

Emerging roles of basophils in protective immunity against parasites

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Basophils, the least common type of granulocyte, have long been considered as minor effector cells in allergic responses because of their ability to release allergy-inducing chemical mediators such as histamine and leukotriene C4. However, it is unlikely that many animal species evolutionarily conserve basophils to only elicit allergic responses without any host-beneficial function. The study of basophils has been hampered by their rarity and difficult identification, as well as the lack of suitable animal models. Recent studies using novel analytical tools, including basophil-depleting antibodies and genetically engineered mice deficient only in basophils, have illuminated the crucial and nonredundant roles for basophils in protective immunity against both ecto- and endoparasites.

New era in basophil research

Basophils are the rarest type of granulocyte, and account for only ~0.5% of peripheral blood leukocytes. Paul Ehrlich was the first to document the existence of basophils in the circulating blood about 120 years ago. Since then, however, the functional significance of this minor population has long been an enigma. Basophils share several characteristics with tissue-resident mast cells, including surface expression of the high-affinity IgE receptor FcεRI and the release of allergy-related chemical mediators in response to various stimuli [1]. Therefore, basophils have been considered a minor, and possibly redundant, circulating relative of mast cells. This view was challenged in the early 1990s by the finding that basophils are an important cellular source of T helper 2 (Th2)-type cytokines (IL-4 and IL-13) in both mice and humans [2,3], which suggests a potential role for basophils in allergic responses and protective immunity against pathogens, particularly parasites [4,5]. However, the contribution of basophils to these immune responses remained to be proven, owing to the absence of animal models suitable for the functional analysis of basophils.

The recent development of novel analytical tools, including basophil-depleting antibodies [6,7] and genetically engineered mice in which only basophils are inducibly or constitutively deficient [8,9] (Figure 1a), has enabled the functional characterization of basophils *in vivo*. Studies using these novel tools have illuminated previously unap-

preciated roles for basophils in immune regulation, protective immunity, and immunological disorders (reviewed in [10–19]). We now appreciate that basophils play an important role in the initiation of Th2-type immune responses by providing IL-4 [7] and even by functioning as antigen-presenting cells under certain conditions [20–22]. Basophils also enhance humoral memory responses by promoting B cell activation and differentiation [23,24]. In addition to these regulatory roles in acquired immunity, they contribute to the development of immunological disorders, including IgE-mediated chronic allergic inflammation in the skin [6,25], IgG-mediated systemic anaphylaxis [26] and autoimmunity [27]. It is well known that parasitic infections commonly induce Th2-type responses that are characterized by production of Th2 cytokines, elevated serum IgE, and accumulation of eosinophils and basophils in affected tissues [4,5,28,29]. This review focuses on emerging roles of basophils in the development of these parasite-induced Th2-type responses and parasite expulsion.

Basophils in protection against ectoparasites (ticks)

Ticks are blood-feeding arthropods of medical and veterinary public health importance because of both direct damage caused by feeding and transmission of infectious agents [30]. On a global basis, ticks are second to mosquitoes as vectors of pathogens that cause various human infectious diseases, including Lyme disease. While taking a blood meal over a period of several days, ticks inject salivary gland-derived substances and pathogens such as virus, bacteria, protozoa and helminths, into the host. Several species of animals develop resistance to tick feeding after a single or multiple tick infestation [31,32], which is characterized by reduced numbers and weight of engorged ticks or tick death in subsequent infestations. Importantly, this acquired resistance to ticks contributes to reducing the transmission of pathogens from infected ticks to host animals [33]. This is the rationale for the development of tick antigen-based vaccines to prevent tick-borne diseases; however, the cellular and molecular mechanisms of naturally acquired protective immunity against ticks remained ill defined.

