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Competing interests statement

The author declares no competing financial interests.

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OPINION

A worm's eye view of the immune system: consequences for evolution of human autoimmune disease

David W. Dunne and Anne Cooke

Abstract | Humans and the many parasites that we can host have co-evolved over millions of years. This has been compared to an arms race in which the immune armoury of the human has evolved to deal with potential pathogens and the pathogen has evolved strategies to evade, and in some cases use, the immune system of the human host. Recently, there have been marked changes in the exposure of individuals in the developed world to both microorganisms and metazoan parasites, so the immune stimuli such organisms provide no longer have a role in our lives. As we discuss here, this is a marked perturbation, and the absence of the associated immunomodulation might have led to the increased emergence of autoimmune diseases.

Autoimmune disease arises when tolerance to self-tissue breaks down and pathology develops. With the exception of rare autoimmune diseases that result from mutations in a single gene, such as autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED)¹, most autoimmune diseases are influenced by variations at several genetic loci and by environmental factors. A role for the environment in the development

of most autoimmune diseases is indicated by the less than 100% concordance of disease development in monozygotic twins; for example, the concordance rate for **type 1 diabetes** in monozygotic twins is only ~40% (REF. 2). The incidence of some autoimmune diseases, such as type 1 diabetes and **systemic lupus erythematosus**, has been markedly increasing in the developed world on a time-scale that rules out genetic change as an explanation. In the case of type 1 diabetes, which is a T helper 1 (T_H1)-cell-mediated autoimmune disease with juvenile onset, this is particularly important, as it was lethal until Banting and Best³ discovered insulin, in the 1920s. This implies that humans have retained potentially lethal allelic variants of certain genes, either because they have historically conferred a strong selective advantage or because they are in linkage disequilibrium with advantageous alleles. Although the increased incidence of type 1 diabetes could be attributed to exposure to a novel environmental agent, such as a virus, given the lethality of this autoimmune disease, it is more probable that the increase is a consequence of the current lack of infection, which forestalled the onset of diabetes in the past. In recent years, the following proposition has been gaining ascendancy: that, over the past

century, in the developed world, changes in economic and social conditions, as well as a concomitant reduction in exposure to infectious agents (including helminths), have altered the balance between our immune system and infections of historical importance and that this is responsible for the observed increase in autoimmunity. This is paralleled by observations in the field of allergy, in which it has been called the 'hygiene hypothesis'⁴. This does not preclude the possibility that some autoimmune conditions are precipitated by exposure to infectious agents⁵, but there are now many examples of both spontaneous and experimental models of human autoimmune diseases in which infection with a given agent inhibits the onset of autoimmune pathology (TABLE 1). There are many ways in which such infections might be expected to impact on autoimmunity, and it is important to consider that an ideal response to a pathogen would be one that does not inflict collateral damage on host tissue. This raises the issue of immunomodulation, which would be advantageous to both the micro-organism and the host. Insights into immunoregulatory processes and how they might regulate autoimmunity are provided by detailed examination of the life cycles of the infectious agents.

Helminths are old adversaries; helminth larvae have been detected in samples of fossilized animal faeces taken from archaeological sites of the Lower and Middle Pleistocene eras⁶. Schistosomes are members of the class trematoda. Ancestral trematodes were probably single-host parasites of ancient marine molluscs, which with the emergence of predatory vertebrates, developed complex life cycles involving two or more different host species and both sexual and asexual reproduction. The parasites successfully diversified and expanded, accompanying the molluscs as they evolved into terrestrial and freshwater forms; consequently, all classes of vertebrate are now host to many species of trematode, all of which still have intermediate hosts that are snails. The ancestors of the schistosomes that inhabit humans now were probably present in our ancestors before the evolution of humans as a species⁷. So, humans co-evolved with these schistosomes, as also occurred for other common parasitic worms, but the complexity and medico-biological implications of this co-evolution are not yet understood⁸. However, it has been shown that infection with schistosomes or exposure to schistosome-derived antigens prevents a range of autoimmune disorders in experimental animal models, including type 1 diabetes in non-obese diabetic (NOD) mice, experimental

allergic encephalomyelitis (EAE) (an animal model of **multiple sclerosis**) and **Graves' disease** (TABLE 1). We consider that, by examining how a helminth such as *Schistosoma mansoni* might have evolutionarily influenced the host immune system⁹, we can gain insight into the mechanisms that enable autoimmunity to develop in the absence of infection.

