the 'weep and sweep' process. Antibodies from B cells also contribute by diminishing worm fitness and fecundity⁴³. **b** | In the tissues, parasites are open to attack by the full range of host innate effectors, including macrophages⁷, neutrophils³⁷, eosinophils¹⁷⁰, basophils³¹ and platelets¹⁷¹ (not shown). The ability of these effector cells to kill helminths is often dependent on one or more isotypes of specific antibody (often IgE, but IgM in the bloodstream) and complement. Armed granulocytes or macrophages can release damaging metabolic oxygen and nitrogen intermediates onto helminths, but *in vivo* killing methods are not yet fully understood. CXCR2, CXC-chemokine receptor 2; FcR, Fc receptor; IL-4R, IL-4 receptor.

arisen from our innate response to tissue injury, with repair responses isolating and encapsulating macroparasites through the deposition of extracellular matrix proteins while simultaneously resolving localized damage⁵⁷ (FIG. 3). Many facets of anti-helminth immunity, such as mucus production by epithelial surfaces, are consistent with evolutionary origins in wound-healing pathways⁵⁸.

Furthermore, IgE functions largely through its ability to bind to eosinophils and mast cells, which are both major players in the response to tissue injury^{59,60}. This suggests that during the evolution of the adaptive immune system, antibody isotypes that enhanced resistance to helminths (or indeed, arthropod ectoparasites) were specifically tailored to work with cells involved in repair.

IgE may also have evolved to provide a mechanism for parasite control that reduces the risk of self damage, because it fails to activate complement, a major mediator of autoimmune disease.

The anti-inflammatory nature of type 2 immunity is consistent with tissue repair pathways because classical inflammation must be controlled before healing can be initiated⁶¹. This is illustrated by the dual anti-inflammatory and wound healing functions of T_H2 -type cytokines, such as transforming growth factor- β (TGF β). Indeed, chronic microbial infections that cannot be fully controlled by T_H1 - or T_H17 -type immune responses progressively induce more T_H2 -type responses, which dampen inflammatory damage, repair injured tissue and restore homeostasis⁶². Strongly linked with T_H2 -type responses are other factors that maintain homeostasis in the face of macropathogen assault, such as the production of toxin-specific neutralizing antibodies⁶³. Importantly, the association of type 2 immunity with wounding and the maintenance of homeostasis can also be observed in fish such as Atlantic salmon (*Salmo salar*)⁶⁴.

Although healing appears to be largely normal in mice that are deficient in key components required for type 2 immunity, subtle differences are emerging, most notably in the rate of repair^{57,65}. T_H2 cell-mediated rapid repair may be essential when the organism or tissue cannot afford to wait for a slow healing process; for example, when gut integrity is compromised by a blood-feeding hookworm. The association of IL-13 and, in particular, alternatively activated macrophages with scar tissue suggests that perhaps T_H2 -type responses promote repair that is 'fast and dirty', allowing rapid wound closure at the cost of full tissue integrity⁵⁷. T_H2 -type responses can induce proteins that are associated with injury or repair — such as arachidonate 12-lipoxygenase and arachidonate 15-lipoxygenase, triggering receptor expressed on myeloid cells 2 (TREM2), arginase 1 and RELM proteins — and many of these proteins also have roles in down-regulating inflammation and/or in parasite killing^{65–70}. Thus, type 2 immunity has three major components: wound repair, inflammatory control and helminth resistance, all of which combine to maintain homeostasis in the infected host.

Innate initiation of the T_H2 -type response

Evolutionary considerations may address a major unknown: how the immune system is alerted to the presence of helminths and can appropriately select the T_H2 -type pathway of immunity. In contrast to the archetypal Toll-like receptor (TLR)-mediated, IL-12-promoted stimulation of T_H1 -type immune responses⁷¹ and the dectin-responsive, spleen tyrosine kinase (SYK)-mediated initiation of the T_H17 cell pathway⁷², the inception of T_H2 cell differentiation is not understood. Earlier hypotheses that T_H2 -type responses represented a 'default' state, resulting from suboptimal stimulation, did not account for helminth antigens that show dominant T_H2 cell-promoting activity in a T_H1 cell-favouring immune environment^{73,74}. As the T_H2 -type outcome is almost universal in helminth infections, one suspects the involvement of a parallel, conserved recognition

pathway that is responsive to metazoan molecular signatures, perhaps those associated with the potential of these organisms to induce tissue injury⁷⁵. Consistent with this, tissue injury alone is sufficient to induce innate type 2 responses⁷⁶.

Exciting and relevant developments have highlighted the importance of mucosal epithelial cells for the initiation of type 2 immunity. Although it is self-evident that the barrier layer is the first to be exposed to, or breached by, pathogens, we have recognized only recently the unique sensitivity of the intestinal epithelium (for example, through the identification of TLR expression) and its capacity to raise the alarm through the production of IL-25, IL-33 and thymic stromal lymphopoietin (TSLP)²⁰. Alarm-driven innate lymphocytes are then recruited and release IL-4 and IL-13, thereby promoting an early T_H2 -skewed response⁴. The newly differentiated T_H2 cells feed back (through an unidentified pathway) to maintain the innate helper cell populations, and also drive goblet cell differentiation and the production of mucus and RELM β within the epithelial layer. Thus, innate IL-25 production not only stimulates IL-13 production from innate helper cells but is further promoted by IL-13 in a positive circuit that maximizes the T_H2 -type response⁷⁷.