Large numbers of basophils and eosinophils are accumulated at tick feeding sites in guinea pigs that have acquired tick resistance [34]. Basophils represent up to 70% of the infiltrating cells, and basophil depletion with

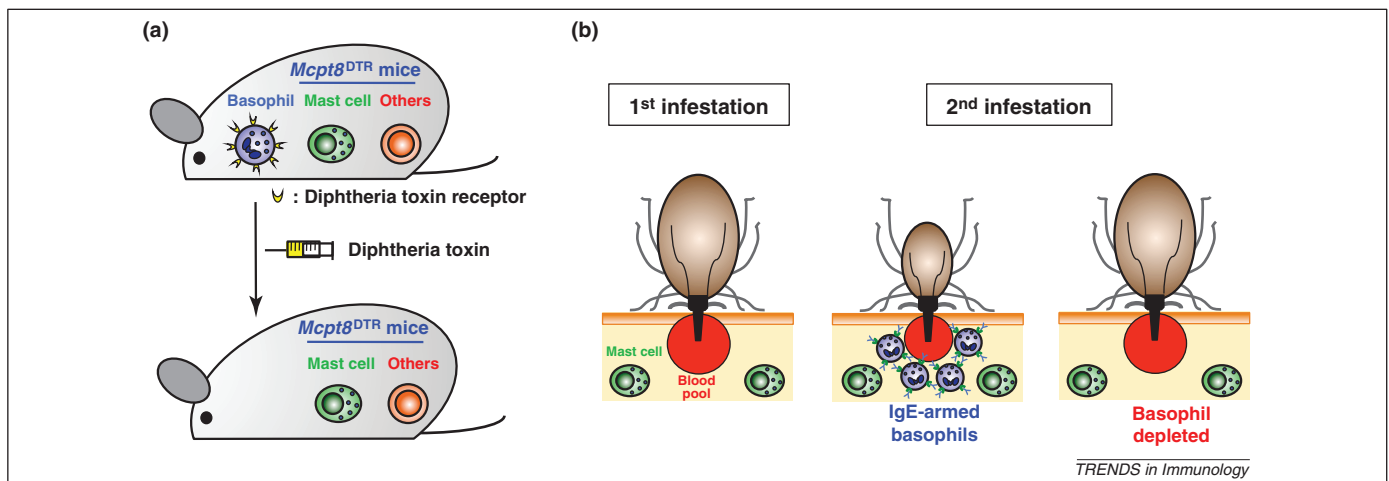


Figure 1. Nonredundant role for basophils in acquired protective immunity against ticks. (a) In *Mcpt8^{DTR}* mice, the diphtheria toxin receptor is genetically engineered to be expressed only on basophils, so that diphtheria toxin injection induces selective and inducible depletion of basophils. (b) Basophils are recruited to tick feeding sites in the skin during the second, but not the first, tick infestation (left and middle panels), concomitant with the manifestation of acquired tick resistance in the second infestation. Acquired tick resistance is characterized by reduced numbers and weights of engorged ticks in the second infestation compared to those in the first infestation (left and middle panels). Treatment of *Mcpt8^{DTR}* mice with diphtheria toxin before the second infestation abolishes basophil recruitment to tick feeding sites, and results in the loss of acquired tick resistance in the second infestation (right panel). Both tick antigen-specific antibodies (IgE) and the IgFc receptor on basophils, but not mast cells, are essential for the manifestation of acquired tick resistance (middle panel).

anti-basophil antiserum abolishes tick resistance [35], which demonstrates the importance of basophils for acquired tick resistance in guinea pigs. However, it remained uncertain whether this important finding could be generalized to other animal species. It is noteworthy that no basophil infiltration is reportedly detected in tick feeding sites on mice, although mice show acquired tick resistance [36–38]. Therefore, based on the observation that mast-deficient mice fail to acquire tick resistance, it was suggested that mast cells, instead of basophils, are important for acquired immunity against ticks in mice, [36,39,40]. However, another study showed that mast cell-deficient mice can develop resistance to a different tick species [37,41]. Thus, the relative contribution and differential roles of basophils and mast cells in protective immunity against ticks was unclear.

