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B cell function in the immune response to helminths

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Abstract

Similar T helper (Th)2-type immune responses are generated against different helminths parasites, but the mechanisms that initiate Th2 immunity, and the specific immune components that mediate protection against these parasites, can vary greatly. B cells are increasingly recognized as important during the Th2-type immune response to helminths, and B cell activation might be a target for effective vaccine development. Antibody production is a function of B cells during helminth infection and understanding how polyclonal and antigen-specific antibodies contribute should provide important insights into how protective immunity develops. In addition, B cells might also contribute to the host response against helminths through antibody-independent functions including, antigen-presentation, as well as regulatory and effector activity. In this review, we examine the role of B cells during Th2-type immune response to these multicellular parasites.

Helminths and the Host Response

Chronic infection with helminth parasites significantly impacts global health; more than 2 billion people world-wide are infected and these parasites can cause high morbidity including malnourishment and anemia. Although drug treatments do exist, re-infection can occur after treatment, typically in parasite endemic areas, and drug resistance is also becoming an issue. As such, the development of effective vaccines against helminths would be a major advance for control and treatment of helminth disease¹. Engineering vaccines that work is benefited by an understanding of the pathogen-specific immune response, so that specific components of immune protection can be targeted. Both antigen specificity and the desired cytokine response should be considered to optimize protective immunity. For many helminths, the T helper (Th)2-type response mediates protection, but the effective components of this response can differ between parasite species and different developmental stages of infection with the same helminth species. This is a result of the specific ecological niche occupied by the invading helminth at different stages of the life cycle, including the microenvironment where the parasite takes up residence and the specific host:parasite interactions that subsequently occur. Parasitic helminths are classified as cestodes (tapeworms), nematodes (roundworms) or trematodes (flukes). Helminth parasites invade both mucosal and nonmucosal tissues and comprise a broad spectrum of different

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pathogens including: microfilaria, Strongyloides (threadworms), Ancylostoma and Necator (hookworms), Trichuris (whipworms), Schistosoma, Taenia, Trichinella, Ascaris, and Anasakis. The course of infection can vary greatly between helminthes. For example, certain filarial nematodes are transmitted by mosquitos and can occupy and obstruct lymphatic vessels with chronic infection causing elephantiasis, while other parasitic nematodes, such as the whipworms, are strictly enteric, residing in the epithelial layer of the large intestine. Nematodes do, however, share a basic life cycle that involves: hatching from eggs into pre-parasitic larval stages (L1 & L2), parasitic larval stages that are often tissue dwelling (L3 & L4) and an adult stage with separate males and females. Often, several different components of the host immune response are required for parasite resistance and these may interact synergistically or independently of each other. In this review, we examine the recent identification of B cells as important players in host immune responses to helminths, both in terms of antibody secretion and their potential role in stimulating and controlling Th2-type immune responses.

Vaccination against helminthes

Current strategies to control helminth-related morbidity involve regular and mass drug administration, integrated with disease control through improved sanitation and hygiene². While safe and effective drugs are currently available for the bulk of human parasitic helminth infections, rapid re-infection and the dramatic rise in drug resistant helminthes of veterinary importance raise concerns over the feasibility of drug administration as a long-term control strategy². Yet there is evidence for naturally acquired immunity against helminth parasites³, which indicates that vaccination could offer a viable alternative. The majority of medically important helminthes reproduce outside their human host, and parasitic burden increases through re-infection by new larvae. Natural protective immunity is normally most evident for tissue invasive larval stages³—thus a combined approach using drugs to clear existing adult helminthes, and vaccination to target newly encountered infectious larvae, might represent an effective method for helminth control.

In the 1960s, several veterinary vaccines containing irradiated larvae of *Dictyocaulus viviparus* and *Ancylostoma caninum*, were developed commercially for use in cattle and dogs, respectively³. Since then, recombinant helminth vaccines have shown promise for several ruminant cestodes⁴. No commercial vaccine for human helminthes exists. There have, however, been some promising developments over the past 5 years (Table 1). The most advanced human vaccines are among those being developed for Schistosomiasis or hookworm, and a number of these have entered clinical development (reviewed in ^{5,6}). Some vaccines are being primarily developed for veterinary use, but also have clinical relevance (Table 1).

The majority of antigens used for development of recombinant anti-helminth vaccines are selected based on antibody reactivity³, and protective immunity often associates with a potent antibody response^{5,6}. Most successful vaccines work through antibody-mediated mechanisms, and increasing experimental evidence shows that antibody plays a crucial role in mediating protective immunity against helminthes. However, many issues need to be addressed before effective recombinant vaccines against human helminthes reach fruition (Box 1). Murine models of helminth infection are becoming increasingly important for identifying mechanisms of antibody-mediated protection and the specific immune effector cells that also contribute to protective immunity.

Box 1**Helminth vaccination: outstanding questions**

As helminths afflict only the poor, most current attempts to produce human helminth vaccines necessarily involve the formation of non-profit product development partnerships (PDPs). These are typically public-private partnerships involving funding from government or non-profit institutes and one or more private sector companies, with manufacturing procedures established by biotechnology industries present in the target countries. However, the development of effective vaccination programs against human helminthes faces many hurdles in addition to the need to raise sufficient financial support. The most pressing requirements for improved vaccine design are outlined below:

- Better understanding and further development of animal models of human disease
- Greater understanding of the mechanisms of host immunity
- New programs for antigen discovery. This would ideally involve the integration of antigen discovery programs with completed and ongoing genome sequencing projects (see <http://www.sanger.ac.uk/resources/downloads/helminthes/>)
- Optimization of adjuvant formulations
- Addressing requirements of delivery to developing world countries (important parameters include cheap production, vaccine stability and adequate distribution).
- An awareness of the influence of maternal antibodies, or pre-existing immune reactivity, on vaccination efficacy
- An understanding of the effects of ongoing infections with other pathogens on helminth vaccine efficacy.

Antibody function during helminth infection in murine models**A protective role for antibodies?**

During helminth infection polarized Th2-type responses promote B cell class switching to IgE and IgG1. IL-4R signaling and cognate T-B cell interactions mediate production of both isotypes. IgE potently activates mast cells and basophils, where antigen cross-links FcεRI-bound IgE to trigger degranulation and release of soluble mediators from these cells (Figure 1). IgE does not play an essential role in protective immunity against *Heligmosomoides polygyrus* (more recently named *H. bakeri*⁷ and hereafter referred to as *H. polygyrus bakeri*)⁸, *Nippostrongylus brasiliensis*⁹ or *Schistosoma mansoni*¹⁰ infection in mice. By contrast, mast cells are crucial for protection against *Trichinella spiralis*^{11,12} or *Strongyloides venezuelensis*¹³, but IgE appears to only partially contribute to *Trichinella*-induced mast cell responses¹⁴ (Table 2).