In keeping with the proteolytic activity of tissue-migrating helminths, proteases have been consistently implicated in T_H2 cell activation and can directly induce epithelial cells to produce TSLP⁷⁸, one of the T_H2 cell-inducing alarmins. Indeed, the defining feature of the alarmin cytokines is their ability to alert the immune system to tissue injury. For example, functionally active IL-33, another potent inducer of T_H2 -type cytokines, is released from the nucleus following necrotic but not apoptotic cell death of fibroblasts, endothelial cells and epithelial cells⁷⁹.

However, tissue injury alone does not induce full T_H2 cell activation⁷⁶, whereas soluble helminth products can^{80–82}. T_H2 cell-inducing helminth-derived molecules have been described, but we are still mostly ignorant of the nature of these molecules and of the receptors that presumably exist on innate immune cells to recognize helminth products. The fact that T_H2 -type responses are intact in the absence of myeloid differentiation primary response protein 88 (MYD88) and TIR-domain-containing adaptor protein inducing IFN β (TRIF)^{83,84} argues that the initiation of T_H2 -type immunity is independent of, if not totally unconnected to, the TLR system. Some early indications are that C-type lectin receptors (CLRs) ligate helminth glycans⁸⁵, activating the SYK intracellular pathway in the case of schistosome egg antigens (SEAs) and the CLR dectin 2 (also known as CLEC6A)⁸⁶. The identification of the SEA-derived antigen omega 1 (REFS 81,84) as an intrinsic driver of the T_H2 -type response may now clarify a receptor pathway on innate cells responsible for this crucial decision.

Although the molecular events remain obscure, the stimulation of T_H2 cell differentiation has been attributed to a diverse range of cell types, including most recently and controversially basophils, which were reported to be able to induce T_H2 cell responses *in vitro* and *in vivo*⁸⁷.

