Th2 Cell Responses in Immunity and Inflammation Following Helminth Infection

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Introduction

Helminth parasites are multicellular pathogens from two distinct phyla—the Platyhelminthes (flatworms) and Nematoda (roundworms). As a group they infect billions of people, largely in the poorest parts of the world where infection transmission is supported by underdeveloped sanitation and poor vector control [1]. While helminth infections have relatively low fatality rates they are increasingly recognized to be the cause of severe morbidity, and as such have recently gained heightened recognition as important but neglected tropical diseases [2, 3].

Despite enormous organismal heterogeneity and life cycle complexity amongst parasitic helminths, these pathogens are united immunologically by the fact that they nearly always induce pronounced Th2 immune responses. The origins of our understanding of this fact date to the observations that elevated IgE levels and eosinophilia are strong indications of helminth infections (see [4–6]). In the 1980s it became clear that the expression of IL-4 and IL-5, cytokines that control immunoglobulin isotype class switching to IgE in B cells, and increased eosinophil release from the bone marrow and survival in the periphery, are linked and characteristic of a subset of $CD4^+$T cells defined as T helper type 2 cells (Th2 cells) [7]. From this finding, it was a relatively straightforward step to the realization that the dominant response to helminth parasites was likely to be Th2 in nature [8]. Helminth infections are often chronic, and sometimes associated with the development of severe pathology, and early work linked Th2 response development during infection with the parasitic flatworm *Schistosoma mansoni* to the onset of disease [9, 10], so there was initially some debate as to whether Th2 responses serve any protective function

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in the context of helminthic disease [11]. However, it quickly became clear that Th2 cells regulate a spectrum of protective responses that allow animals to eradicate, or live with, helminth parasites [12–15].

The "Th2 Response": Innate and Adaptive Components

Put most simply, Th2 cells are MHC class II restricted CD4 T cells which make physiologically relevant levels of IL-4, IL-5, and/or IL-13. In humans and mice, the IL-4 allele is in a clustered locus with IL-5 and IL-13 and although each allele can be expressed independently, all three are often coordinately regulated, such that production of these "Th2 cytokines" is considered to be a mark of a Th2 response [16, 17]. In detail, the situation is more complex and the production of IL-4, IL-5, and IL-13 is often accompanied by the expression of additional genes, such as *Il9*, *Il10*, and *Areg*, that add to the overall Th2 signature (e.g. [18, 19]). While IL-4 is not strictly necessary for the development of Th2 cells, it is strongly supportive of the expansion and establishment of Th2 cell responses [20]. Th cells were named based on their perceived role in helping B cells to make antibody, and the production of IgG1 and IgE by B cells requires T cell help including the provision of IL-4, and increased amounts of specific and non-specific antibodies in these classes typify helminth infections [21]. It is now clear that a subset of Th cells, T follicular helper (Tfh) cells, which differ from naïve or effector cells in being specialized to enter B cell follicles and germinal centers, is specialized for helping B cells [22]. In helminth infections these cells share with Th2 cells the ability to make IL-4 (thus accounting for their ability to induce class switching to IgG1 and IgE production) but additionally produce IL-21 [23–25], a cytokine that is critical for plasma cell differentiation.

Helminth infection-induced immune responses in which Th2 cells are prominent are best considered "type 2" responses, since they are usually characterized by the additional participation of a range of cells of the innate immune system, including eosinophils, basophils, mast cells, and type 2 innate lymphoid cells (ILC2s), all of which have the potential to produce one or more of the canonical Th2 cytokines [26–30].

The Protective Roles of Type 2 Responses During Helminth Infection

Immunity to helminth infections is manifested in at least three ways (Fig. 1): (1) The resolution of a primary infection; (2) Resistance to reinfection; and (3) Protection of vital functions during chronic, immunologically unresolvable infection. Specific examples of these types of immunity will be discussed below.