Despite this seemingly limited role for IgE in mediating protective immunity against helminthes, parasite burdens are decreased in the absence of B cells following challenge (secondary) infection with *Litomosoides sigmodontis*¹⁵, *S. mansoni*¹⁶, *Trichuris muris*¹⁷ or *H. polygyrus bakeri*^{8,18,19} (Table 2). Although B cell derived cytokines were reported to play a role in Th2 cell development and sustained antibody production, a direct role for antibodies themselves in mediating protective immunity against *H. polygyrus bakeri* was demonstrated using AID deficient mice^{8,19} (Table 2). IgG was identified as the antibody isotype that provides the most effective protective immunity against *H. polygyrus bakeri*⁸,

whilst IgM, which is normally produced in a T cell-independent manner, has been linked to the timely expulsion of filarial parasites²⁰ (Table 2). These data indicate that antibodies, particularly IgG and IgM, can act as potent mediators of protective immunity following helminth infection.

These findings are supported by observations that protective immunity against helminthes is passively transferred to naïve experimental animals using immune serum, or purified IgG, (Table 2). Antibody-mediated passive immunity has been demonstrated for *A. caninum*²¹, *Schistosoma* species¹⁶, *Taenia* species²², *Ascaris suum*²³, *Strongyloides ratti*²⁴, *T. muris*¹⁷, *Trichostrongylus colubriformis*²⁵, *N. brasiliensis*¹⁸ and *H. polygyrus bakeri*^{8,18,19,26–28}. Passive immunity has also been shown using: IgG monoclonal antibodies (mAbs) specific for *Fasciola hepatica*²⁹ and *S. mansoni*³⁰; IgM mAbs specific for *Brugia malayi*³¹; and IgG or IgA mAbs specific for *T. spiralis*^{32–36}. Maternal antibodies provide effective passive immunity against a variety of pathogens and parasite-specific maternal IgG have been reported to protect neonates against infection with the helminthes *T. spiralis*³⁷ or *H. polygyrus bakeri*³⁸.

It is important to note, however, that not all studies employing the passive transfer of immune serum or monoclonal antibodies report a protective effect^{18,19,25}. This indicates that the ability of antibodies to mediate protective immunity will depend on the species investigated. It might also result from differences in the quality and quantity of serum used. Numerous studies note a positive correlation between the number of challenge infections given prior to collection of immune serum and the ability of serum to provide passive immunity to naïve animals^{16,28}.

Mechanisms of antibody-mediated protection

Primary inoculation with *H. polygyrus bakeri*, results in chronic infection. If, however, adult parasites are cleared from the intestine with an anti-helminthic drug, secondary challenge results in memory Th2-type-dependent worm expulsion two weeks after inoculation. Worms are not expelled in B cell-deficient mice, but can be rescued by exogenous antibody administration, suggesting that antibodies contribute to the protective memory response to *H. polygyrus bakeri*^{8,18}. Egg production by adult worms remains inhibited in B cell-deficient mice, suggesting that other protective mechanisms mediated by the CD4+ T cell-dependent memory response are intact. The immune response is similarly impaired when macrophages are depleted³⁹, and antibodies and macrophages might mediate protective effects at a similar stage of the *H. polygyrus bakeri* life cycle.

H. polygyrus bakeri enters the intestine after oral ingestion of L3 and infection can be mimicked experimentally by oral L3 inoculation. After 24 hours, larvae penetrate the intestinal wall and migrate to the submucosa, where they reside and develop into adult worms over a period of 8 days. After this tissue dwelling phase, they migrate back to the intestinal lumen. The tissue dwelling phase is associated with a Th2-type granuloma response, which is primarily composed of alternatively activated macrophages (M2) and other immune cell populations including granulocytes, CD4+ T cells and dendritic cells (DCs)^{40,41}.

To examine the importance of antibodies during the early stage of *H. polygyrus bakeri* infection, parasite number and length were examined in the small intestine in B cell-deficient mice¹⁸. Both parameters increased as early as 4 days after secondary inoculation, indicating a role for B cells in larval migration to the submucosa and subsequent worm development (Figure 1). Protective immunity during secondary challenge was restored by serum from WT mice, indicating a role for antibody. Antibody seems to influence worm migration: in WT mice larvae distribution in the small intestine is different during the

primary and protective memory response, but in B cell-deficient mice the distribution is similar and administration of immune serum restores distribution associated with protective immunity¹⁸.

These findings indicate a protective role for antibodies during the tissue-dwelling stage of *H. polygyrus bakeri* infection, although antibodies might also contribute to immunity against other parasitic stages (Figure 1). In an experimental murine model of *Strongyloides* infection, antibodies are essential for the killing of larvae housed in diffusion chambers implanted subcutaneously into mice for a 24 hr period that allow transfer of serum and cells, but not of larvae^{42–44}. It is possible that antibodies might bind directly to parasites, impairing their capacity to migrate or develop properly. Studies with *T. spiralis* have shown that antibodies can bind to specific parasite structures and soluble (excretory secretory) products, and can impair migration, possibly by interfering with chemosensory reception^{32,45}. Alternatively, antibodies might work through more indirect mechanisms, perhaps by recruiting other immune cell populations, which then mediate direct effects on the parasite. Antibodies are abundant in the Th2-type granuloma surrounding the developing *H. polygyrus bakeri* larvae⁸. As B cells are infrequent in the granuloma, the antibody presumably binds FcγRs receptors on the innate immune cells that surround the parasite. FcγRs are expressed on innate immune cells including basophils, eosinophils, mast cells, monocytes and macrophages, and depending on the effector cell type, FcγR cross-linking can result in cell degranulation, release of cytokines and chemokines, enhanced phagocytosis or antibody dependent cellular cytotoxicity (ADCC) (Figure 1)⁴⁶. The impact of antibodies on M2 macrophages during *H. polygyrus bakeri* infection is of interest given the recent identification of this cell type as an important mediator of larval killing³⁹.