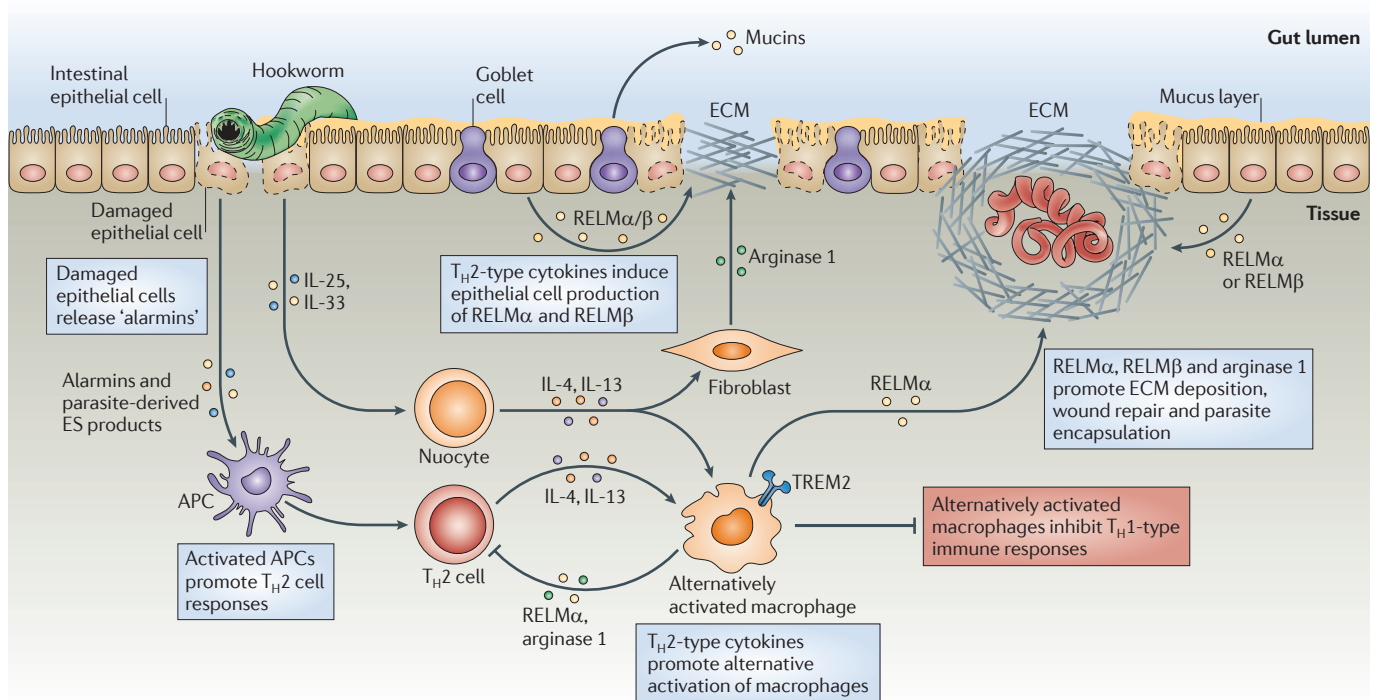


Figure 3 | Type 2 immunity in the repair of parasite-induced damage. Parasites such as hookworms repeatedly breach the gut wall, and the resulting cell death leads to the release of alarmins, such as interleukin-33 (IL-33). These molecules, along with parasite products, promote a type 2 response, either directly by acting on innate cells or indirectly through antigen-presenting cells (APCs) that induce T helper 2 (T_H2) cells. Macrophages in this setting may be predominantly anti-inflammatory, suppressing T cell responses through arginase 1 production and inhibiting classical macrophage inflammation and recruitment through the production of arginase 1, triggering receptor expressed on myeloid cells 2 (TREM2) and other molecules. Epithelial cells stimulated by T_H2 -type cytokines can induce resistin-like molecule- α (RELM α) or RELM β , which contribute to wound repair, while arginase 1 from fibroblasts may promote extracellular matrix (ECM) deposition that can either repair damage or encapsulate worms. ES, excretory secretory.

However, although *in vivo* depletion of dendritic cells (DCs) inhibits the induction of a T_H2 -type immune response to *S. mansoni*, T_H2 cell differentiation in response to this pathogen is not affected by basophil depletion⁸⁸. Hence, as shown by adoptive transfer of helminth-pulsed DCs^{73,89}, the adaptive T_H2 -type response is dependent on and driven by conventional DC populations. In human DCs too, exposure to SEAs leads, via CLR recognition, to the induction of T_H2 cells⁸⁵. Taken together, these data demonstrate that DCs alone can drive T_H2 cell differentiation, even when other innate populations have not been exposed to helminths. Basophils, therefore, may only rarely be responsible for the initiation of T_H2 -type immunity against helminths⁸⁷, and their main role could instead be to amplify the type 2 response^{30,90}. With intensifying interest in the helminth–DC interface (reviewed in REF. 91), the outstanding issue is now to identify which particular DC signals induce the T_H2 cell differentiation programme in naive T cells⁹².

Duplication and diversity in type 2 immunity

The controversy over the role of basophils in T_H2 cell induction may illustrate a more general point that the immune system has repeatedly duplicated and reduplicated essential functions, generating widespread

operational redundancy. Hence, identifying the physiologically important cell population (or the particular cytokine) necessary for T_H2 -type immunity is highly context dependent, with the type 2 response itself incorporating both the innate and adaptive arms of the immune system, mirroring the important roles of both natural killer (NK) cells and T_H1 cells in interferon- γ (IFN γ) production. For example, worm expulsion normally requires the presence of T_H2 cells, but exogenous IL-25 or IL-33 can induce sufficient IL-13 production from innate helper cells to stimulate goblet cell-dependent worm expulsion in the intestinal epithelium¹⁶. Similarly, innate sources of IL-4 and IL-13 drive full alternative macrophage activation in recombination activating gene (RAG)-deficient mice^{41,76}, but CD4⁺ T cells are needed for sustained activation during chronic helminth infection⁷⁶. Often, then, the innate immune system offers a less potent force, but one that maintains a close parallel to the adaptive response.

The requirement for T cell licensing of ongoing innate reactivity imposes an inherent limitation on the innate type 2 response, ensuring that it is appropriately calibrated and directed *in vivo*. Furthermore, multiple cell types participate in responding to IL-13 and in amplifying type 2 immune responses; for example, even when only smooth muscle cells fail to express

Recombination activating gene (RAG)-deficient mice
Recombination activating genes are involved in creating the double strand DNA breaks necessary for producing the rearranged gene segments that encode the complete protein chains of T cell and B cell receptors. Mice that are deficient for these genes fail to produce B and T cells owing to a developmental block in the gene rearrangement that is necessary for antigen receptor expression.

IL-4Ra, goblet cell hyperplasia is diminished and expulsion of *N. brasiliensis* is significantly delayed⁹³. TSLP illustrates a further example of the highly context-dependent nature of cellular crosstalk in T_H2-type immunity. TSLP sensitizes DCs to promote a T_H2 cell developmental pathway, but although the TSLP–DC dialogue is essential for T_H2-type immunity to *Trichuris muris*⁹⁴ it is not required for T_H2-type responses to other intestinal nematodes, such as *H. polygyrus* and *N. brasiliensis*⁹⁵. This perhaps reflects the fact that the T_H1/T_H2 dichotomy is more finely balanced in *T. muris* infection, whereas during other helminth infections TSLP may act as an enhancer rather than as an essential stimulus of type 2 immunity. In addition, the fact that *H. polygyrus* and *N. brasiliensis* can mimic the activity of TSLP and block DC production of IL-12p70 (REFS 73,96) could explain why TSLP is not essential for T_H2 cell development following infection with these species.