In accordance with the results of earlier studies [36,39,40], we reported recently that mast cell-deficient mice fail to show resistance against *Haemaphysalis longicornis* ticks in secondary infestation [8]. Neither B cell-deficient nor IgFc receptor-deficient mice acquire tick resistance, suggesting that the mast cell- and IgE-mediated, immediate-type hypersensitivity reaction is involved in acquired tick resistance, as proposed previously [40]. Unexpectedly, however, adoptive transfer of mast cells from IgFc receptor-deficient mice can confer tick resistance on mast cell-deficient mice [8], indicating that IgFc receptor-expressing cells other than mast cells contribute to antibody-mediated acquired tick resistance. To address this issue, a murine basophil-specific mAb TUG8, which recognizes the basophil granular enzyme mouse mast cell protease 8 (mMCP-8), was used [42]. Although Giemsa staining of skin tissue sections failed to detect basophils infiltrating tick-feeding sites in mice, consistent with earlier reports [36–38], a TUG8 mAb [42] clearly demonstrated that basophils are recruited to and clustered around the tick mouthparts during the second, but rarely the first, infestation, in parallel with acquisition of tick resistance

[8] (Figure 1b). Importantly, no acquired tick resistance was observed when mice were treated before the second tick infestation with a basophil-depleting mAb, either Ba103 specific to CD200R3 or MAR-1 specific to FcεRIα, suggesting the involvement of basophils in acquired tick resistance. However, the possibility that the impaired tick resistance is attributed to a deleterious off-target effect on mast cells rather than basophil depletion could not be excluded, because both mAbs react to mast cells as well as basophils [6,9,23].

Mcpt8^{DTR} mice were created to solve this potential problem with antibody-mediated basophil depletion. These mice express the human diphtheria toxin receptor only in basophils, which makes it possible to induce the specific ablation of basophils by treatment with diphtheria toxin [8] (Figure 1a). Diphtheria toxin treatment before the second tick infestation caused the loss of acquired tick resistance in *Mcpt8^{DTR}* mice (Figure 1b), which clearly demonstrates that basophils, in addition to mast cells, play a pivotal role in the manifestation of acquired tick resistance. Of note, adoptive transfer of basophils isolated from once-infested wild type but not IgFc receptor-deficient mice conferred tick resistance on uninfested wild type mice, showing that IgFc receptors on basophils rather than mast cells are required for acquired tick resistance [8] (Figure 1b). Thus, basophils but not mast cells are responsible for the antibody (most likely IgE) and IgFc receptor-mediated manifestation of tick resistance, even though both types of cells contribute to tick resistance. Because tick infestation induces increased levels of serum IgE regardless of basophil depletion, the loss of acquired tick resistance in the basophil-depleted mice might not be the result of failure in Th2-induced IgE production. The recruitment of eosinophils and neutrophils to the tick feeding sites is not impaired in basophil-depleted mice, suggesting that their recruitment is independent of basophils and might be insufficient or dispensable for the manifestation of tick resistance. Basophils surrounding tick mouthparts

appear to degranulate and release mMCP-8, a granzyme B-like serine protease, suggesting that molecules stored in basophil secretory granules, including mMCP-8, might contribute to tick resistance. Although the molecular mechanism underlying the basophil-mediated tick resistance remains to be clarified, the study reconciles the apparent discrepancy between guinea pigs and mice in the cellular components each species requires for acquired tick resistance [35–37,39–41], and illuminates a nonredundant role for basophils in protective immunity to ticks. Future studies are needed to clarify whether basophils also contribute to the protection against other ectoparasites. In this regard, it is notable that infestation of guinea pigs with tsetse fly induces accumulation of basophils in feeding sites with systemic basophilia [43]. Intriguingly, a patient with no detectable basophils or eosinophils was reported with widespread scabies in his body [44], suggesting that basophils might contribute to protective immunity to ectoparasites in humans.