The dependence on antibody for protective immunity against *H. polygyrus bakeri*, is not strictly applicable to responses to all helminth infections. Although exogenously administered antibody can impair successful *Trichinella* invasion, the natural protective response leading to adult worm expulsion is effective without B cells, although mast cell degranulation is reduced as much as 50%⁴⁷. However, parasite-specific IgE contributes to the killing of L1 present in tissues, suggesting some effectiveness of antibody at the early stages of development¹⁴. The rapidly developing CD4+ T cell-dependent protective response that leads to *N. brasiliensis* expulsion after primary inoculation is also intact in the absence of B cells. Furthermore, the more rapid memory Th2-type response is equally effective in *N. brasiliensis* inoculated WT and B cell-deficient mice¹⁸. One important difference between the life cycle of *N. brasiliensis* and *H. polygyrus bakeri* is that larval stages of the former migrate through the lung, whilst those of the later dwell within the intestinal tissue. Both parasites then develop into adult worms that reside within the intestinal lumen. Given that antibody can have important protective effects resulting in impaired parasite development in the tissue-invasive stages, it is thus possible that antibodies differ in their ability to attack larval present in the lung or intestine and that adult parasites restricted to the lumen are not as readily damaged by antibody. Instead, other effector mechanisms might preferentially mediate protection at these later stages during infection. For example, RELM-beta, which is secreted into the lumen by goblet cells and can inhibit parasite feeding, is most effective after adult parasites enter the lumen⁴⁸.

Helminth-induced production of polyclonal antibodies: help or hindrance?

Helminth infection has long been associated with the marked production of polyclonal IgE antibodies. Formal proof that helminth infection can lead to the production of irrelevant antibody specificities was provided by *H. polygyrus bakeri* infection of TgH(VI10)xYEN mice⁸. Almost all B cells in these mice express a neutralizing immunoglobulin against the vesicular stomatitis virus glycoprotein (VSV-GP). In these mice, the immunoglobulin heavy chain locus can undergo class switch recombination to all isotypes and *H. polygyrus bakeri*

infection of TgH(VI10)xYEN mice resulted in the robust production of VSV-GP specific IgE and IgG1 antibodies. The exact function of polyclonal antibody production is not known, but polyclonal IgG in response to *H. polygyrus bakeri* infection reduces the fecundity of female worms⁸. Thus polyclonal antibody production in response to helminth infection might represent an ancient evolutionary mechanism to benefit both the parasite and host by allowing the parasite to avert the production of protective antibody specificities, while at the same time reducing worm fecundity and limiting transmission through the host population.

IgG1 antibodies exhibit a higher affinity for the inhibitory FcγRIIB than toward the activating FcγRs, and can thus induce a higher activation threshold in innate immune cells that express both types of receptors⁴⁶. Alterations in IgG glycosylation can also alter the activating versus inhibitory potential of IgG antibodies, with sialic acid rich IgG glycovariants reported to exhibit potent anti-inflammatory activity^{46,49}. The latter finding appears to explain the anti-inflammatory activity of high dose IgG therapy⁴⁹. Thus helminth-induced polyclonal IgG production might also serve to restrict excessive inflammatory responses during chronic infection.

Polyclonal antibody production during helminth infection might also provide an explanation for the lowered efficacy observed for some vaccines in helminth-infected animals and humans (reviewed in^{50,51}). Although this possibility has not been directly investigated, there are reports of helminth infection reducing antigen-specific antibody production following vaccination of humans^{52–55}, pigs⁵⁶ or rodents^{57,58}. However, the relationship between helminth infection and antibody production is complex because although *H. polygyrus bakeri* infection impaired antibody production following DNA vaccination against *Plasmodium falciparum*, it did not impact on responses raised against irradiated sporozoites⁵⁸. Moreover, individuals infected with *Onchocerciasis volvulus* were shown to mount attenuated humoral responses to BCG, whilst exhibiting normal antibody production in response to rubella vaccination⁵⁴ and tetanus toxoid⁵⁹. Nevertheless the exact impact of helminth infection on specific antibody production elicited by vaccination deserves further attention.

Do B cells enhance Th2-type responses

B cells have several important activities in addition to antibody production including antigen-presentation, co-stimulatory molecule signaling, and cytokine production. However, the importance of B cells in driving a T cell-dependent response can vary with the particular antigen and the type of immune microenvironment. In the draining lymph node antigen-presenting DCs first interact with naïve T cells in the T zone and activated T cells then migrate to the B zone^{60,61}. In the T:B zone⁶², and also in the B zone⁶³, IL-4 expressing T cells can develop and it has been proposed that here B cells provide the sustained co-stimulatory molecule interactions required for Th2 cell differentiation. In one study, OX40L but not IL-4 expression by B cells was required for Th2 cell differentiation⁶⁴. Interactions of T cells with B cells might be preferentially important for Th2 cell development, as skewing of Th2 to Th1 differentiation occurs in the absence of B cells in different models^{17,64,65}, including immunization of B cell-deficient mice with *S. mansoni* eggs⁶⁶. Some helminth infections, including the immune responses to *N. brasiliensis* and *H. polygyrus bakeri*, are strongly polarized towards Th2 cytokine production and blockade of co-stimulatory molecules does not deviate the response toward a Th1 cytokine pattern^{67,68}. To examine whether these Th2-type responses were refractory to B cell-deficiency, mice were inoculated in the ear with *N. brasiliensis*. This blocked the Th2-type response in the draining cervical lymph node but an alternative Th1-type response was not observed⁶⁹. This suggests that B cells are required for Th2 cell differentiation through mechanisms other than blockade of

Th1-type cytokine production. In this system, B cell IL-4 production is not required as the Th2-type response was rescued after adoptive transfer of either wildtype or IL4^{-/-} B cells. However, B cell surface B7 was required, consistent with other studies suggesting an important role for B cell co-stimulatory signals in Th2 cell differentiation⁶⁴. These studies thus suggest that expression of costimulatory molecules rather than Th2 cytokines by B cells can contribute to the development of Th2 cells, although it is certainly possible that B cell-derived IL-4 might be important in other in vivo systems, as previously suggested from in vitro findings⁷⁰.