This mix of redundancy and diversification is further seen in the broad range of cells targeted by type 2 cytokines. Although basophils, eosinophils, mast cells, neutrophils and macrophages each express a specific set of effector molecules, they also share expression of a number of proteins associated with type 2 immunity, such as chitinase 3-like protein 3, RELMα and arginase 1. These molecules are also expressed by several non-haematopoietic cells, in particular epithelial cells. However, expression patterns (of both RNA and protein) differ depending on the tissue localization and the stage of infection⁷. The challenge will be to determine when proteins have cell-specific as opposed to redundant roles. For example, arginase 1 can suppress fibrosis, but this function is lost when the arginase 1 gene is specifically deleted in macrophages⁶⁹, suggesting that arginase 1 may be anti-inflammatory when produced by macrophages but have tissue reparative functions when produced by fibroblasts. Similarly, the immune suppressive properties of RELMα^{68,70} may be confined to RELMα produced by antigen-presenting cells (APCs), with epithelial cell production of RELMα being more important for tissue remodeling. Thus, consistent with their expression of IL-10 (REF. 97), TGFβ⁹⁸ and programmed cell death 1 ligand 2 (PDL2)^{99,100}, alternatively activated macrophages may have a predominant regulatory role. But when proteins expressed by alternatively activated macrophages (such as arginase 1 or RELMα) are produced in a different tissue or in the absence of IL-10, these proteins may promote effector immune functions, such as repair or parasite killing. Determining whether molecules exhibit context-specific or cell-specific functions is particularly important for the translation of research findings to the treatment of human disease, as the human cellular expression patterns of many proteins are fundamentally different from those in mice. For example, neutrophils rather than monocytes and macrophages are the primary source of constitutive arginase 1 expression in humans¹⁰¹, but human monocytes have been observed to produce arginase 1 during patent infection with *Brugia malayi*¹⁰².

Selection, competition and anergy among T cells

Despite the dominant T_H2 cell phenotype evident in helminth infections, other CD4⁺ T cell populations can expand during these infections and the T_H2 cell population may diminish over time. This ebb and flow may reflect constant competition between T_H cell subsets, either for the same pool of naive T cell precursors or, subsequently, in the choice of more specialized outcomes, such as differentiation into T follicular helper (T_{FH}) cells¹⁰³ or T_H9 cells, which can arise following combined stimulation with IL-4 and TGFβ¹⁰⁴. Fate competition can also operate when cells that are considered to be ‘committed’ to a particular T_H cell subset are, in fact, relatively plastic and able to switch phenotype under the influence of a differing cytokine milieu¹⁰⁵. In many infections, T_H2 cell dominance is maintained by IL-10-mediated suppression of competing T_H1 and T_H17 cell populations¹⁰⁶, reflecting the role of IL-10 as a necessary component of the T_H2 cell response to helminth infections¹⁰⁷. The importance of this can be seen in schistosome-infected CBA mice, in which this regulatory network fails and exacerbated pathology occurs owing to increased T_H17 cell activity against the schistosome eggs, in place of the T_H2-type response generated in other mouse strains¹⁰⁸. Many other potential interactions between T_H2-type immunity and non-CD4⁺ T cell subsets have yet to be properly explored during helminth infections, although the expansion of CD8⁺ T cell¹⁰⁹ and natural killer T (NKT)¹¹⁰ cell populations is known to occur in many instances.

When the immune system fails to reject parasites and a chronic infection takes hold, the T cell compartment changes more with regard to its state of responsiveness than in its composition of T_H cell subsets. Classic studies on schistosomiasis documented the diminution of hepatic granulomas as the immune response subsides in chronically infected mice¹¹¹. A parallel is clearly seen in chronic human helminth infections, in which a T_H2 cell-dominated immune profile, with high levels of IL-4 and IL-10 production, is accompanied by a muted IL-5 and IL-13 response and an overall loss of T cell proliferative responses towards parasite and bystander antigens^{50,112}. This is suggested to represent a ‘modified T_H2-type response’, as discussed above. The host immune system can thus be in a state of effective tolerance even though many key markers of T_H2-type immunity are still evident.

In human filariasis and in a mouse filariasis model using *Litomosoides sigmodontis*, the chronic phase of infection is marked by T cell anergy, loss of proliferative responses to parasite antigen challenge, reductions in effector cytokine levels and elevated expression of inhibitory immune molecules, such as cytotoxic T lymphocyte antigen 4 (CTLA4). In the mouse model, parasite survival is linked to regulatory T (T_{Reg}) cell activity (see below), and immunity to infection can be boosted only if T_{Reg} cell depletion is accompanied by delivery of CTLA4-specific blocking antibodies or glucocorticoid-induced TNFR-related protein (GITR)-specific stimulatory antibodies to re-stimulate the anergized effector T cell populations^{113,114}. Similarly, anergic T cells are

Anergy

A state of unresponsiveness that is sometimes observed in T and B cells that are chronically stimulated or are stimulated through the antigen receptor in the absence of co-stimulatory signals.

found in both humans¹¹⁵ and mice with schistosomiasis and, in the latter case, these T cells express the anergy protein GRAIL (gene related to anergy in lymphocytes; also known as RNF128)¹¹⁶. Interestingly, anergy induction in murine schistosomiasis, as in filariasis, is linked to a co-inhibitory signalling pathway, in this case via PDL1 interactions¹¹⁷. In humans, if the anergic phenotype is not imprinted on the memory T cell populations, then following curative drug therapy it may be possible to reset the T cell compartment to generate protective immunity. New immunological strategies, particularly those aimed at neutralizing regulatory populations, may achieve this goal.