Schistosome–host interactions

Schistosome survival in the host. A diagrammatic representation of the life cycle of *S. mansoni* is shown in FIG. 1. At present, in tropical and subtropical areas, ~200 million people are suffering from chronic **schistosomiasis** (BOX 1). Infection of humans occurs when free-living, freshwater schistosome larvae, known as cercariae, come into contact with and penetrate intact human skin. In the skin, the cercariae transform into a schistosomular stage; these parasites then migrate in the blood to the lungs and the liver. After migration, the schistosomulum matures into a male or female adult worm. Schistosomes do not multiply in humans, but adult worms mate in the blood vessels around the gut or bladder, depending on the species. Each female worm produces hundreds of eggs each day, and these need to reach fresh water to release free-swimming larvae (known as miracidia), which actively seek and penetrate the intermediate aquatic snail host. Asexual reproduction in the snail produces thousands of infective cercariae, which can then infect humans. People living in areas in which schistosomiasis

is endemic become infected in early childhood and might remain infected for life, owing to continuing susceptibility to infection and longevity of adult worms¹⁰.

Schistosomes are adapted to, and might promote genetic change in, both their snail and human hosts. In snails, evidence for this is provided by the observation that snail lines can be selected for resistance and susceptibility to specific parasite strains, with specificity being shown by resistance to the parasite strain used for selection and not to a novel strain¹¹. Schistosomes use a wide range of strategies to evade the host immune response: for example, they use molecular mimicry to evade the immune defences of the snail host¹². Schistosome-derived immunomodulating neuropeptides seem to be equally effective in both humans and snails. These might aid immune evasion by the parasite, as their release from parasites at stages of the life cycle that occur in both mammals and snails inhibits the locomotory activity of immune cells from both hosts¹³. In humans, a testament to the ability of these parasites to avoid immune destruction is provided by the observation that individual schistosomes live, fully exposed to the immune system, in the bloodstream for up to 40 years¹⁴. Schistosomes have an impressive array of immune evasion and repair mechanisms, which include the ability to coat themselves in host antigen, to enzymatically cleave antibodies, and to rapidly replace their surface with unique double membranes, using pre-formed membrane vesicles^{15–18}.

Table 1 | **Infectious agents, or their products, that prevent autoimmunity**

Agent or product	Autoimmune disease	References
<i>Schistosoma mansoni</i>	Type 1 diabetes	67
	Experimental allergic encephalomyelitis	68
	Graves' thyroiditis	69
<i>Schistosoma mansoni</i> eggs	Type 1 diabetes	67,71
	Experimental allergic encephalomyelitis	70
	Experimental colitis	72
Soluble <i>Schistosoma mansoni</i> egg and worm products	Type 1 diabetes	32
<i>Hymenolepis diminuta</i>	Experimental colitis	82
<i>Acanthocheilonema viteae</i> secreted product (ES-62)	Collagen-induced arthritis	79
<i>Trichuris suis</i>	Crohn's disease	65,66
<i>Heligmosomoides polygyrus</i>	Inflammatory bowel disease	80
<i>Trichinella spiralis</i>	Experimental colitis	81
<i>Trypanosoma brucei</i>	Collagen-induced arthritis	73
<i>Mycobacterium bovis</i>	Type 1 diabetes	74
	Experimental allergic encephalomyelitis	75
<i>Mycobacterium avium</i>	Type 1 diabetes	76
<i>Streptococcus sanguinis</i> *	Collagen-induced arthritis	77
<i>Bordetella pertussis</i>	Experimental allergic encephalomyelitis	78

*Previously known as *Streptococcus sanguis*.