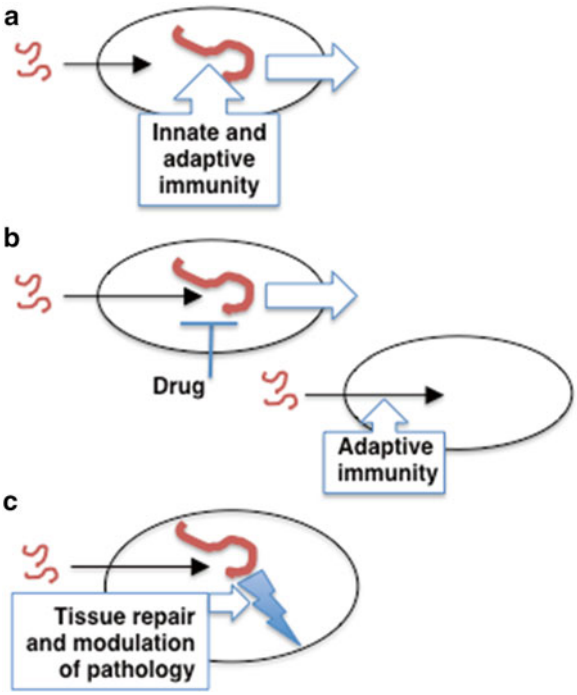

Fig. 1 Immunity to helminth infections is manifested in at least three ways. (**a**) The resolution of a primary infection. Some intestinal nematodes are killed as a result of the effects of IL-4/IL-13 produced by innate type 2 cells and Th2 cells on intestinal epithelial cells, including goblet cells, and on associated musculature. (**b**) Following drug treatment of some helminth infections, hosts are resistant to reinfection. Immunity may be mediated by cytokines from Th2 cells and cooperating innate system cells, through mechanisms similar to those that mediate resolution of primary infection, but enhanced by faster kinetics associated with the secondary immune response. Immunity is additionally more potent in some cases because of antibody that has developed as a result of initial infection and clearance, and because of the rapid recruitment of cells such M2 macrophages to the immune reaction that targets incoming larval parasites and prevents their establishment. (**c**) Protection of vital functions during chronic, immunologically unresolvable infection. In these settings, the immune response promotes tissue repair and sequesters parasites and any toxic molecules that they may make (indicated by the *lightning symbol*). In these settings, excessive tissue damage is prevented by immune system intrinsic regulatory mechanisms and immunomodulatory molecules released by the parasites themselves

Functionally, protective responses in each of these categories are largely mediated by the direct or indirect effect of type 2 cytokines on other cells, which assume effector functions under their influence. The primary effector cells of immunity to helminth infections are B cells (the antibody products of which can work in conjunction with other cell types), macrophages, granulocytes, epithelial cells, and muscle cells.

Resolution of Primary Infection

The resolution of primary infection is perhaps the exception rather than the rule since many parasitic helminths cause chronic infection—indeed, chronicity is often considered a hallmark of helminth infection. Nevertheless, various intestinal nematodes, including the whipworm *Trichuris muris* and the hookworm *Nippostrongylus brasiliensis*, are immunologically expelled by murine hosts shortly after adult worms establish in the intestine and initiate egg production (Fig. 1a). These protective responses are often heavily dependent on the early production of IL-13 and/or IL-4, and the ability of these cytokines to stimulate intestinal smooth muscle contraction [31, 32], altered intestinal epithelial cell function leading to increased luminal fluid flow [33, 34], increased epithelial cell turnover [35], and goblet cell expression of effector RELMβ, which inhibits parasite feeding and chemotaxis [36, 37], and Muc5ac, which is directly detrimental to *T. muris* and *N. brasiliensis*, as well as to another intestinal nematode *Trichinella spiralis* [38] (Fig. 2). Together these effects lead to worm expulsion. These processes can be stimulated by IL-4/IL-13 made by innate type 2 cells, or by Th2 cells and therefore additionally play essential roles in the spectrum of protective responses from those that begin to work during early primary infection to those recalled in immune animals upon re-exposure to infection. Interestingly, the ability of innate type 2 cells to participate in resolution of primary infection, as discussed below, is dependent on the presence of $CD4^+$ T cells (discussed in [28, 39]). Thus there is an intimate reciprocal link between innate and adaptive immunity during the development of responses that will lead to expulsion of primary infections and resistance to secondary infection.