Basophils in protection against endoparasites (helminths)

Helminths are the most common infectious agents of humans in developing countries. The major helminthiasis are those caused by intestinal helminths (ascariasis, trichuriasis and hookworm), followed by schistosomiasis and lymphatic filariasis [45]. Helminth infections typically provoke Th2-type immune responses characterized by eosinophilia, high levels of IgE, and T cell production of Th2 cytokines (IL-4, IL-5 and IL-13) [4,5,28,29]. Basophil numbers are increased in several animal models of helminth infection [46], in a T cell- and IL-3-dependent manner [47–49]. Basophils in humans and in mice readily generate large quantities of IL-4, both in an IgE-dependent and -independent manner, in response to various stimuli, including parasite-derived antigens [50–55]. IL-4 has a fundamental role in driving the differentiation of naïve T cells to Th2 cells [56]. However, the role for basophils in induction of Th2-type immune responses and worm expulsion was uncertain until recently [4,5]. Recent studies using novel analytical tools demonstrated clearly that basophils contribute to protective immunity against helminths to various extents, depending on the kinds of helminthes and types of infection (primary versus secondary), as we describe.

Nippostrongylus brasiliensis infection

N. brasiliensis causes short-lived infection with induction of a strong Th2-type immune response in mice, and is used as a model of human hookworm infection. The third stage larvae of *N. brasiliensis* infect mice through the skin, and migrate to the lung where an inflammatory response including eosinophil infiltration is induced. The larvae are coughed up and swallowed, and develop into egg-laying mature adults that reside in the gut lumen, and are finally expelled from the gut approximately 10 days post-infection. Expulsion of intestinal adult worms is crucially dependent on T cells [57,58] and Th2 cytokines (IL-4 and IL-13) as well as their receptor IL-4R α and signal transducer STAT6 [29,59]. The cellular source of these cytokines has been the subject of extensive study. A study on the effect of

IL-4 and IL-13 deficiency in T cells versus non-T cells demonstrated that IL-4 and IL-13 derived from innate cells, rather than CD4 T cells, play a crucial role in worm expulsion, while Th2 cell development depends largely on CD4 T cell-derived IL-4 and IL-13 [58]. Neither mast cells nor eosinophils are a major source of the IL-4 and IL-13 necessary for worm expulsion [58].

Studies with IL-4-green fluorescent protein reporter mice demonstrated that basophils produce IL-4 and accumulate in the lung during infection with *N. brasiliensis* [52,53]. The important role for basophils in worm expulsion was demonstrated in an experimental setting in which T cells cannot produce Th2 cytokines [60]. T cell and B cell-deficient *Rag*^{−/−} mice with the Thy1.2 phenotype were reconstituted with lymphocytes from IL-4 and IL-13-deficient Thy1.1-congenic mice, so that anti-Thy1.2 treatment depleted Thy1.2⁺ basophils, but not Thy1.1⁺ T cells, in these mice. The anti-Thy1.2-treated mice showed impaired worm expulsion and reduced accumulation of eosinophils in the lung, suggesting that IL-4 and IL-13-producing basophils crucially contribute to a Th2-type response to worm infection and worm expulsion. However, later studies questioned this role of basophils. Mice depleted of basophils with anti-Fc ϵ RI α mAb MAR-1 before *N. brasiliensis* infection show intact Th2-type responses and complete worm expulsion [17,61]. To address this issue, an alternative approach was taken using *Mcpt8Cre* transgenic mice [9]. These mice were originally engineered to express Cre-recombinase in a basophil-specific manner, with the aim of basophil-restricted deletion of any gene of interest. In contrast to the expected phenotype, however, most (>90%) basophils are deleted spontaneously, probably owing to the ‘Cre toxicity’ that comes from high copies of the transgene. *N. brasiliensis*-infected *Mcpt8Cre* mice show intact Th2-type responses and can expel worms efficiently [9]. Thus, basophils do not seem to be a major source of IL-4 and IL-3 that are necessary for induction of Th2-type responses and worm expulsion during primary infection with *N. brasiliensis*. Recent studies have identified novel innate lymphoid cells, designated natural helper cells, nuocytes, MPP^{type2} or Ih2 cells [62–65] that represent the predominant early source of IL-13 during infection with helminths, including *N. brasiliensis*. IL-13 rather than IL-4 crucially contributes to the expulsion of *N. brasiliensis* by means of goblet cell hyperplasia [29,59]. Taken together, the novel innate lymphoid cells, rather than basophils, appear to play an important role through their production of IL-13 in worm expulsion in primary infection with *N. brasiliensis* (Figure 2a). As these innate lymphoid cells express Thy1, the impaired worm expulsion in the mice depleted of basophils with anti-Thy1 treatment [60] might be explained by concomitant depletion of these cells. Alternatively, the effect of basophil depletion in this setting might represent the situation in secondary, but not primary, infection because the mice were sensitized by transfer of serum from worm-infected mice before basophil depletion [60].