Until recently, few studies had examined the role of B cells in the mucosal immune response to helminthes in the enteric region. One early study found that in the absence of B cells the Th2-type response deviated to a Th1-type response after *T. muris* infection. In this system, B cells apparently blocked IL-12 up-regulation thereby creating an environment permissive for Th2 cell differentiation¹⁷. However, only recently has the role of B cells in the development of the highly polarized Th2-type mucosal responses to *H. polygyrus bakeri* and *N. brasiliensis* been examined^{8,18,19}. Although one study in B cell-deficient mice concluded that Th2 cytokine production might be compromised in response to *H. polygyrus bakeri*¹⁹, further analyses indicated that the development of Th2 cells and associated Th2 cytokine production was intact in the immune responses to both *H. polygyrus bakeri* and *N. brasiliensis*^{8,18}. In the immune response to *H. polygyrus bakeri*, CD4⁺ T cell cytokine gene and protein expression were comparable in both the primary and secondary immune responses. Furthermore, in the memory response to *H. polygyrus bakeri*, peripheral Th2 cytokine expression in the granuloma surrounding the developing larvae was also unaffected. Consistent with this finding, the Th2-cytokine dependent immune cell architecture at the host-parasite interface, which includes CD4⁺ Th2 cells and M2 macrophages, was similar in *H. polygyrus bakeri*-inoculated B cell deficient and WT mice¹⁸. These studies suggest that B cells are not essential for the development of polarized enteric Th2-type responses to helminth parasites. Apparently, other signaling pathways can compensate for the absence of B cells in this milieu. Interestingly, the *H. polygyrus bakeri* Th2-type enteric polarized Th2-type response is also refractory to a requirement for thymic stromal cell lymphopoietin (TSLP) interactions⁷¹, a cytokine shown to be essential for Th2 cell differentiation in response to antigens in other immune microenvironments. Recently, several novel enteric immune cell populations, including nuocytes⁷² and natural helper cells⁷³, have been discovered that can support Th2 cell differentiation. It will be important to examine whether these populations contribute to the pathways that support robust B cell-independent development of the polarized Th2-type gut immune response that can be induced during certain helminth infections.

Regulatory B cells

Immune regulation by B cells was first recognized for autoimmune conditions (Box 2). Regulatory B cells also play a role during helminth infection. B cell deficiency results in enhanced Th2-dependent immunopathology following experimental *S. mansoni* infection. A similar increase in immune pathology is observed in mice deficient for FcγRs, indicating a complex relationship between antibody secretion and B cell function in this model⁷⁴. Regulatory B cells also play a role during *Schistosoma* infection, where their activity correlates with enhanced FasL expression and an increased apoptosis of activated CD4⁺ T cells⁷⁵. Although data showing a regulatory role for B cells in suppressing immunopathology after helminth infection has been limited to Schistosomiasis, B cells also negatively regulate neutrophil infiltration and parasite clearance following infection with the intracellular protozoan *Leishmania donovani*⁷⁶. Thus induction of regulatory B cells might represent a broad mechanism of immune modulation by parasites.

Box 2**A brief history of regulatory B cells**

Immune regulation by B cells was first recognized for autoimmune conditions and has been reported for rodent models of experimental autoimmune encephalomyelitis (EAE), inflammatory bowel disease (IBD), collagen-induced arthritis (CIA), Type I diabetes, lupus, contact hypersensitivity (CHS), anti-tumor immunity and oral tolerance^{91,92}. In addition, human B cell markers were recently found to correlate with spontaneous tolerance of kidney grafts raising speculation that regulatory B cells may facilitate transplantation tolerance⁹³. Although the ability of regulatory B cells to suppress CIA and EAE could be related to the selective suppression of Th1 type cytokines, regulatory B cells play an equally important role in modulating Th2-driven intestinal inflammation in TCR α deficient mice and helminth infection, indicating that the action of regulatory B cells is likely to be pleiotropic⁹⁴.

The majority of these studies associate regulatory B cell function with IL-10 production. IL-10 is well known to exert broad anti-inflammatory effects⁹⁵ and B cell-derived IL-10 has been reported to be essential for their regulation of IBD, EAE, CIA, lupus and CHS^{91,92}. The exact mechanisms by which IL-10 acts differs between reports but includes the suppression of pro-inflammatory cytokine production by macrophages or DC^{91,94}, and has been predicted to additionally involve modulation of regulatory T cells⁹⁴. IL-10-producing B cells often express the markers CD5 and CD1d, found on B-1a cells or marginal zone (MZ) B cells and transitional-2 (T2) B cells, respectively^{91,94}. However ascribing regulatory function to any one B cell subset has been difficult and regulatory function may lie within other B cell populations⁹⁴. Whether regulatory B cells represent a distinct lineage or whether they acquire regulatory potential in response to environmental cues is also not clear. Signals reported to play an important role in the development and/or activation of regulatory B cells include triggering of the B cell receptor, CD40 ligation and Toll-like receptor (TLR) engagement^{91,94}. Finally, in addition to producing IL-10, regulatory B cells have been described to produce transforming growth factor (TGF)- β ^{91,92} and to express Fas ligand⁹¹, indicating that multiple mechanisms of suppression may exist.

Helminthes are potent modulators of chronic inflammatory diseases⁷⁷ which might, in part, lie in their ability to invoke regulatory B cells. Supporting this, *S. mansoni*-induced regulatory B cells can attenuate allergic disease through an IL-10-dependent mechanism^{78–80}. Interestingly, *S. mansoni* infection promotes the expansion of peritoneal B1 cells and splenic B cells, and egg-derived oligosaccharides promote B cell proliferation and IL-10 production^{81,82}. *H. polygyrus bakeri* infection also induces regulatory B cells capable of attenuating OVA-induced allergic airway disease. In this case, however, the regulatory population was contained within a follicular (B2) cell population and did not involve B cell production of IL-10⁸³. Thus multiple mechanisms of immune modulation by helminth-induced regulatory B cells are likely to exist.

Although these studies all utilize experimental models, helminth therapy represents a new, but increasingly popular, tool for the treatment of chronic inflammatory diseases⁸⁴. It will be of interest to assess the ability of human helminthes to invoke regulatory B cells, and to determine the potential contribution of these cells to helminth-induced modulation of inflammatory diseases. One recent study reported that B cell production of IL-10 was increased in multiple sclerosis patients suffering from natural helminth infection⁸⁵ which correlates with reduced disease severity^{86,87}.

Concluding remarks

It is clear that B cells are important in protective immunity against helminthes. However, their significance and function can differ greatly depending on the specific parasite. During mucosal responses to helminthes, where B cells are essential for protective immunity, antibody secretion appears most significant and exogenous antibody administration can largely substitute for B cell-deficiency. Other helminths elicit host protective responses in the absence of B cells, although even in these cases, administration of exogenous antibody can accelerate expulsion. Passive maternal antibody transfer is also protective against helminthes in the neonate, further demonstrating the importance of antibody-mediated protection in the gut. In other immune microenvironments, B cells appear to be more important in promoting Th2 cell differentiation. More studies are needed to examine how antibodies actually mediate protective affects against helminthes and why mucosal Th2-type responses can develop through B cell-independent mechanisms. B cells have also emerged as playing an important role in controlling harmful inflammatory responses and helminthes might be powerful elicitors of such regulatory B cells. Elucidation of the immune microenvironments, types of helminth parasites, and stages of parasite development when antibodies are most efficacious in protective immunity may provide an important basis for the development of more effective helminth vaccines.