Innate type 2 cells are present in naïve mice, poised to produce Th2 cytokines upon appropriate stimulation, and are mobilized within hours/days during the early stage of the response to helminth parasites. Because of the kinetics of the innate type 2 response, which occurs at a time when the adaptive Th2 response is at its very earliest stage of development, there has been a focus on whether the cells that make up this response are able to mediate innate protective responses against helminths and/or to help promote Th2 cell responses, by perhaps secreting IL-4 and/or IL-13. Of special current interest in this regard are ILC2s (Fig. 2). Discovered only recently, these cells are derived from lymphoid progenitors, but do not express markers of other immune cell lineages, or clonotypic antigen receptors [40–42]. ILC2s produce IL-5 and IL-13, exist throughout the body and play important homeostatic roles (e.g. [43]). However, ILC2s can become activated and increase in numbers in response to helminth infection, a response that is mediated by IL-25 and IL-33 [28, 40–42]. These cytokines are released by epithelial cells (and possibly other cells such as mast cells and macrophages) in response to necrotic damage or other signals (e.g. Trefoil Factor 2 [44]), and through their effects on ILC2s acts as "alarmins" to initiate innate responses [28] (Fig. 2). Conceptually, this mode of action fits well with the idea of intestinal or skin epithelial surfaces being broached by invading or migrating helminth larvae. Indeed, ILC2s are engaged rapidly following infection with *N. brasiliensis* [42, 45], and stimulated by IL-25 released by intestinal epithelial

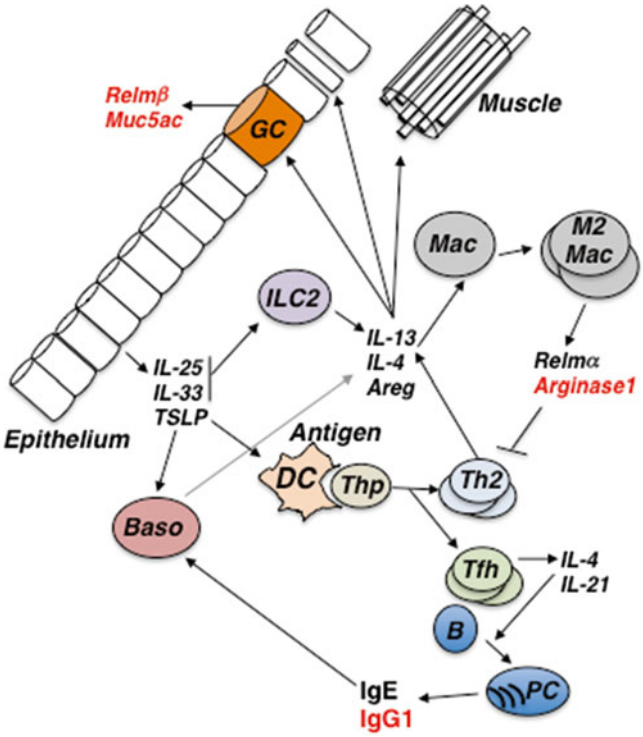

Fig. 2 Innate and adaptive type 2 immunity is tightly integrated. Innate responses to helminth parasites can be initiated by epithelial cell damage, leading to the production of the alarmins IL-25, IL-33, and TSLP. IL-25 and IL-33 can activate ILC2s to make IL-13 (but not IL-4), which has marked effects on epithelial cell (EC), goblet cell (GC), and muscle cell biology that together can promote the expulsion of intestinal parasites. IL-13 also alternatively activates macrophages, which can then proliferate and begin making mediators that lead to parasite damage, but which also promote tissue healing and regulate Th2 cell responses to prevent overt immunopathology. TSLP made by epithelial cells can promote basophil hematopoiesis and activation, and by inhibiting IL-12 production by DCs promotes the induction of Th2 cell responses. Many helminths also produce molecules that limit the ability of DCs to make IL-12. T-cell response initiation involves the extensive proliferation of T cells that are specific for the target antigens and the emergence of Th2 cells that make IL-13 and IL-4, and of Tfh cells that make IL-4 and IL-21 and are specialized to help IgG1 and IgE B-cell responses. Th2 cells can move into sites of infection where the cytokines that they make perpetuate effects on epithelial cells, muscle cells, and macrophages initiated by ILC2s. T cells also sustain ILC2 populations. Eosinophils are not depicted in this figure. However, these cells participate in type 2 immunity due to the strong production of IL-5 by ILC2s and Th2 cells. Mast cells are also absent from the figure, but would be expected to participate in type 2 responses. Mediators in *red* have been shown to have detrimental effects on helminth parasites. *PC* plasma cell. *Areg* amphiregulin, a cytokine made by Th2 cells and ILC2s that promotes epithelial cell turnover