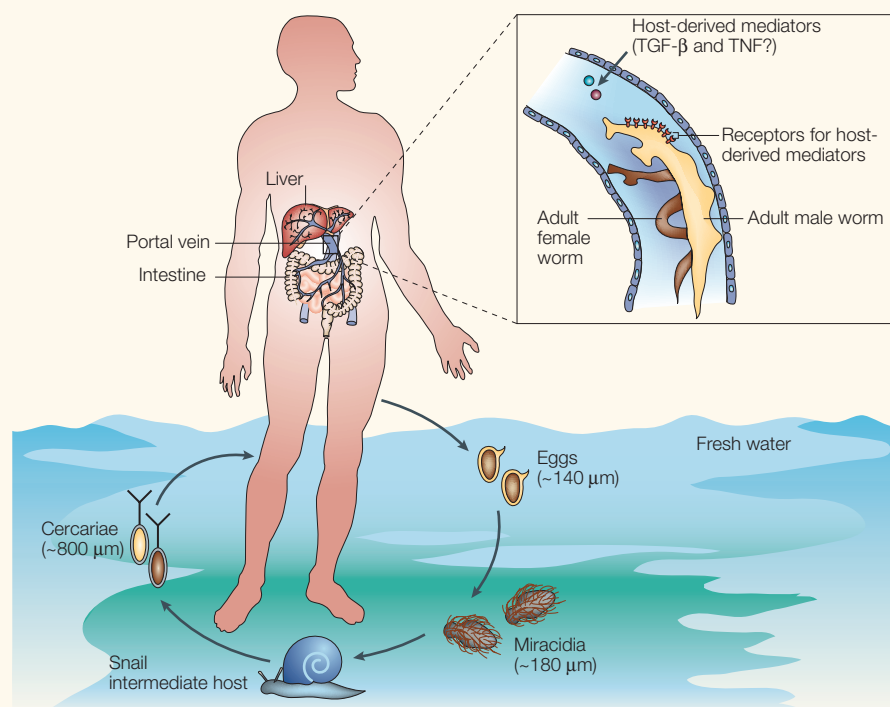


Figure 1 | *Schistosoma mansoni* life cycle. Infection of humans with *Schistosoma mansoni* is initiated by cercariae, which burrow into the skin, transform into schistosomula, enter the vasculature and migrate to the portal system, where they mature into adult worms. *S. mansoni* adult worms mate in the blood vessels. The eggs, which have tough shells, are released by female parasites within the vasculature; they then cross the endothelium and basement membrane of the vein and traverse the intervening tissue, basement membrane and epithelium of the intestine (*S. mansoni* and *Schistosoma japonicum* eggs) or bladder (*Schistosoma haematobium* eggs) en route to the exterior. The passage of eggs to the outside depends on the host immune response. After they have reached fresh water, the eggs release a free-swimming larva (known as the miracidium), which actively seeks and penetrates its intermediate snail host. Asexual reproduction in the snail produces thousands of infective cercariae, which can then infect humans. TGF- β , transforming growth factor- β ; TNF, tumour-necrosis factor.

Schistosomes not only use immune-evasion tactics but also subvert and utilize the host immune response to facilitate their own development and transmission. To move from a human host to a snail host, *S. mansoni* eggs must first translocate from the portal capillaries to the gut lumen. This process depends on host immune responses, as it does not occur in mice that are immuno-suppressed¹⁹ or in mice that have been tolerized to *S. mansoni* eggs²⁰. Egg excretion is also greatly reduced in HIV-infected individuals, in a manner that is proportional to the number of circulating CD4⁺ T cells²¹. The production of eggs by female worms has been suggested to depend on host tumour-necrosis factor (TNF)²². *S. mansoni* worms might also use host transforming growth factor- β (TGF- β) as a regulator of their growth and development²³. A type I receptor serine/threonine kinase (RK1; also known as SmRK1) has been identified on the surface tegument of *S. mansoni* worms²⁴, and it can be activated by human TGF- β and signals through the schistosome molecule Smad2. The recently published transcriptomes of *S. mansoni*²⁵ and *Schistosoma*