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References

1. Hotez PJ, et al. Helminth infections: the great neglected tropical diseases. *J Clin Invest.* 2008; 118 (4):1311–1321. [PubMed: 18382743]
2. Bethony J, et al. Soil-transmitted helminth infections: ascariasis, trichuriasis, and hookworm. *Lancet.* 2006; 367 (9521):1521–1532. [PubMed: 16679166]
3. Maizels RM, et al. Vaccination against helminth parasites--the ultimate challenge for vaccinologists? *Immunol Rev.* 1999; 171:125–147. [PubMed: 10582168]
4. Lightowlers MW. Cestode vaccines: origins, current status and future prospects. *Parasitology.* 2006; 133(Suppl):S27–42. [PubMed: 17274847]
5. Diemert DJ, et al. Hookworm vaccines. *Clin Infect Dis.* 2008; 46 (2):282–288. [PubMed: 18171264]
6. McManus DP, Loukas A. Current status of vaccines for schistosomiasis. *Clin Microbiol Rev.* 2008; 21 (1):225–242. [PubMed: 18202444]
7. Cable J, et al. Molecular evidence that *Heligmosomoides polygyrus* from laboratory mice and wood mice are separate species. *Parasitology.* 2006; 133 (Pt 1):111–122. [PubMed: 16536883]
8. McCoy KD, et al. Polyclonal and specific antibodies mediate protective immunity against enteric helminth infection. *Cell Host Microbe.* 2008; 4 (4):362–373. [PubMed: 18854240]
9. Watanabe N, et al. Protective immunity and eosinophilia in IgE-deficient SJA/9 mice infected with *Nippostrongylus brasiliensis* and *Trichinella spiralis*. *Proc Natl Acad Sci U S A.* 1988; 85 (12): 4460–4462. [PubMed: 3380800]
10. El Ridi R, et al. *Schistosoma mansoni* infection in IgE-producing and IgE-deficient mice. *J Parasitol.* 1998; 84 (1):171–174. [PubMed: 9488359]
11. Grecis RK, et al. The in vivo role of stem cell factor (c-kit ligand) on mastocytosis and host protective immunity to the intestinal nematode *Trichinella spiralis* in mice. *Parasite Immunol.* 1993; 15 (1):55–59. [PubMed: 7679484]
12. Ha TY, et al. Delayed expulsion of adult *Trichinella spiralis* by mast cell-deficient W/W^v mice. *Infect Immun.* 1983; 41 (1):445–447. [PubMed: 6345400]
13. Lantz CS, et al. Role for interleukin-3 in mast-cell and basophil development and in immunity to parasites. *Nature.* 1998; 392 (6671):90–93. [PubMed: 9510253]

14. Gurish MF, et al. IgE enhances parasite clearance and regulates mast cell responses in mice infected with *Trichinella spiralis*. *J Immunol*. 2004; 172 (2):1139–1145. [PubMed: 14707089]
15. Martin C, et al. B-cell deficiency suppresses vaccine-induced protection against murine filariasis but does not increase the recovery rate for primary infection. *Infect Immun*. 2001; 69 (11):7067–7073. [PubMed: 11598082]
16. Bickle QD. Radiation-attenuated schistosome vaccination--a brief historical perspective. *Parasitology*. 2009; 136 (12):1621–1632. [PubMed: 19327194]
17. Blackwell NM, Else KJ. B cells and antibodies are required for resistance to the parasitic gastrointestinal nematode *Trichuris muris*. *Infect Immun*. 2001; 69 (6):3860–3868. [PubMed: 11349052]
18. Liu Q, et al. B cells have distinct roles in host protection against different nematode parasites. *J Immunol*. 2010; 184 (9):5213–5223. [PubMed: 20357259]
19. Wojciechowski W, et al. Cytokine-producing effector B cells regulate type 2 immunity to *H. polygyrus*. *Immunity*. 2009; 30 (3):421–433. [PubMed: 19249230]
20. Rajan B, et al. Critical role for IgM in host protection in experimental filarial infection. *J Immunol*. 2005; 175 (3):1827–1833. [PubMed: 16034125]
21. Ghosh K, Hotez PJ. Antibody-dependent reductions in mouse hookworm burden after vaccination with *Ancylostoma caninum* secreted protein 1. *J Infect Dis*. 1999; 180 (5):1674–1681. [PubMed: 10515831]
22. Lightowers MW, et al. Vaccination against cestode parasites: anti-helminth vaccines that work and why. *Vet Parasitol*. 2003; 115 (2):83–123. [PubMed: 12878418]
23. Khoury PB, et al. Immune mechanisms to *Ascaris suum* in inbred guinea-pigs. I. Passive transfer of immunity by cells or serum. *Immunology*. 1977; 32 (4):405–411. [PubMed: 608676]
24. Murrell KD. Protective role of immunoglobulin G in immunity to *Strongyloides ratti*. *J Parasitol*. 1981; 67 (2):167–173. [PubMed: 7241275]
25. Harrison GB, et al. Antibodies to surface epitopes of the carbohydrate larval antigen CarLA are associated with passive protection in strongylid nematode challenge infections. *Parasite Immunol*. 2008; 30 (11–12):577–584. [PubMed: 19067838]
26. Behnke JM, Parish HA. Expulsion of *Nematospiroides dubius* from the intestine of mice treated with immune serum. *Parasite Immunol*. 1979; 1 (1):13–26. [PubMed: 551374]
27. Behnke JM, Parish HA. Transfer of immunity to *Nematospiroides dubius*: cooperation between lymphoid cells and antibodies in mediating worm expulsion. *Parasite Immunol*. 1981; 3 (3):249–259. [PubMed: 7301409]
28. Dobson C. Passive transfer of immunity with serum in mice infected with *Nematospiroides dubius*: influence of quality and quantity of immune serum. *Int J Parasitol*. 1982; 12 (2–3):207–213. [PubMed: 7076392]
29. Marcet R, et al. Passive protection against fasciolosis in mice by immunization with a monoclonal antibody (ES-78 MoAb). *Parasite Immunol*. 2002; 24 (2):103–108. [PubMed: 11874565]
30. Attallah AM, et al. Induction of resistance against *Schistosoma mansoni* infection by passive transfer of an IgG2a monoclonal antibody. *Vaccine*. 1999; 17 (18):2306–2310. [PubMed: 10403599]
31. Parab PB, et al. Characterization of a monoclonal antibody against infective larvae of *Brugia malayi*. *Immunology*. 1988; 64 (1):169–174. [PubMed: 3384450]
32. McVay CS, et al. Antibodies to tyvelose exhibit multiple modes of interference with the epithelial niche of *Trichinella spiralis*. *Infect Immun*. 2000; 68 (4):1912–1918. [PubMed: 10722582]
33. Ortega-Pierres G, et al. Protection against *Trichinella spiralis* induced by a monoclonal antibody that promotes killing of newborn larvae by granulocytes. *Parasite Immunol*. 1984; 6 (3):275–284. [PubMed: 6377201]
34. Ellis LA, et al. Glycans as targets for monoclonal antibodies that protect rats against *Trichinella spiralis*. *Glycobiology*. 1994; 4 (5):585–592. [PubMed: 7881172]
35. Inaba T, et al. Impeded establishment of the infective stage of *Trichinella* in the intestinal mucosa of mice by passive transfer of an IgA monoclonal antibody. *J Vet Med Sci*. 2003; 65 (11):1227–1231. [PubMed: 14665753]