cells [46]. In the absence of IL-25, or IL-25R, mice have fewer ILC2s and exhibit delayed parasite expulsion kinetics [41, 45]. However, injection of IL-25 into infected WT mice or transfer of activated WT ILC2s into infected IL-25R-deficient infected mice is sufficient to mediate rapid expulsion through an IL-13-dependent mechanism [41, 45]. Interestingly, in mice lacking the IL-33R (T1/TS2), or in which T1/TS2 is blocked, expansion of the ILC2 population following infection with *N. brasiliensis* fails to occur, and the mice are unable to rapidly clear the parasite [41, 44], indicating that despite their similar roles in promoting ILC2 activation, IL-33 and IL-25 must each have essential non-redundant functions in immunity, although what these are is currently unclear. IL-33 has also been shown to play a role in immunity to the nematode parasite to *T. spiralis* [47], and to be able to induce immunity to *T. muris* [48].

Multi-potent projenitor type 2 cells ($MMP^{type\ 2}$), IL-25-dependent but T1/ST2-negative and IL-33-independent cells associated with type 2 immunity but distinct from ILC2s, have been implicated in resistance to *T. muris* [49, 50]. As their name suggests, these cells have the potential to differentiate into other cell types, including basophils, monocytes, mast cells, and macrophages, and are thought to promote the expression of Th2 immunity in part through extramedullary hematopoiesis to produce cell types that contribute to protection.

Basophils, circulating cells that enter tissues from the blood, are also activated early following helminth infection during which they can rapidly accumulate in affected tissues and enter reactive lymphoid organs [51]. Based on the outcome of depletion by antibodies directed at the FcεR, basophils were implicated as antigen-presenting cells responsible for activating naïve $CD4^+$ T cells during the development of Th2 responses following infection with helminths [52]. However, the more recent use of engineered mice in which basophils are deleted with high specificity has shown that these cells are dispensable for polarized Th2 responses elicited by *N. brasiliensis* or *S. mansoni* [53]. Nevertheless, IL-4 and IL-13 from these cells contribute to the expulsion of primary *N. brasiliensis* infection [54]. Basophils also play an important role in the clearance of primary *T. muris* infection [55]. Immunity to this parasite is dependent on TSLP, another alarmin made by epithelial cells. In contrast to the situation in WT mice, peripheral basophil numbers along with Th2 responses and associated downstream effector functions (discussed below) fail to develop in infected $Tslpr^{-/-}$ mice, and adult parasites persist as a chronic infection. However, transfer of WT basophils into infected $Tslpr^{-/-}$ mice is able to partially restore the spectrum of type 2 immune responses and resulting worm expulsion [55]. This study revealed that TSLP can selectively promote basophil hematopoiesis and the emergence of a population of basophils that differs transcriptionally from basophils elicited by IL-3 (Fig. 2). TSLP has other important functions in Th2 immunity, as discussed further below.

Mast cells are found throughout the body, especially adjacent to epithelia. Mastocytosis is a common feature of helminth infections [56], and mast cells have been implicated in resistance to the nematodes *T. spiralis* [57] and *Strongyloides* spp. [58, 59]. There is recent evidence that mast cell-deficient mice have diminished Th2 responses and are more susceptible to primary infection with *T. muris* and to the trichostrongyle nematode *H. polygyrus* (once known as *Nematospiroides dubius*,

and more recently referred to as *H. polygyrus bakeri*) [60], due to a failure of ILC2 activation resulting from a deficit in IL-25, IL-33, and TSLP production by epithelial cells. Thus mast cells may play an important role in initiating type 2 immunity by provoking the production of alarmins, although the mechanism underlying this response is unclear at present.

Resistance to Reinfection

The second important role for type 2 responses in helminth infection is in adaptive immunity to reinfection. This is well illustrated by infection with *H. polygyrus*. Primary infection in mice with this intestinal nematode can be chronic even when the host mounts a type 2 response, but in these cases chemotherapy leaves the cured host immunologically resistant to secondary infection [61] (Fig. 1b).