*japonicum*²⁶ are now revealing more parasite components that are characteristic of all metazoans, including humans, implying that there are many direct interactions between the parasite and the physiological and immunological processes of its human host. This ability to subvert the host immune response has far reaching consequences and has been shown to influence the immune response to exogenous

antigens, including concomitant infections. In this way, it also has the potential to influence autoimmunity.

Immune response to schistosomes. The initial immune response after an individual is infected is difficult to define, because children gradually acquire more adult worms throughout early childhood. However, this response has been studied in mice infected with *S. mansoni* (FIG. 2). In this model of human infection, a T_H1-cell response to the parasite develops during the first 5 weeks of infection. However, as the infection progresses, and the worms mate and produce eggs, a T_H2-cell response emerges, and the T_H1-cell response wanes²⁷. By the time the immune response is assessed in infected humans, there is a strongly polarised T_H2 response, with increased numbers of eosinophils, basophils and mast cells, and high circulating levels of IgE. There is evidence to indicate that helminths also downmodulate this T_H2 response, because after clearance of the parasite from humans treated with drugs, the *in vitro* parasite-specific T_H2-cell response of peripheral-blood mononuclear cells is further increased²⁸. Interleukin-10 (IL-10)-secreting cells have been found in increased numbers in the peripheral blood of helminth-infected patients, and inclusion of IL-10-specific antibodies in *in vitro* cultures of peripheral-blood mononuclear cells has been shown to increase the cytokine response to parasite-derived antigens²⁹. The production of regulatory cytokines and T cells is therefore also a feature of chronic helminth infections.

The early T_H1-cell response that has been noted after the initial infection in mice might be important for the parasite. When the parasite first enters the host, prostaglandin D₂ (PGD₂) that is produced by the skin stage of *S. mansoni* inhibits the migration of

Box 1 | Human schistosomiasis

Three parasite species — *Schistosoma mansoni*, *Schistosoma japonicum* and *Schistosoma haematobium* — cause most of the human cases of schistosomiasis. After penetrating human skin, the parasites undergo complex transformations while migrating to their preferred intravenous sites, which they reach as mature worms 3–6 weeks later. Most severe morbidity is associated with chronic schistosome-egg-specific inflammation in the tissues of the gut (for infection with *S. mansoni* or *S. japonicum*) or the urogenital tract (for infection with *S. haematobium*). *S. mansoni* and *S. japonicum* eggs also become trapped in the liver, where after many years of infection, chronic T helper 2 (T_H2)-cell-mediated granulomatous responses can lead to gross periportal liver fibrosis and life-threatening hepato-splenic schistosomiasis. Effective treatment, using the drug praziquantel, has been available for 25 years, but the growth of human populations in high-risk areas, as well as the difficulties of delivering mass treatments and the high probability of rapid re-infection after treatment, have thwarted efforts to control the number of human infections worldwide. The *S. mansoni*-infected mouse has proved an invaluable model for the study of many aspects of granulomatous inflammation, fibrosis and T_H1-cell versus T_H2-cell regulation.

Langerhans cells to the draining lymph nodes, thereby delaying the immune response³⁰. Mice that are deficient in DP1, a receptor for PGD₂, do not show this inhibited migration of skin dendritic cells (DCs), and cells in the draining lymph node produce considerably less interferon- γ (IFN- γ) and IL-10, but equal amounts of IL-4, leading to a more T_H2-cytokine-biased response to the parasite³¹. This is associated with a reduced number of developing adult worms and decreased immune responses to parasite eggs, implying that this initial T_H1-cell response favours infection. By studying mice and by examining cell populations *in vitro*, it has been possible to dissect key immunological interactions that influence the outcome of the immune response to parasite infection.