36. Inaba T, et al. Monoclonal IgA antibody-mediated expulsion of *Trichinella* from the intestine of mice. *Parasitology*. 2003; 126 (Pt 6):591–598. [PubMed: 12866798]
37. Appleton JA, McGregor DD. Characterization of the immune mediator of rapid expulsion of *Trichinella spiralis* in suckling rats. *Immunology*. 1987; 62 (3):477–484. [PubMed: 3499383]
38. Harris NL, et al. Mechanisms of neonatal mucosal antibody protection. *J Immunol*. 2006; 177 (9): 6256–6262. [PubMed: 17056555]
39. Anthony RM, et al. Memory T(H)2 cells induce alternatively activated macrophages to mediate protection against nematode parasites. *Nat Med*. 2006; 12 (8):955–960. [PubMed: 16892038]
40. Patel N, et al. Characterisation of effector mechanisms at the host:parasite interface during the immune response to tissue-dwelling intestinal nematode parasites. *Int J Parasitol*. 2009; 39 (1):13–21. [PubMed: 18804113]
41. Anthony RM, et al. Protective immune mechanisms in helminth infection. *Nat Rev Immunol*. 2007; 7 (12):975–987. [PubMed: 18007680]
42. Herbert DR, et al. The role of B cells in immunity against larval *Strongyloides stercoralis* in mice. *Parasite Immunol*. 2002; 24 (2):95–101. [PubMed: 11874564]
43. Ligas JA, et al. Specificity and mechanism of immunoglobulin M (IgM)- and IgG-dependent protective immunity to larval *Strongyloides stercoralis* in mice. *Infect Immun*. 2003; 71 (12): 6835–6843. [PubMed: 14638770]
44. Kerepesi LA, et al. Human immunoglobulin G mediates protective immunity and identifies protective antigens against larval *Strongyloides stercoralis* in mice. *J Infect Dis*. 2004; 189 (7): 1282–1290. [PubMed: 15031798]
45. McVay CS, et al. Participation of parasite surface glycoproteins in antibody-mediated protection of epithelial cells against *Trichinella spiralis*. *Infect Immun*. 1998; 66 (5):1941–1945. [PubMed: 9573073]
46. Nimmerjahn F, Ravetch JV. FcγRs in Health and Disease. *Curr Top Microbiol Immunol*. 2010
47. Finkelman FD, et al. Interleukin-4- and interleukin-13-mediated host protection against intestinal nematode parasites. *Immunol Rev*. 2004; 201:139–155. [PubMed: 15361238]
48. Herbert DR, et al. Intestinal epithelial cell secretion of RELM-β protects against gastrointestinal worm infection. *J Exp Med*. 2009; 206 (13):2947–2957. [PubMed: 19995957]
49. Anthony RM, et al. Recapitulation of IVIG anti-inflammatory activity with a recombinant IgG Fc. *Science*. 2008; 320 (5874):373–376. [PubMed: 18420934]
50. Labeaud AD, et al. Do antenatal parasite infections devalue childhood vaccination? *PLoS Negl Trop Dis*. 2009; 3 (5):e442. [PubMed: 19478847]
51. Urban JF Jr, et al. Infection with parasitic nematodes confounds vaccination efficacy. *Vet Parasitol*. 2007; 148 (1):14–20. [PubMed: 17587500]
52. Cooper PJ, et al. Albendazole treatment of children with ascariasis enhances the vibriocidal antibody response to the live attenuated oral cholera vaccine CVD 103-HgR. *J Infect Dis*. 2000; 182 (4):1199–1206. [PubMed: 10979918]
53. Cooper PJ, et al. Impaired tetanus-specific cellular and humoral responses following tetanus vaccination in human onchocerciasis: a possible role for interleukin-10. *J Infect Dis*. 1998; 178 (4):1133–1138. [PubMed: 9806045]
54. Kilian HD, Nielsen G. Cell-mediated and humoral immune responses to BCG and rubella vaccinations and to recall antigens in onchocerciasis patients. *Trop Med Parasitol*. 1989; 40 (4): 445–453. [PubMed: 2623427]
55. Nookala S, et al. Impairment of tetanus-specific cellular and humoral responses following tetanus vaccination in human lymphatic filariasis. *Infect Immun*. 2004; 72 (5):2598–2604. [PubMed: 15102768]
56. Steenhard NR, et al. *Ascaris suum* infection negatively affects the response to a *Mycoplasma hyopneumoniae* vaccination and subsequent challenge infection in pigs. *Vaccine*. 2009; 27 (37): 5161–5169. [PubMed: 19524617]
57. Haseeb MA, Craig JP. Suppression of the immune response to diphtheria toxoid in murine schistosomiasis. *Vaccine*. 1997; 15 (1):45–50. [PubMed: 9041665]