There is a long-standing recognition that, while IL-4 and IL-13 made by memory Th2 cells may contribute heavily to resistance to secondary *H. polygyrus* infection by directly modulating epithelial cell, muscle cell, and macrophage responses [62], antibody is also playing a crucial role in adaptive immunity in this system [21]. Thus μMT mice and JhD mice, which lack B cells, and AID mice, which have B cells but are unable to secrete antibodies, are unable to resist secondary infection with *H. polygyrus*, despite developing what for the most part appear to be normal Th2 responses [63–65]. Moreover, IgG1 antibody from animals immune to *H. polygyrus* is able to passively confer immunity to naïve animals [63, 65, 66], and mice deficient in IL-21 fail to develop IgG1 secreting plasma cells and subsequently are unable to resist reinfection following drug cure [67]. Antibodies are also recognized to be important for protection against primary infection with *T. spiralis*, or *H. polygyrus* following maternal transfer in milk from immune mothers to offspring [68, 69].

Parasite-specific antibodies have also been shown to be capable of conferring protection against a broad spectrum of other helminth infections following experimental passive transfer, even in cases where there is not demonstrable role for antibody in naturally acquired immunity (reviewed in [21]). However, some of these findings have been difficult to reproduce, a problem that may be ultimately due to differences in antibody titer between different experiments. This would be consistent with the fact that there is a correlation between the efficacy of immune serum in passive immunization and the number of times the donor animals have been infected/boosted [21, 61], since titer would be expected to rise with each boost. In a real world setting, the role of immunologic boosting due to the death of existing parasites and reinfection has been postulated in human immunity to infection against schistosomes [70, 71]; in this infection, resistance can develop following drug treatment, and is correlated with the amount of IgE antibody against key parasite antigens [72].

Antibodies exert protective roles through a variety of mechanisms that vary depending on the infection and life stage targeted. For example, in the intestine, antibodies promote the entrapment of *T. spiralis* worms in mucus, leading to

expulsion [73], whereas in tissues antibody can mediate FcR-dependent cytotoxic effects by neutrophils and eosinophils, as illustrated in the case of immunity to the nematode *Strongyloides stercoralis* [74]. In *H. polygyrus* infection, antibodies associated with FcR on basophils allow the antigen-specific production of IL-4/IL-13 during challenge infection [75], leading to the induction of protective intestinal responses linked to the activation of epithelial cells, goblet cells, and muscle cells (Fig. 2), which together promote expulsion of worms from the gut [15]. Moreover, basophils can mediate protection against secondary infection with *N. brasiliensis* independently of Th2 cells [76].

In addition to antibody, macrophages also play a crucial role in immunity to *H. polygyrus*. These cells exist throughout the body as resident components of most tissues. These cells are embryonically derived, seeded into tissues in utero, and maintained by in situ proliferation [77, 78]. It is well established that during inflammation, additional macrophages of hematopoietic origin can develop from monocytes recruited from the bone marrow [77]. Macrophages play crucial roles in immunity and can adopt different activation states depending on context. Interferon-γ in combination with TLR agonists promotes M1 (or classical) activation, whereas IL-4 and IL-13 promote M2 (or alternative) activation by the IL-4Rα [79, 80]. From the host defense standpoint, M1 macrophages are inflammatory. In contrast, M2 macrophages are pro-angiogenic and pro-fibrotic, and make a range of molecules that serve to modulate inflammation, promote tissue repair, and regulate adaptive immunity [80, 81] (Fig. 2). Recent work has revealed that increases in macrophage numbers at sites of infection with helminth parasites can additionally, or exclusively, be driven by IL-4-stimulated proliferation of local macrophages [82] (Fig. 2), a finding that has spurred significant re-examination of the origin of these cells in different inflammatory settings.

M1 macrophages can kill growing schistosomes, and may be important for immunity to these pathogens in certain experimental vaccination settings where deliberately induced Th1 responses are protective [83]. However, M2 macrophages dominate during naturally developing type 2 responses during helminth infection, and play a significant protective role in some instances, such as *H. polygyrus* infection. In this case, ingested infectious larvae invade the intestinal wall before emerging into the intestinal lumen to grow into adult parasites. Whilst in their tissue invasive life stages, the parasites become foci of granulomatous inflammation, which by definition involves macrophages. Global deletion of macrophages during this period of a challenge infection in infected and cured mice effectively ablates protective immunity [62]. Immunity in this setting is sensitive to inhibition of arginase1, which is strongly expressed by M2 macrophages, and it appears as though larvae are being killed through a mechanism that induces metabolic stress [62]. M2 macrophages also play a role in inducing the IL-4/IL-13-dependent smooth muscle contractions that lead to the expulsion of *N. brasiliensis* worms [31].