In contrast to little or no contribution to worm expulsion in primary infection with *N. brasiliensis*, basophils play a host-protective role in secondary infection [9,66] (Figure 2b). Mice expel worms earlier in the second infection (by 5 days

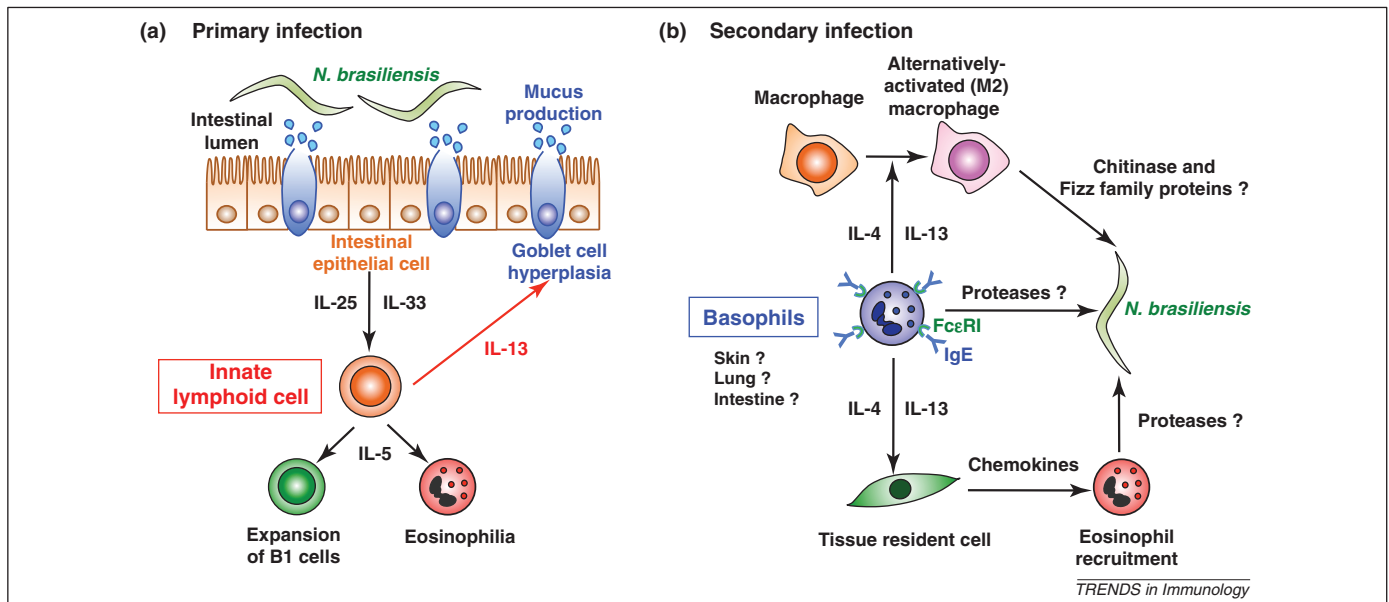


Figure 2. Protective immunity against helminth *N. brasiliensis* in the first versus the second infection. (a) In primary infection, basophils are dispensable for worm expulsion and induction of Th2-type responses. Intestinal epithelial cells produce IL-25 and IL-33, which in turn stimulate innate lymphoid cells to secrete large quantities of IL-13 and IL-5. IL-13 induces hyperplasia and mucus production of goblet cells, which promote worm expulsion from the intestine. IL-5 induces eosinophilia and expansion of peritoneal B1 cells. (b) In secondary infection, basophils play an important role in worm expulsion but not in induction of Th2-type responses. Location and mechanism of worm expulsion by basophils during secondary infection remain to be determined. Proteases released from activated basophils might attach worms directly. IL-4 and IL-13 secreted from activated basophils might differentiate macrophages to alternatively activated (M2) macrophages, which might in turn produce chitinase and Fizz family proteins to attach worms. These cytokines might also stimulate tissue-resident cells such as fibroblasts to secrete chemokines that attract eosinophils. Recruited eosinophils might attach worms through release of toxic proteases.

post-infection) than in the first infection (by 10 days post-infection). Mice depleted of basophils with either MAR-1 (anti-FcεRIα) or Ba103 (anti-CD200R3) before the second infection show impaired worm expulsion, regardless of the presence or the absence of mast cells [66], demonstrating the importance of basophils in worm expulsion in secondary infection. Of note, basophil-deficient *Mept8Cre* mice also show impaired expulsion, whereas they display no apparent defect in Th2 cell and eosinophil recruitment to the lung, IgE production or mucosal mastocytosis [9], suggesting that basophils are dispensable for these Th2-type responses in the second infection. It remains to be clarified how basophils contribute to worm expulsion in the second infection. Mice deficient for STAT6, which is necessary for IL-4 and IL-13 signal transduction, show impaired worm expulsion in the second