Regulation: the crucial factor

Human helminth infections exhibit many immune downregulatory phenomena, with helminth-infected populations showing lower levels of immunopathological disease in cohort studies of allergy and autoimmunity. Model system studies have linked helminth infections with marked expansion of populations of immunoregulatory cells, such as alternatively activated macrophages, T_{Reg} cells and regulatory B cells. For example, in *H. polygyrus*-infected mice, forkhead box P3 (FOXP3)⁺ T_{Reg} cells are not only present in greater frequencies than in naive animals, but they also express higher levels of CD103 and are more potent immune suppressors than T_{Reg} cells from uninfected mice^{118,119}. Moreover, many allergic and autoimmune inflammatory conditions can be ameliorated by a range of different helminth infections^{120–123}. One key question is whether regulatory cells are simply reacting homeostatically to control helminth-induced pathology. As live, but not dead, parasites can expand T_{Reg} cell populations¹²⁴ and parasites secrete factors that directly induce the conversion of naive T cells into functional T_{Reg} cells¹²⁵, we conclude that the activation of regulatory pathways in response to parasite infection does not solely reflect the immune system's response to inflammation associated with infection.

Accordingly, evidence from humans and mouse models argues for a major role of CD25⁺FOXP3⁺ T_{Reg} cells in controlling pathology and immunity during helminth infections. In patients with filariasis, helminth-induced pathology is associated with a deficiency in CD25⁺FOXP3⁺ T_{Reg} cells¹²⁶, and intestinal nematode infection levels correlate with both the production of IL-10 and TGFβ¹²⁷ and generalized T cell hyporesponsiveness¹²⁸. In mice, CD25⁺ T_{Reg} cells restrain the immunopathological response towards eggs during schistosome infection¹²⁹ and towards *T. muris*¹³⁰ in the gut. Moreover, as mentioned above, depletion of CD25⁺ T_{Reg} cells results in enhanced immunity to filarial nematodes in mice when combined with antibodies to GITR or CTLA4 (REFS 113,114).

FOXP3-expressing T_{Reg} cells may arise either directly from developing T cells in the thymus, or subsequently when naive peripheral T cells are induced (for example, by TGFβ) to convert and express FOXP3. Expansion of both types of regulatory T cell population has been demonstrated in helminth infections. In *L. sigmodontis* infection, prior depletion of natural T_{Reg} cells reduces the

total FOXP3⁺ T_{Reg} cell response to infection and results in greater filarial worm survival⁵. However, we have also shown that FOXP3⁺ ovalbumin-specific T cells are converted at a high rate to FOXP3⁺ cells in *H. polygyrus*-infected mice, and that this parasite releases a product that mimics mammalian TGFβ in driving the conversion of naive peripheral T cells into suppressive FOXP3⁺ T_{Reg} cells¹²⁵. Other helminths adopt different ploys; for example, SEAs from *S. mansoni* do not directly induce T_{Reg} cells, but instead act on DCs to promote their induction of FOXP3-expressing CD4⁺ T cells¹³¹. Furthermore, T regulatory type 1 cells (T_R1 cells) are also induced by human DCs exposed to schistosome-derived lysophosphatidylserine¹³² and show increased frequency in patent (microfilaraemic) filariasis carriers¹³³.

Other key immunoregulatory populations demonstrate that the immune system has also duplicated and diversified its regulatory mechanisms. For example, regulatory B cells are active in patients with multiple sclerosis whose remission is associated with helminth infections¹³⁴, and schistosome-infected mice are protected from anaphylactic shock¹³⁵ and airway allergy¹³⁶ by an IL-10-producing B cell population. Moreover, *H. polygyrus*-infected mice generate regulatory B cells that can, on transfer to naive hosts, downmodulate both allergy and autoimmunity in a manner that is not IL-10 dependent¹³⁷.

Innate effectors targeted by T_H2 -type cytokines can also act as regulators. Alternatively activated macrophages are able to block inflammatory proliferation of lymphocytes at the same time as mediating immunity to tissue helminths and repairing tissue that has been damaged by parasites^{7,138}. Eosinophils, the prototypical ' T_H2 -type effector cell', produce TGFβ¹³⁹ and promote tissue remodelling¹⁴⁰, exemplifying the type 2 triad of counter-inflammation, repair and parasite killing. Such multitasking illustrates how the regulatory network *in vivo* recruits non-professional suppressive cells that are influenced by their signalling and cytokine environment. Equally, epithelial cells are major producers of TGFβ and IL-10, particularly in the gut and airways.

The cost of immunity

A consistent feature of mammalian infection with macropathogens is that complete expulsion or killing of all parasites is rarely achieved¹⁴¹, presumably because the costs of achieving sterilizing immunity exceed the benefits. These costs include not only the energy resources of the immune response itself but also the damage associated with attempting to contain large, often migrating parasites¹⁴². Indeed, immunopathology is frequently the overt disease manifestation associated with helminth infection, as T_H2 -type immune reactivity in excess is not necessarily 'anti-inflammatory'. In mouse schistosomiasis, IL-13-mediated granulomatous inflammation to eggs lodged in the liver causes severe disease, mirroring life-threatening human hepatosplenic schistosomiasis^{143,144}. In this case, pathology is restrained by IL-10 (REF. 145) and by a decoy receptor for IL-13 (REF. 143), illustrating the fact that T_H2 -type responses can be protective or pathological depending on the balance of

Regulatory B cells

Populations of B cells that downregulate immune responses. These cells are most often associated with production of the immunosuppressive cytokine interleukin-10.