Recently, M2 macrophages were shown to be capable of cooperating with neutrophils to kill *S. stercoralis* larvae in vivo [84]. While not restricted to roles in type 2 immunity, neutrophils do participate in inflammation associated with

helminth infections [15], playing a role in the promotion of type 2 immune responses during *N. brasiliensis* infection, for example [85]. However, they can assume pathologic roles in settings where type 2 immunity is less robust and Th17 responses emerge. This has been well documented in mouse strains which are genetically susceptible to developing acutely lethal disease when infected with *S. mansoni*, and in strains which normally develop chronic infection with this parasite, but which have been immunized prior to infection with schistosome egg antigens in complete Freund's adjuvant [86, 87].

The Protection of Vital Functions During Chronic Infection

The third role for protective type 2 responses is to allow host survival during chronic infection (Fig. 1c). This is the case during infection with the parasitic flatworm *S. mansoni*. Despite mounting a strong type 2 response during infection with this parasite, the host is unable to clear infection, which consequently is chronic. Nevertheless, loss of function of IL-4 in this system leads to severe morbidity and death associated with excessive inflammation in the absence of any increase in infectious burden [14]. During infection with this organism, eggs produced by the parasites (living in the portal vasculature) can become trapped in the sinusoids of the liver where they act as foci for $CD4^+$ T-cell-dependent granulomatous inflammation, a process that serves a critical host-protective role by participating in the sequestration of parasite eggs and the toxins that they secrete [88]. In the absence of IL-4 or IL-4Rα, schistosomiasis is acutely lethal [14, 89, 90], and this phenotype is recapitulated in mice that lack IL-4Rα expression on macrophages [89]; this indicates that the protective effects of IL-4 are mediated by macrophages and therefore, presumably, that M2 activation is critical. A failure to heal damage caused by the transit of parasite eggs into the gut lumen appears to be at least partially responsible for increased morbidity and mortality in the absence of M2 macrophages, although the emergence of M1 macrophages and associated inflammation also appears to play a contributing role [89]. A role for M2 macrophages in controlling acute tissue damage has also been noted in mice infected with the *N. brasiliensis*. Following transcutaneous infection, larval *N. brasiliensis* migrate through the lungs prior to entering the digestive system and maturing as adult worms in the intestine. In wild-type mice, pulmonary migration is associated with rapidly developing hemorrhage, inflammation, and reduced lung function, that resolves coincidently with the appearance of M2 macrophages at the site, but fails to resolve and rather is lethal in mice that lack IL-4Rα or are depleted of macrophages [91].

M2 macrophages also play an important role in regulating the intensity of the immune response to the benefit of the host. Several IL-4-induced genes are implicated in this process. For example, in *S. mansoni* infection, Relmα negatively regulates $CD4^+$ T-cell responses and in so doing prevents the development of severe type 2-associated immunopathology [92, 93] and Arginase1 produced by macrophages suppresses Th2 cell cytokine production and associated downstream inflammation

and fibrosis [94, 95]. Moreover, following exposure to the filarial nematode *Brugia malayi*, M2 macrophages develop the ability to potently suppress the proliferation of other cells through a cell contact-dependent mechanism that is presumably distinct from those mediated by Arginase1 or Relmα [96].

In the steady state, eosinophils have a clear role in adipose metabolic homeostasis [97]. During infections with helminths they increase in number and accumulate at tissue sites of invasion and inflammation. However, it has been difficult to assign eosinophils a defining role in either immunity or immunopathology commensurate with the magnitude at which they are involved in the response, and there remains a sense that the primary role of these cells during infection is yet to be discovered. Nevertheless, eosinophils have been shown to be capable of killing helminth larvae of various types [98], and can, along with M2 macrophages, make mediators such as Relmα, that regulate the intensity of type 2 inflammation [92].

The Modulation of Th2 Responses and Associated Inflammation During Chronic Helminth Infection: Everyone Benefits?