Glycosylated components of schistosome eggs have been shown to affect the production of cytokines by DCs³², and DCs stimulated by egg-derived antigens *in vitro* can promote T_H2-cell responses *in vivo*³³. Indeed, schistosome eggs are such powerful T_H2-cell-response-promoting adjuvants that they can promote T_H2-cell responses to unrelated antigens *in vivo*³⁴. The glycoconjugates that influence DC maturation³⁵ and function such that a T_H2-cell response is induced include lacto-*N*-fucopentaose III (REF. 36), which binds the DC-specific C-type lectin DC-SIGN (DC-specific intercellular adhesion molecule 3 (ICAM3)-grabbing non-integrin)³⁷, and glycoproteins that contain α 3-fucose and core β 2-xylose epitopes³⁸. Recent experiments have shown that lyso-phosphatidylserine from helminth eggs activated Toll-like receptor 2 (TLR2) at the cell surface of DCs and influenced their functional maturation such that they induced IL-10-secreting regulatory T cells³⁹. A schistosome-egg glycoprotein has also been identified that induces the release of IL-4 and IL-13 from basophils, by non-specifically binding and possibly crosslinking cell-surface IgE⁴⁰. Natural killer T (NKT) cells are also activated and stimulated to proliferate by glycolipids that are present in both eggs and worms³². NKT cells, eosinophils and mast cells are therefore all potential sources of IL-4; however, the absence of these cell types does not prevent the establishment of T_H2-cell responses in infected mice^{41,42}. Egg glycoproteins can also bind macrophage mannose receptors, and this might be important in enabling alternatively activated macrophages to dampen inflammatory responses to schistosome eggs, thereby preventing organ damage. These macrophages require IL-4 for their development, and mice that have macrophages deficient in the IL-4 receptor α -chain are extremely