T regulatory type 1 cells

(T_R1 cells). A subset of CD4⁺ regulatory T cells that secrete high levels of interleukin-10 (IL-10) and downregulate T helper 1 (T_H1) and T_H2 cell responses *in vitro* and *in vivo* by a contact-independent mechanism mediated by the secretion of soluble IL-10 and transforming growth factor-β.

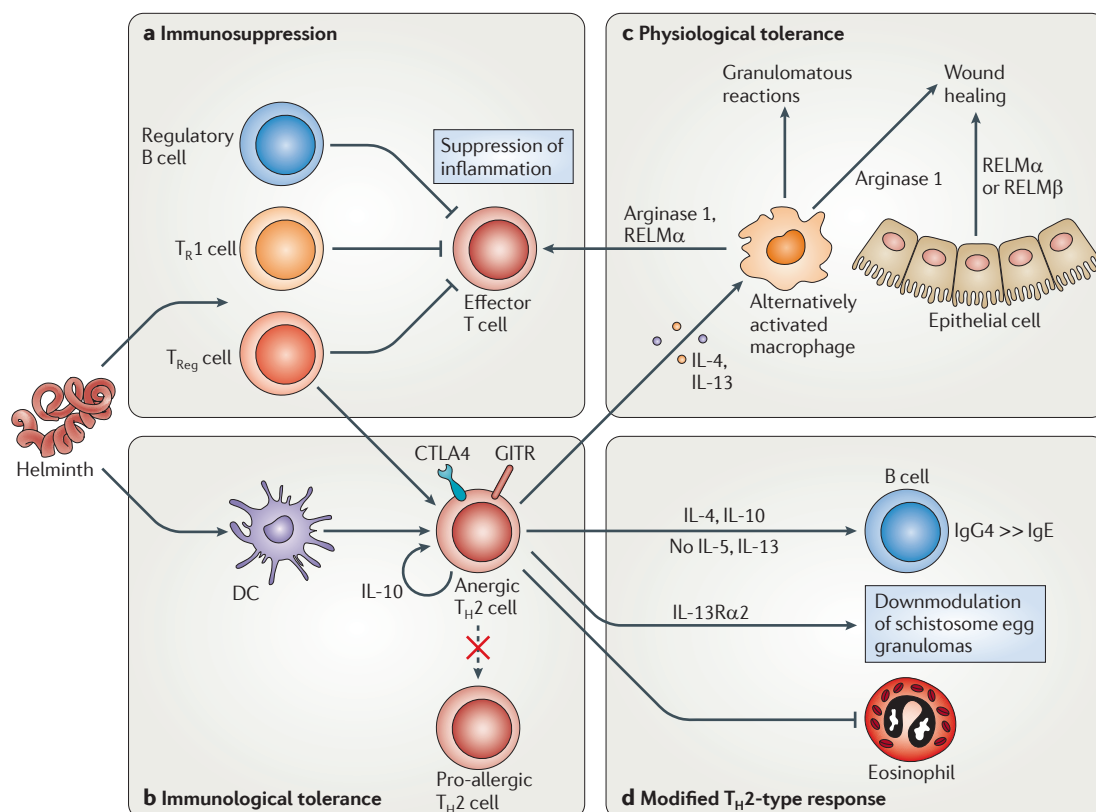


Figure 4 | Homeostasis and tolerance in helminth infections. Four interrelated states of tolerance are illustrated. **a** | In immunosuppression, effector responses are negated by suppressive cytokines released from regulatory lymphocytes, through mechanisms that are well characterized in diverse immunological systems. **b** | In immunological tolerance, effector T helper 2 (T_H2) cells enter a state of anergy and do not progress through to effector cells that would otherwise mediate allergy, for example. The anergic state is marked by the expression of cytotoxic T lymphocyte antigen 4 (CTLA4) and glucocorticoid-induced TNFR-related protein (GITR) and may be maintained by autocrine interleukin-10 (IL-10). **c** | In physiological tolerance, innate cell populations participate in damage limitation and repair, so that the cost of infection is minimized. **d** | In the modified T_H2 -type response, the downstream effects of regulatory mechanisms are muted. This includes switching antibody production to the non-inflammatory isotype IgG4 (in humans), ablation of the eosinophil response (for example in the allergic airway setting) and modulation of the granulomas that form around schistosome eggs. DC, dendritic cell; RELM α , resistin-like molecule- α ; T_{Reg} , regulatory T.

type 2 cytokines produced. Pathology is not restricted to overzealous T_H2 -type responses but, as described above, poor regulation can unleash pro-inflammatory T_H1 - and T_H17 -type immune responses, which are associated with chronic pathology in filariasis¹²⁶ and schistosomiasis¹⁰⁸.

The solution for the host is to create a balance in which the parasite is tolerated, as long as homeostasis can be maintained. Elucidating how this balance is achieved is crucial for our understanding, not only of helminth infection, but of immune regulation in general. Such tolerance (in the physiological sense) requires that self-damage is minimized, and T_{Reg} cells may be crucial for invoking specific immunological tolerance, as discussed above. However, when damage does occur, a more physiological tolerance mechanism will include the ability to repair the damage. Ecologists elegantly describe this balance between resistance and tolerance¹⁴⁶, but infer that these are opposing forces. In fact, T_H2 -type effector pathways provide evidence that tolerance, in the form of immune regulation, and wound repair can occur simultaneously with anti-parasite effector function. Type 2

immunity probably evolved as a means to maintain homeostasis in the face of macroparasite attack (FIG. 4), requiring both tolerance and resistance mechanisms to achieve optimal fitness.