During chronic helminth infections caused by schistosomes and by filarial nematodes, Th2 responses peak during early stages of infection and then decline despite the fact that parasites, and therefore parasite antigens, persist [99–102] (Fig. 3). This process is reminiscent of the development of $CD8^+$ T-cell exhaustion during chronic viral infection [103]. It has been argued that loss of Th2 cell function over time in helminth infections reflects the development of adaptive immunologic tolerance to parasite antigens [104], resulting from persistent antigenic stimulation [105], and/or

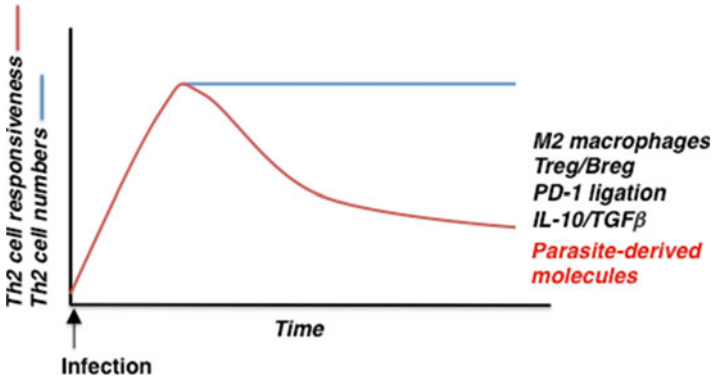

Fig. 3 The modulation of Th2 responses and associated inflammation during chronic helminth infection. Th2 cell responsiveness declines during chronic antigen despite the persistence of parasites. Immunomodulation does not reflect the loss of Th2 cells, but rather their regulation by M2 macrophages, Treg and Breg cells, cytokines, inhibitory receptor ligation, and parasite-derived molecules

extrinsic processes in which hyporesponsiveness is imposed by other cells such as M2 macrophages (discussed above, and [106]) or regulatory T (and B) cells (discussed by Maizels in "Regulatory T Cell Control of Type 2 Inflammation", and [107, 108]) (Fig. 3). The regulatory cytokines TGFβ and IL-10 have been implicated in this process [109], and IL-10 serves the additional function of suppressing residual Th1 responses that can occur in certain helminth infections, and therefore further polarizes the adaptive response in the Th2 direction [110, 111] (Fig. 3).

Downregulation of Th2 responses during chronic infection is generally thought of as being advantageous in settings where the immune response is incapable of clearing the infection and Th2 cells are causing immunopathology. This is the case in schistosomiasis, where despite the fact that the type 2 response plays a vital tissue-protective role there is a risk that the inflammatory and wound healing components of this type of immunity can themselves become pathological. Specifically, ongoing schistosome egg deposition and focused production of the pro-fibrotic cytokine IL-13 (which is linked to protective IL-4 production) in the liver can lead to severe fibrosis with portal hypertension [112]. In the absence of appropriate regulatory mechanisms, these processes can become overwhelmingly damaging (e.g. [94]).

Antibody can also play a protective role during helminth infection by regulating inflammation [21]. This is apparent in chronic *S. mansoni* infection in B-cell-deficient mice, in which immunopathology is exaggerated, leading to greater morbidity and mortality than is the case in infected wild-type mice [113]. Mechanistically, immunoregulation by antibody is likely to reflect the binding of IgG1-containing immune complexes to macrophages [114], with resultant anti-inflammatory effects, since in other systems macrophages that interact with immune complexes assume marked regulatory roles [115, 116], by producing IL-10 and TGF-β1, two cytokines which play important roles in regulating inflammation during schistosomiasis [117]. More broadly, the roles of B cells and antibody in survival during chronic schistosomiasis may reflect a mechanism analogous to that mediated by intravenous immunoglobulin therapy (IVIG), which is used successfully in humans for the treatment of autoimmune diseases [118]. Recent work has shown that the canonical type 2 cytokine IL-4 induces the increased expression of FcγRIIB on monocytes in humans and mice, and that mice which lack IL-4 or FcγRIIB are not protected against inflammation by IVIG [119].