infection, whereas depletion of CD4 T cells before the second infection has no apparent impact on worm expulsion [66]. This suggests the importance of basophil-derived IL-4 and IL-13 in host protection during the second infection (Figure 2b). Macrophages might be activated by these cytokines to differentiate into alternatively activated (M2) macrophages, which might contribute to worm expulsion through production of chitinase and Fizz family proteins. Tissue-resident cells such as fibroblasts might also respond to basophil-derived cytokines to secrete chemokines, which recruit protease-rich eosinophils to attach worms. Proteases released from activated basophils might also attach worms. The novel innate lymphoid cells might contribute mainly to worm expulsion from the small intestine [62–65] (Figure 2a), while basophils might execute their protective function upstream of the gut, somewhere in their migration route from the skin to the gut, during the secondary infection (Figure 2b).

Trichuris muris infection

T. muris is a gastrointestinal-dwelling nematode parasite of mice, and is studied as a model for infection by human *Trichuris trichiura*. It was shown recently that basophils are important for protective immunity in the primary infection of *T. muris* [22]. MAR-1-mediated basophil depletion results in impaired worm expulsion and poor Th2-type responses (IL-4 expression, goblet cell hyperplasia and luminal secretion of RELMβ). Protective immunity is impaired also in MHC II^{CD11c} mice in which MHC class II expression is restricted to CD11c⁺ dendritic cells (DCs), whereas DC depletion shows no apparent impact on worm expulsion. It is noteworthy that basophils express IL-4 and MHC class II (albeit at low level), and can function *in vitro* as antigen-presenting cells for Th2 cell differentiation [22], in accordance with two other independent studies in different experimental settings [20,21]. On the basis of these observations, it was concluded that MHC class II-dependent basophil-CD4 T cell interactions (rather than or in addition to DC-CD4 T cell interactions) promote Th2 cytokine responses and protection against *T. muris* infection. It is notable that a subset of DCs in lung draining lymph nodes expresses FcεRI in an asthma model, and can be ablated by MAR-1 treatment *in vivo* [67]. It remains to be determined whether such MAR-1-mediated DC depletion occurs in the *T. muris* infection model.