The IL-4R α -STAT6 pathway ideally illustrates the concept that tolerance and resistance can be sequential points in the same effector pathway. Receptor ligation results in the production of characteristic alternatively activated macrophage markers (namely, arginase 1, RELM α , chitinase 3-like protein 3 and chitinase 3-like protein 4 (REFS 147, 148)), which are also produced by a range of other cells in response to IL-4 and IL-13 (REF. 7). Arginase 1 provides the best example of a molecule contributing directly to regulation and wound repair as well as to resistance to infection, as its activity generates proline, which is essential for collagen synthesis, and polyamines for cell growth¹⁴⁹. The substrate for arginase 1, L-arginine, is also metabolized by inducible nitric oxide synthase (iNOS; also known as NOS2), which is expressed by IFN γ - and LPS-induced classically activated macrophages. Thus, by competing

Hygiene hypothesis

This hypothesis originally proposed that the increased incidence of atopic diseases in westernized countries was a consequence of living in an overly clean environment, with reduced bacterial exposure predisposing to increased T helper 2 (T_H2)-type allergic responses to harmless antigens. More recently, it has been proposed that an absence of exposure to a broader range of pathogens, including helminths, may weaken the immunoregulatory controls that exist to restrain allergy and autoimmune disease.

for the substrate required for nitric oxide production, arginase 1 is broadly anti-inflammatory. Arginase 1 is also a potent suppressor of T cell activation owing to its ability to deplete local L-arginine, which is essential for T-cell activation¹⁵⁰. Although in chronic helminth infection alternatively activated macrophage-derived arginase 1 suppresses fibrosis through the negative regulation of T_H2 cells⁶⁹, arginase 1 is required for *H. polygyrus* expulsion following challenge of immune mice, possibly through localized deprivation of an essential amino acid²⁸. Thus, arginase 1 contributes to parasite control as well as to immune regulation and tissue repair.

Similar dichotomies exist for RELM α ; this molecule contributes to tissue remodelling^{151–153}, but RELM α -deficient mice exhibit enhanced fibrosis because RELM α can suppress T_H2 cells^{68,70}. A protective function for RELM α has yet to be described during helminth infection but its close relative, RELM β , has direct anti-nematode activity²². Both RELM α and RELM β are induced by IL-4R α signalling and, with 49% amino acid identity, have very similar physical properties. However, RELM α is expressed in alternatively activated

macrophages throughout the body, as well as in bronchial epithelium, whereas RELM β is predominantly expressed in the gut epithelium^{23,40,68}. It seems likely that RELM α will also be found to possess anti-worm properties. Chitinase 3-like protein 3 is similarly implicated in the response to injury^{76,154} and immune regulation^{155,156}, and its relationship to the chitinase family and its abundant secretion by macrophages make it an excellent candidate anti-worm effector molecule. The diversity of arginase 1, RELM α and chitinase 3-like protein 3 functions may correspond to differences in context and in the specific cell-type responding to IL-4 or IL-13, as discussed above. Overall, the picture is emerging in which the immune system is economical with its resources, using pathways that are compatible with both tolerance and resistance and that can be tailored to minimize harm while maximizing parasite exclusion and repair.

Co-evolution of the immune response

It is a truism that the immune system co-evolved with pathogens, even if its evolutionary origins are rooted in cell recognition, tissue repair and the regulation of commensals¹⁵⁷. Generally, this principle is conceptualized in terms of a molecular arms race between effector mechanisms and immune evasion strategies in which receptors, ligands and signalling pathways are constantly matched and mismatched. However, a more quantitative aspect should also be considered — that the intensity of the immune response has evolved in concert with the universe of pathogens. In particular, the immune system has evolved in the constant presence of helminths, while helminths have evolved to dampen, rather than disable, the immune system of their hosts.

A quantitative evolutionary approach can link the reduced incidence of immunopathological diseases in helminth-endemic nations with the identification of genetic loci that increase the likelihood of developing these diseases in Western countries¹⁵⁸. Many of the alleles at such loci regulate the extent and rate of the production of immunologically active proteins. In this adaptation of the ‘hygiene hypothesis’ (which originally posited that increased allergy resulted from diminished bacterial stimulation), we would argue that the immune system has evolved to operate optimally in the presence of helminth downmodulation, so that the level of immune reactivity has been calibrated by evolution to compensate for parasite-induced dampening of immune responses, while minimizing the risk of incurring life-threatening helminth-generated pathology from either uncontrolled worm loads or overzealous inflammatory reactions (shown in red in FIG. 5a). In contemporary societies without endemic helminth infections, pro-inflammatory alleles that evolved to maintain immune fitness are now seen as responsible for immunopathologies in the human population (FIG. 5b). Helminths may also have driven diversification of immunological genes, as populations from countries with high numbers of different helminth species show more extensive single-nucleotide polymorphism (SNP) variation in 100 major immunological loci than populations from historically helminth-sparse regions¹⁵⁹.