58. Noland GS, et al. Helminth infection impairs the immunogenicity of a *Plasmodium falciparum* DNA vaccine, but not irradiated sporozoites, in mice. *Vaccine*. 2010; 28 (17):2917–2923. [PubMed: 20188676]
59. Kilian HD, Nielsen G. Cell-mediated and humoral immune response to tetanus vaccinations in onchocerciasis patients. *Trop Med Parasitol*. 1989; 40 (3):285–291. [PubMed: 2617034]
60. Itano AA, et al. Distinct dendritic cell populations sequentially present antigen to CD4 T cells and stimulate different aspects of cell-mediated immunity. *Immunity*. 2003; 19 (1):47–57. [PubMed: 12871638]
61. Ekkens MJ, et al. The role of OX40 ligand interactions in the development of the Th2 response to the gastrointestinal nematode parasite *Heligmosomoides polygyrus*. *J Immunol*. 2003; 170 (1): 384–393. [PubMed: 12496423]
62. Liu Z, et al. *Nippostrongylus brasiliensis* can induce B7-independent antigen-specific development of IL-4-producing T cells from naive CD4 T cells in vivo. *J Immunol*. 2002; 169 (12):6959–6968. [PubMed: 12471130]
63. King IL, Mohrs M. IL-4-producing CD4+ T cells in reactive lymph nodes during helminth infection are T follicular helper cells. *J Exp Med*. 2009; 206 (5):1001–1007. [PubMed: 19380638]
64. Linton PJ, et al. Costimulation via OX40L expressed by B cells is sufficient to determine the extent of primary CD4 cell expansion and Th2 cytokine secretion in vivo. *J Exp Med*. 2003; 197 (7):875–883. [PubMed: 12668647]
65. Bradley LM, et al. Availability of antigen-presenting cells can determine the extent of CD4 effector expansion and priming for secretion of Th2 cytokines in vivo. *Eur J Immunol*. 2002; 32 (8):2338–2346. [PubMed: 12209647]
66. Hernandez HJ, et al. In infection with *Schistosoma mansoni*, B cells are required for T helper type 2 cell responses but not for granuloma formation. *J Immunol*. 1997; 158 (10):4832–4837. [PubMed: 9144498]
67. Lu P, et al. CTLA-4 ligands are required to induce an in vivo interleukin 4 response to a gastrointestinal nematode parasite. *J Exp Med*. 1994; 180 (2):693–698. [PubMed: 8046343]
68. Liu Z, et al. Requirements for the development of IL-4-producing T cells during intestinal nematode infections: what it takes to make a Th2 cell in vivo. *Immunol Rev*. 2004; 201:57–74. [PubMed: 15361233]
69. Liu Q, et al. The role of B cells in the development of CD4 effector T cells during a polarized Th2 immune response. *J Immunol*. 2007; 179 (6):3821–3830. [PubMed: 17785819]
70. Harris DP, et al. Reciprocal regulation of polarized cytokine production by effector B and T cells. *Nat Immunol*. 2000; 1 (6):475–482. [PubMed: 11101868]
71. Massacand JC, et al. Helminth products bypass the need for TSLP in Th2 immune responses by directly modulating dendritic cell function. *Proc Natl Acad Sci U S A*. 2009; 106 (33):13968–13973. [PubMed: 19666528]
72. Neill DR, et al. Nuocytes represent a new innate effector leukocyte that mediates type-2 immunity. *Nature*. 2010; 464 (7293):1367–1370. [PubMed: 20200518]
73. Moro K, et al. Innate production of T(H)2 cytokines by adipose tissue-associated c-Kit(+)Sca-1(+) lymphoid cells. *Nature*. 2010; 463 (7280):540–544. [PubMed: 20023630]
74. Jankovic D, et al. CD4+ T cell-mediated granulomatous pathology in schistosomiasis is downregulated by a B cell-dependent mechanism requiring Fc receptor signaling. *J Exp Med*. 1998; 187 (4):619–629. [PubMed: 9463412]
75. Lundy SK, Boros DL. Fas ligand-expressing B-1a lymphocytes mediate CD4(+)-T-cell apoptosis during schistosomal infection: induction by interleukin 4 (IL-4) and IL-10. *Infect Immun*. 2002; 70 (2):812–819. [PubMed: 11796615]
76. Smelt SC, et al. B cell-deficient mice are highly resistant to *Leishmania donovani* infection, but develop neutrophil-mediated tissue pathology. *J Immunol*. 2000; 164 (7):3681–3688. [PubMed: 10725726]
77. Smits HH, et al. Chronic helminth infections protect against allergic diseases by active regulatory processes. *Curr Allergy Asthma Rep*. 2010; 10 (1):3–12. [PubMed: 20425508]

78. Amu S, et al. Regulatory B cells prevent and reverse allergic airway inflammation via FoxP3-positive T regulatory cells in a murine model. *J Allergy Clin Immunol.* 2010; 125(5):1114–1124. e1118. [PubMed: 20304473]
79. Mangan NE, et al. Helminth infection protects mice from anaphylaxis via IL-10-producing B cells. *J Immunol.* 2004; 173 (10):6346–6356. [PubMed: 15528374]
80. Smits HH, et al. Protective effect of *Schistosoma mansoni* infection on allergic airway inflammation depends on the intensity and chronicity of infection. *J Allergy Clin Immunol.* 2007; 120 (4):932–940. [PubMed: 17689595]
81. Velupillai P, Harn DA. Oligosaccharide-specific induction of interleukin 10 production by B220+ cells from schistosome-infected mice: a mechanism for regulation of CD4+ T-cell subsets. *Proc Natl Acad Sci U S A.* 1994; 91 (1):18–22. [PubMed: 7904066]
82. Velupillai P, et al. B-1 cell (CD5+B220+) outgrowth in murine schistosomiasis is genetically restricted and is largely due to activation by polylactosamine sugars. *J Immunol.* 1997; 158 (1): 338–344. [PubMed: 8977208]
83. Wilson MS, et al. Helminth-induced CD19+CD23hi B cells modulate experimental allergic and autoimmune inflammation. *Eur J Immunol.* 2010; 40 (6):1682–1696. [PubMed: 20306466]
84. Weinstock JV, Elliott DE. Helminths and the IBD hygiene hypothesis. *Inflamm Bowel Dis.* 2009; 15 (1):128–133. [PubMed: 18680198]
85. Correale J, et al. Helminth infections associated with multiple sclerosis induce regulatory B cells. *Ann Neurol.* 2008; 64 (2):187–199. [PubMed: 18655096]
86. Correale J, Farez M. Association between parasite infection and immune responses in multiple sclerosis. *Ann Neurol.* 2007; 61 (2):97–108. [PubMed: 17230481]
87. Fleming J, Fabry Z. The hygiene hypothesis and multiple sclerosis. *Ann Neurol.* 2007; 61 (2):85–89. [PubMed: 17315205]
88. Islam MK, et al. Vaccination with recombinant *Ascaris suum* 24-kilodalton antigen induces a Th1/Th2-mixed type immune response and confers high levels of protection against challenged *Ascaris suum* lung-stage infection in BALB/c mice. *Int J Parasitol.* 2005; 35 (9):1023–1030. [PubMed: 15998515]
89. Rolink A, et al. The SCID but not the RAG-2 gene product is required for S mu-S epsilon heavy chain class switching. *Immunity.* 1996; 5 (4):319–330. [PubMed: 8885865]
90. Perona-Wright G, et al. Cutting edge: Helminth infection induces IgE in the absence of mu- or delta-chain expression. *J Immunol.* 2008; 181 (10):6697–6701. [PubMed: 18981085]
91. DiLillo DJ, et al. B10 cells and regulatory B cells balance immune responses during inflammation, autoimmunity, and cancer. *Ann N Y Acad Sci.* 2010; 1183:38–57. [PubMed: 20146707]
92. Mizoguchi A, Bhan AK. A case for regulatory B cells. *J Immunol.* 2006; 176 (2):705–710. [PubMed: 16393950]
93. Schroppel B, Heeger PS. Gazing into a crystal ball to predict kidney transplant outcome. *J Clin Invest.* 2010; 120 (6):1803–1806. [PubMed: 20501950]
94. Fillatreau S, et al. Not always the bad guys: B cells as regulators of autoimmune pathology. *Nat Rev Immunol.* 2008; 8 (5):391–397. [PubMed: 18437156]
95. Couper KN, et al. IL-10: the master regulator of immunity to infection. *J Immunol.* 2008; 180 (9): 5771–5777. [PubMed: 18424693]