Litomosoides sigmodontis infection

L. sigmodontis is a filarial nematode parasite used as a model of human filarial diseases. This parasite causes chronic infection, in contrast to *N. brasiliensis* and *T. muris*, and adult worms inhabit the pleural cavity. Th2-type responses are induced late (peak at 6–8 weeks) in the

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course of *L. sigmodontis* infection, after parasite-specific IgE becomes detectable in the circulation. Ba103-mediated basophil depletion throughout the course of infection causes significant decreases in total and parasite-specific IgE, eosinophilia, and parasite antigen-driven CD4 T cell proliferation and IL-4 production [68]. However, basophil depletion does not alter the numbers of adult worms recovered from the pleural cavity [68]. Thus, basophils amplify Th2-type immune responses (probably through IgE-mediated activation), but do not serve a host protective role, during chronic infection with *L. sigmodontis*. It remains to be determined whether basophils contribute to worm expulsion in secondary infection.

Schistosoma mansoni infection

S. mansoni is a blood-dwelling trematode that causes schistosomiasis in humans. *S. mansoni* eggs induce strong Th2-type responses in mice. When eggs are injected into the footpads of mice, IL-4- and MHC class II-expressing basophils are transiently recruited to the draining lymph node where acute and synchronous Th2 cytokine responses occur [22]. MHC II^{CD11c} mice show poorer proliferation of CD4 T cells in the draining lymph nodes in response to egg injection, compared to wild type mice. Adoptive transfer of basophils isolated from egg-injected mice into naïve MHC II^{CD11c} mice rescues this impaired T cell proliferation, suggesting the contribution of basophils in addition to DCs to the efficient expansion of worm-responsive CD4 T cells *in vivo* [22]. However, another study showed that MAR-1-mediated basophil depletion has no measurable effect on Th2 cytokine production by CD4 T cells in the draining lymph nodes of egg-injected mice, whereas DC depletion results in impaired Th2 induction [69]. Impaired Th2 immunity by DC depletion, including reduced levels of serum IgE, is observed also in mice infected with *S. mansoni* cercariae, indicating that DCs play a major role in the induction of Th2 immunity to *S. mansoni* [69]. The contribution of basophils remains to be assessed by using genetically engineered mice deficient for basophils.

Concluding remarks

Basophils are evolutionarily conserved in many animal species. The recent development of useful tools for basophil research, including basophil-depleting antibodies and genetically engineered mice deficient only in basophils, has greatly advanced our understanding of the *in vivo* roles of basophils, and indicates that the primary function of basophils is the protection of the host from both ecto- and endoparasites. Basophils are often accumulated in affected tissues during parasitic infections, and can produce large quantities of Th2 cytokines, including IL-4, an important inducer of Th2 cell differentiation. Although parasitic infections commonly induce Th2-type immune responses, the requirement of basophils for such responses and protection against parasites is not always absolute, and the extent of their contribution varies, depending on the types of helminths and infection (primary versus secondary). This sounds reasonable, given that parasitic infections and the corresponding host immune responses are the consequences of a prolonged dynamic co-evolution between the host and parasite, and that the host utilizes different

strategies to protect it from distinct types of parasite. The involvement of basophils in protective immunity to protozoan parasites remains less well defined than it is for helminths. However, it is notable that in mice infected with that malaria parasite *Plasmodium chabaudi chabaudi*, a prominent switch from a Th1- to a Th2-type response occurs at the time of peak parasitemia or shortly thereafter, in parallel with increased numbers of IL-4-producing mMCP-8⁺ basophils in the spleen [70]. Future studies with the newly developed basophil-deficient mice [8,9] will dissect the role of basophils in immune responses to different types of parasites, and at different phases of parasitic infections. Elucidation of the molecular mechanisms by which basophils execute their anti-parasitic functions will help the development of efficient vaccination against parasites, and might cast new light on the pathogenesis of allergic disorders that share many characteristics with parasitic infections.

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