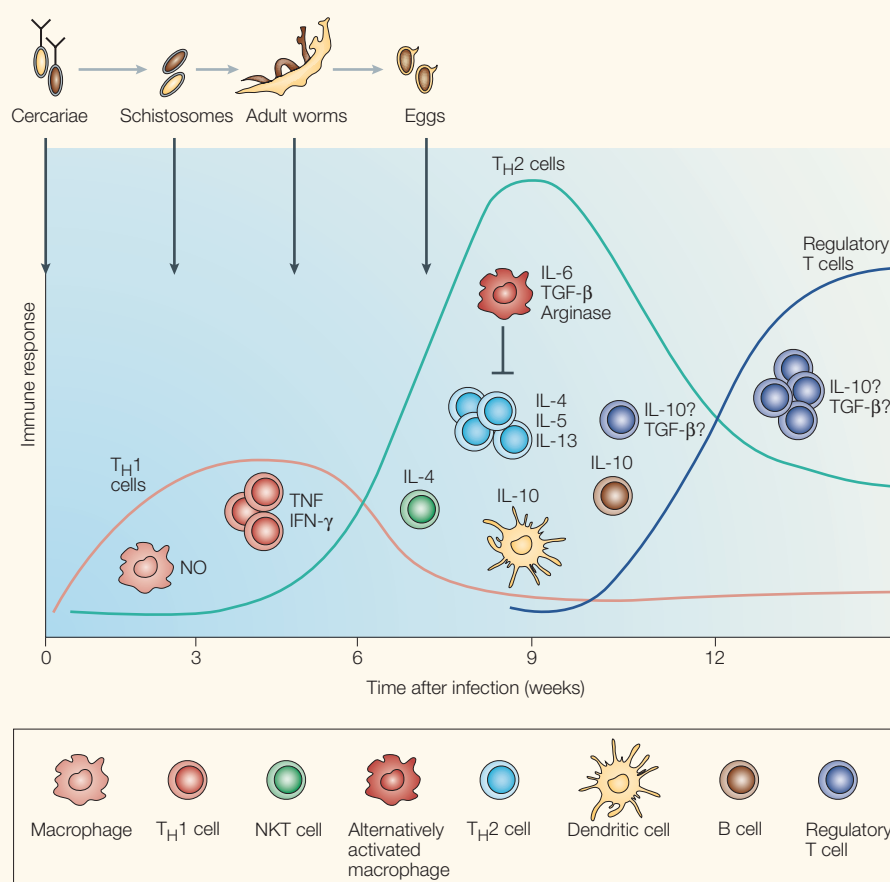


Figure 2 | Induction of T-helper-1- and T-helper-2-cell responses and development of regulatory T cells after infection with *Schistosoma mansoni*. After infection with *Schistosoma mansoni*, the initial immune response that develops is a T helper 1 (T_H1)-cell response. As the worm develops and eggs are deposited, natural killer T (NKT) cells are activated, dendritic cells produce more interleukin-10 (IL-10) and less IL-12, and a T_H2-cell response develops. In addition, both B1 and B2 cells produce IL-10, in response to egg-derived antigens and worm-derived antigens, respectively. Furthermore, populations of alternatively activated macrophages and regulatory T cells also develop. IFN- γ , interferon- γ ; NO, nitric oxide; TGF- β , transforming growth factor- β ; TNF, tumour-necrosis factor.

susceptible to acute morbidity after infection with *S. mansoni*. This morbidity occurs concomitantly with increased levels of T_H1-cell cytokines⁴³.

In addition to a possible role in the maturation of worms, TGF- β might also dampen the host immune response. However, it is not clear which cells in the host produce this cytokine or whether the worms themselves have a role in the activation of latent TGF- β . By contrast, the immunoregulatory cytokine IL-10 is generated by cells of both the innate and adaptive immune systems in response to egg- and worm-derived antigens. Sources of IL-10 include DCs, B cells and CD4⁺CD25⁺ regulatory T cells⁴⁴⁻⁴⁷. The production of IL-10 by DCs and B cells would also facilitate the development of regulatory T cells. Recent studies have highlighted the importance of the cooperative interaction between innate and adaptive sources of IL-10 in the generation of a hyporesponsive state during chronic

schistosome infection⁴⁶. Schistosome-specific phosphatidylserine activates TLR2 at the cell surface of DCs, generating mature DCs with the ability to promote the development of IL-10-secreting regulatory T cells⁴⁸. Regulatory T cells induced by helminths have the potential to suppress the T_H1-cell response to helminth-derived antigens, thereby ensuring T_H2-cell polarization⁴⁹. The induction of regulatory T cells by these mechanisms might be an important way of controlling over-vigorous immune responses during the course of chronic schistosome infection. Indeed, there is evidence of regulation not only of T_H1- but also of T_H2-cell responses in individuals who are infected with *Schistosoma* spp., and infected individuals have been shown to have reduced allergic responses⁵⁰. This is associated with diminished IL-5 production and increased IL-10 production by peripheral-blood mononuclear cells in response to antigens derived from the house dust mite *Dermatophagoides*

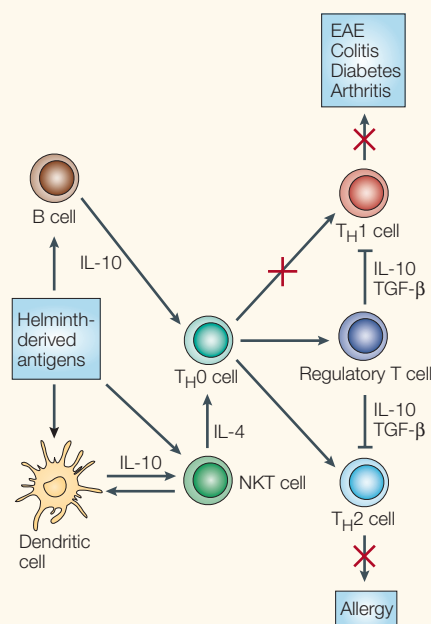


Figure 3 | **Mechanisms by which helminths could impact on autoimmunity and allergy.**