Figure 1. Protective role for antibodies during challenge infections with *H. polygyrus bakeri*

Antibodies could potentially provide protective immunity at three points of the parasite life cycle: 1) antibodies present in the intestinal lumen or inflamed mucosal tissue might interfere with parasitic enzymes or other essential processes required for L3 invasion and migration to the sub-mucosa. 2) leukocytes present within the Th2-type granuloma that forms around the invading larva might be activated by the surface bound antibodies IgG or IgE, or antibody (IgM and IgG)-dependent complement activation could result in additional leukocyte infiltration, cytokine production and cytotoxicity. 3) antibodies present within the inflamed mucosal tissue of the small intestine might interfere with essential processes involved in feeding and/or migration of adult worms out of the granuloma and into the intestinal lumen.

Table 1Recent developments in vaccination against helminthes of clinical interest^a.

Parasitic species (common name)	Host		Target antigen ^b	Development ^c
	Definitive	Intermediate		
<i>Necator americanus</i>				
<i>Uncinaria stenocephala</i> (hookworm)	Humans	-	Na-ASP-2 Na-GST-1 Na-APR-1	Clinical and Experimental
<i>Schistosoma haematobium</i>	Humans	Freshwater snails	Sh28GST ^d	Clinical
<i>Schistosoma japonicum</i>	Wide range of mammalian hosts including humans	Freshwater snails	Sj23	Veterinary ^e
<i>Schistosoma Mansoni</i>	Humans	Freshwater snails	Sm14 Smp80 SmTSP-2 Sm29	Experimental
<i>Taenia solium</i> (tapeworm)	Humans	Pigs	TSOL-18	Veterinary
<i>Taenia saginata</i> (tapeworm)	Humans	Cattle	TSA-9 TSA-18	Veterinary
<i>Ascaris suum</i> (roundworm)	Pigs	Humans	AS24	Veterinary

^a Vaccines undergoing development and published within the previous five years.^b Data was compiled from references^{4–6,88}.^c Vaccines being developed for human use are categorized as clinical (Phase I or II trials) or experimental (antigen discovery and/or testing in animal models). Vaccines listed as veterinary are being developed primarily for use in livestock but may benefit human health by blocking transmission.^d Registered as Bilhvax[®], <http://www.bilhvax.inserm.fr/>.^e Vaccine development is aimed at water buffalo in China.

Table 2

Experimental models used to determine the impact of antibodies on helminth infection

Experimental model ^a	Explanation of experimental system	Parasitic species ^b	Refs
<i>Altered mast cell responses</i>	Use of mice exhibiting defects in mast cell development (W/W ^v or IL-3 ^{-/-}), mast depletion using anti-c-kit mAb or IgE-mediated mast cell activation (IgE ^{-/-}).	<i>Trichinella spiralis</i> , <i>Strongyloides venezuelensis</i>	11–14
<i>B cell deficiency</i>	Use of mice exhibiting a developmental defect in B cells (μ MT ^{-/-} or JHD ^{-/-}) ^c as a result of gene targeting	<i>Litomosoides sigmodontis</i> , <i>Schistosoma mansoni</i> , <i>Trichuris muris</i> , <i>Heligmosomoides polygyrus bakeri</i>	8, 15–19, 42
<i>Specific lack of isotype switched antibodies</i>	Use of mice rendered deficient in activation- induced deaminase (AID). These mice retain naïve B cells but are unable to undergo class switch recombination or somatic hypermutation.	<i>Heligmosomoides polygyrus bakeri</i>	8, 19
<i>FcγR deficiency</i>	Use of mice rendered deficient in the gamma- chain and exhibiting defective expression of all activating Fc receptors (FcRI, FcRIII and FcRIV).	<i>Heligmosomoides polygyrus bakeri</i> , <i>Strongyloides stercoralis</i> , <i>Schistosoma mansoni</i>	8, 43, 44, 74
<i>Passive immunization</i>	Transfer of protective antibodies to naïve animals in the form of serum (whole or purified antibody components) or monoclonal antibodies.	<i>Ancylostoma cacinum</i> , <i>Schistosoma</i> species, <i>Taenia</i> species, <i>Ascaris suum</i> , <i>Strongyloides ratti</i> , <i>Trichuris muris</i> , <i>Trichostrongylus colubrififormis</i> , <i>Nippostrongylus brasiliensis</i> , <i>Heligmosomoides polygyrus bakeri</i> , <i>Fasciola hepatica</i> , <i>Brugia malayi</i> , <i>Trichinella spiralis</i> , <i>Strongyloides stercoralis</i>	8, 17, 18, 20–36, 44
<i>Maternal antibody transfer</i>	Transfer of protective maternal antibodies (IgG and SIgA) via milk to suckling neonates	<i>Trichinella spiralis</i> , <i>Heligmosomoides polygyrus</i>	37, 38

^a Only experimental models using rodents are listed^b Parasitic species where antibodies have been reported to afford protection against primary or secondary infections

^c C57BL/6 μ MT deficient mice carry stop codon and a neomycin gene cassette in the first transmembrane exon immunoglobulin M (IgM) heavy chain leading to a developmental arrest at the pro-B cell stage and cellular apoptosis. However IgM independent B cell development and immunoglobulin isotype switching can occur *in vitro* if the anti-apoptotic gene Bcl-2 is overexpressed in B cell precursors and the appropriate stimulation (IL-4 and anti-CD40) is provided⁸⁹. Notably helminth infection has been reported to drive IgE production in C57BL/6 μ MT deficient mice, despite a continued block in B cell development⁹⁰. Deletion of the JH gene segment in C57BL/6 JHD mice also results in defective B cell development but these mice do not exhibit the ‘leakiness’ apparent in μ MT deficient mice.