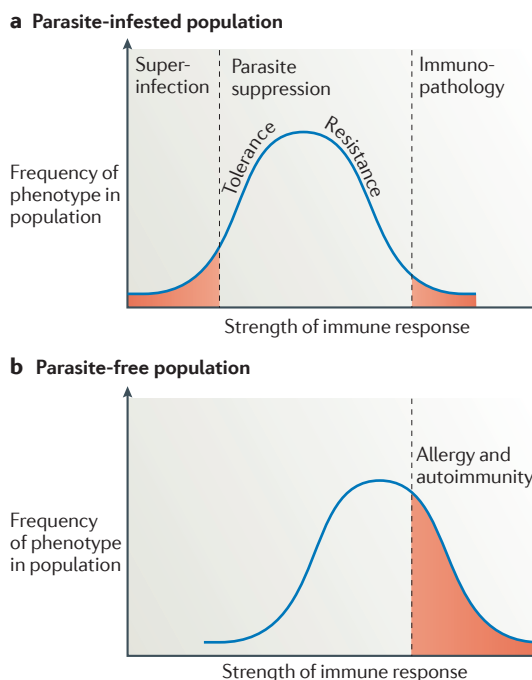


Figure 5 | Evolution of immune responsiveness to compensate for parasite immunosuppression. The human population displays extensive polymorphism in immune-related genes, many of which are non-coding alleles that exert small quantitative rheostat-like effects on the level of immune responsiveness. To evolve the optimal level of responsiveness, alleles that compensate for the mildly suppressive effect of parasites will have been positively selected, with extremes of under- or over-responders relatively rare (a). In modern-day environments, in the absence of parasite immune modulation, more pro-inflammatory genotypes that previously provided a high level of immune fitness may now be associated with the development of pathological allergy and autoimmunity (b).

The immune modulation by helminths in humans and in laboratory rodents, discussed above, has recently been complemented by studies on wild mice (*Apodemus sylvaticus*), in which *H. polygyrus*-infection downregulated tumour necrosis factor (TNF) responses to TLR stimulation¹⁶⁰. Hence, the dampening of immunoreactivity by helminths is likely to have been a significant feature in the evolution of most extant mammalian species, and further investigations into the immunology of wild animal populations may be very rewarding. Indeed, a recent study of Soay sheep showed that a strong immune response allows female sheep to survive harsh winters, during which high nematode burdens are the major determinant of death, but at the cost of reduced reproductive success that was associated with self-reactive antibodies¹⁶¹. Such fitness trade-offs may maintain the observed genetic variation in immune responsiveness.

The host and the parasite: a continuing dialogue

Once T_H2 -type immune responses are initiated by the presence of a helminth, the dialogue is not just between cells of the immune system — the parasites themselves actively contribute to the conversation. As discussed above, helminth parasites induce multiple immunosuppressive mechanisms in the host (including regulatory T and B cells), through the use of molecular pairing between parasite ligands and host receptors (such as the binding of *H. polygyrus* secreted products to TGF β receptors). Perhaps less well appreciated is how helminths themselves specifically respond to their immunological environment. In both human infection and mouse models, *S. mansoni* appear to require host T cells for normal worm development and transmission^{162–164}. In a different scenario, filarial larvae develop normally in the absence of host immune responses but accelerate their development and produce offspring sooner in the presence of eosinophils, the host cell most responsible for larval destruction¹⁶⁵. A similar dependence on host eosinophils has also been reported for *Trichinella spiralis* infections in mice¹⁶⁶. This suggests

that worms are able to adjust their developmental schedule to maximize fitness in the immune environment of a particular host.

Crucially, the dialogue is not just between the host and a single parasite but will normally include additional parasites (both microorganisms and metazoans), which compete with the host and each other for resources. This three-way (or many-way) dynamic has the capacity to dramatically alter patterns of host susceptibility and resistance¹⁶⁷. In the intestinal setting, we increasingly appreciate that these interactions include the commensal flora. As microbial composition can affect systemic responses, in terms of both T_H cell subset development and specific responsiveness to a particular antigen challenge, more attention will need to be paid to how helminths interact with bacterial cohabitants and whether they manipulate the microbial population for their own ends. An early insight into this exciting area has recently been provided by the observation that, on entering the intestine, *T. muris* eggs delay the point of hatching until they detect the presence of colonic bacteria¹⁶⁸, thus ensuring that the larvae emerge into the most favourable environment.

Conclusions

The multiplicity of type 2 components that respond to helminths continues to expand with the discovery not only of new cell types, but of increasing overlap, parallelism and interdependence between cells and their molecular mediators. To understand this complexity, we need to move away from paradigms based on enzyme and signalling cascades and see the type 2 response as akin to a neural network, with a web of interactions and alternative pathways from which activated cell populations can integrate information to select and calibrate their output appropriately. A better appreciation of these circuits will pave the way to understanding helminths and how our response to them has evolved, as well as how to achieve effective immunity in the absence of pathology and, more broadly, how best to modulate the immune system in allergy, autoimmunity and cancer.

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Competing interests statement

The authors declare no competing financial interests.

FURTHER INFORMATION

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