Helminth-derived antigens influence the development of T-cell responses through interactions with dendritic cells (DCs), natural killer T (NKT) cells and B cells. Interleukin-10 (IL-10) production by B cells and DCs could induce regulatory T-cell activity and thereby prevent the development of autoaggressive T helper 1 (T_H1)-cell responses, skewing the response towards a non-autoimmune-disease-promoting T_H2-cell response instead. In addition, regulatory T cells might prevent the development of a range of autoimmune disorders, as well as allergy, through the production of IL-10 and transforming growth factor- β (TGF- β). EAE, experimental allergic encephalomyelitis.

*pteronyssinus*⁵¹. The observation that a range of infectious agents have evolved strategies to induce IL-10 production, or to encode their own surrogate IL-10, indicates that it has proven to be an important mechanism for suppressing host immune responses, even if it is used only in the short term to establish a latent infection (in the case of some viruses) while limiting pathology in the host^{52–54}.

Infection and autoimmunity

From the studies that we have discussed here, it is clear that organisms such as *Schistosoma* spp., which have long been part of the human environment, influence the immune response in infected individuals and have the potential to influence autoimmune responses. Experimental studies in rodents have shown that infection with *S. mansoni* prevents the onset of diabetes, as well as of other autoimmune disorders (TABLE 1). Molecules produced by *S. mansoni* at different stages of its life cycle in the mammalian host have the potential to inhibit both T_H1- and T_H2-cell-mediated

autoimmune pathology through a variety of mechanisms (FIG. 3). First, worm-derived antigens, through their ability to activate NKT cells and induce IL-10 production by B cells, have the potential to inhibit type 1 diabetes and possibly other autoimmune pathologies, such as EAE and arthritis, which are influenced by NKT-cell activity⁵⁵. Interactions of egg-derived antigens with DCs, together with the induction of IL-10, could polarize the immune response to a T_H2-cell response and induce regulatory T-cell populations. In the context of T_H1-cell mediated autoimmune diseases, a skewing of the immune response towards a T_H2-cell response would prevent disease onset, as would the increased activity of regulatory T cells. T_H2-cell-mediated autoimmune pathologies would then be controlled by IL-10 and TGF- β . However, there are additional mechanisms by which autoimmune pathologies could be regulated. For example, adult worms have been shown to secrete opioids and opioid neuropeptides, such as pro-opiomelanocortin-derived peptides and enkephalin, which might modulate the immune response⁵⁶. Alternatively activated macrophages are also induced during infection with *S. mansoni*, and these have the potential to inhibit inflammatory responses⁴³.

Although this article focuses on the effects of infection with *S. mansoni* on autoimmunity, other helminths and microorganisms have been shown to inhibit self-reactivity (TABLE 1). In the past, individuals would have commonly been infected or exposed to more than one of these agents that give rise to chronic infections, and they would have been selected on the basis of their ability to survive such infections. For example, similar to schistosomes, it has been estimated that mycobacteria found a niche in humans 10,000–20,000 years ago; therefore, humans and mycobacteria have had a considerable period to engage in mutual co-adaptation and selection. Indeed, mycobacterial infections and mycobacteria-derived antigens also prevent the onset of diabetes and EAE in mouse models of autoimmunity

(TABLE 1). Protection from the ravages of pulmonary tuberculosis is associated with the production of cytokines such as TNF, IFN- γ and IL-12. It might be predicted, therefore, that there would have been strong selective pressure on human populations for individuals able to mount a robust pro-inflammatory response. This type of response is also one that is associated with autoimmune diseases such as type 1 diabetes or rheumatoid arthritis. Although mycobacterial infections are associated with T_H1-cell responses, it has recently been shown that mycobacteria elicit IL-10 production by host cells. Indeed, the ability to induce IL-10 rapidly might be a virulence factor of mycobacteria, as this dampens down the pro-inflammatory response⁵⁷. The mycobacterial cell-wall component mannoseylated lipoarabinomannan targets DC-SIGN at the cell surface of DCs and induces IL-10 production⁵⁸. This production of IL-10 might contribute to the development of regulatory T-cell populations and inhibit inflammatory responses not only to the pathogen but also to self-antigens (FIG. 3).