In some cases, Th2 response downregulation favors parasite persistence. For example, reversal of hyporesponsiveness by blockade of the inhibitory receptor PD-1 expressed by Th2 cells during chronic infection with the filarial worm *Litomosoides sigmodontis* infection allows the expression of effective antiparasite immune responses [120]. The realization that type 2 immunity is often tightly regulated during helminth infections, and that these processes can favor parasite survival, led to the realization that parasites are able to produce molecules that strongly influence the immune response [121] (Fig. 3). The characterization of these molecules, and the possibility that they might be developed for therapeutic use in conditions where immune responses (particularly type 2 responses) are pathogenic, such as allergy and asthma,

is a subject of considerable current interest (discussed by Loukas in "Developments in the Design of Anti-helminth Vaccines," and [122]). The fact that many inflammatory conditions are alleviated by helminth infection attests to the promise of this approach [123].

How Do Helminth Antigens Promote Type 2 Responses?

One of the greatest advances in our understanding of the how type 2 immunity develops following exposure to helminth parasites has come from recent work on the "alarmins," IL-25, IL-33 and TSLP, cytokines made by damaged or activated epithelial cells that trigger innate immune responses and help orchestrate complementary adaptive immune responses (Fig. 2). IL-25 and IL-33 have been discussed above. The third alarmin, TSLP, has at least 2 known functions in type 2 immunity. The first is to suppress IL-12 production, thereby favoring the induction of Th2 responses [124]. TSLP is critical for type 2 response development during infection with *T. muris* [55, 124] but not during infection with *H. polygyrus*, *N. brasiliensis* [125] or *S. mansoni* [126], which may reflect differences in the inherent abilities of these parasites to suppress the production of IL-12 by DCs [125]. The second function of TSLP is to promote basophil hematopoiesis that is independent of IL-3, the cytokine conventionally associated with basophilia [55]. Wild-type basophils induced by TSLP, which are functionally distinct from IL-3-elicited basophils, are capable of restoring immunity to *T. muris* in otherwise susceptible $Tslpr^{-/-}$ mice [55].

The fact that IL-4 is essential for Th2 cell differentiation in vitro led to much speculation that an innate source of IL-4 would be critical for Th2 cell development in vivo, and consistent with this there have been many reports that type 2 innate cells are key players in Th2 cell activation. However, early observations showed that DCs exposed to helminth antigens preferentially induce Th2 cell differentiation, suggesting that despite the ability of many other cell types to contribute to type 2 immunity, direct contact of parasite products with these APCs is sufficient for Th2 polarization [127, 128]. The subsequent establishment of the primary importance of DCs in Th2 response development during helminth infections [129, 130], and the molecular identification of helminth products such as nematode chitin [131], and *S. mansoni* Omega 1, that possess Th2 adjuvanticity and are, at least in the case of the latter, able to drive Th2 cell development through effects on DCs [132, 133], has led to considerable interest in specific pathways activated in DCs that condition them to preferentially induce Th2 responses [29]. A major focus of this work has been on the identification of lectins that recognize and permit the uptake of helminth glycoproteins [134, 135], with mannose receptor being implicated as playing a major role in this process [136]. A detailed discussion of the role of distinct dendritic cell subtypes in Th2 immune response induction can be found elsewhere in this volume in the chapter "Dendritic Cells and Type 2 Inflammation" by Lambrecht.

Summary

The response to helminth infections involves the engagement of innate type 2 cells that in the steady state play important roles in metabolic homeostasis and sterile wound healing, and the overlapping initiation of adaptive immune responses in which Th2 cells, in an antigen-specific manner, make many of the same cytokines that are made by the innate type 2 cells. The type 2 cytokines IL-4 and IL-13 made during these innate and adaptive responses activate a variety of other cell types, notably including macrophages, that play crucial roles in parasite expulsion, or in establishing an environment in which infected hosts can survive in the face of ongoing tissue damage associated with worm persistence. A key feature of the adaptive response is the emergence of B cells making helminth-specific antibodies that can interact with other cell types, or act directly, to provide protection against further infection. During chronic infection with helminths, regulatory mechanisms develop, in part stimulated by immunomodulatory parasite products, that promote host and (directly or indirectly) parasite survival and have beneficial effects that can ameliorate unrelated inflammatory conditions. Rapid advancements in our understanding of type 2 immunity raise the possibility of the rationale development of new immunologic approaches for preventing or treating helminth infections, and developing approaches to minimize the effects of the inflammatory diseases that emerge in areas where helminth parasite transmission is prevented.

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