Perturbing the balance

Whereas immunoparasitologists might talk about a balance between the parasite and the host, and between an immune response and immune regulation, those concerned with evolution might discuss the arms race between the host and the pathogen or the 'Red Queen hypothesis'⁵⁹ (BOX 2). This states that, from the point of view of the host, the host is running to a stand still on an evolutionary treadmill driven by parasites. This idea could be relevant to the sudden disappearance of parasitic worms (and other infectious organisms) from a proportion of the human population, thereby changing a previously constant part of our immunomodulating internal environment. What happens if the treadmill suddenly stops or if one of the teams in a tug of war lets go of the rope? Relationships between host and guest species range from the virulent to the benign, from mutualism to symbiosis. Although being

Box 2 | **The ‘Red Queen hypothesis’**

The Red Queen hypothesis was originally proposed by Leigh Van Valen⁵⁹ as an explanation for the evolution of sex. During gamete formation, at meiosis, there is the possibility of reassortment and exchange of genetic information between chromosomes, so together with mutation, this contributes to the development of genetically diverse individuals. Such genetic diversity enables the host organism to combat infection. As the host organism evolves in this way, so too does the infectious agent. It is, in essence, a description of the events that occur during the co-evolution of a host and its parasite, in which each is attempting to evade the defences of the other. It is known as the Red Queen hypothesis because it is taken from Lewis Carroll's *Through the Looking Glass* (1872), when the Red Queen tells Alice, "[I]t takes all the running you can do, to keep in the same place."

detrimental to its hosts is a key element in the definition of a parasite, it has been suggested that there might be some contexts, particularly outside the natural ecological environment of the host, in which parasitized individuals have an advantage over uninfected individuals⁶⁰. A particular immune response bias, a T_H1 -cell bias in the case of infections with intracellular pathogens or a T_H2 -cell bias for infections with helminths, could be advantageous for the host until the parasite that this response protects against is no longer present. However, if the checks and balances that prevent the immune response from causing damage to the host also depend on the parasite, the immune response could become a liability. In this situation, we are outside the realm of evolution and into the realm of public health, where perhaps a few parasites are a good thing; if so, they are no longer parasitic but have become symbiotic.

In the context of autoimmunity, studies in animal models show that infection with helminths or with some bacteria prevent the onset of disease. In terms of the mechanism of prevention of autoimmune disease, many of the schistosome-induced host immune responses that are outlined here could have a role. Removal of these infections, and therefore removal of exposure to the immunomodulating agents they encode, could allow the development of type 1 diabetes and other autoimmune disorders, as well as allergy^{61–64} (FIG. 3). In addition, the loss of our former helminth companions might exacerbate T_H1 -cell-mediated autoimmunity through a lack of T_H2 -cell-dependent counter-regulation. It is on this basis that infection with live worms has been advocated as a therapy for inflammatory bowel disease^{65,66}. Owing to our increasing understanding of how these infectious agents harness, utilize and subvert the immune response, it is probable that molecules derived from parasites and bacteria will replace live infection to prevent or control pro-inflammatory pathological responses.

Conclusion

Our immune system has been shaped over time by exposure to infectious agents, some of which harness the host immune response to facilitate their own life cycles. A key element in this co-evolution is the need to dampen down the immune response such that host pathology is minimized. Here, we have considered how alterations in the balance between the host and the parasite could enable pathological responses to emerge in the host. As the molecular mechanisms by which infectious agents interface with the immune system become clearer, we anticipate that a range of parasite-derived biomodulators that can elicit

anti-inflammatory responses will be identified, and these could be of considerable therapeutic value.

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Competing interests statement

The authors declare no competing financial interests.

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