

MINI-REVIEW:

Mapping immune response profiles: The emerging scenario from helminth immunology

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Metazoan parasites of mammals (helminths) belong to highly divergent animal groups and yet induce a stereotypical host response: Th2-type immunity. It has long been debated whether this response benefits the host or the parasite. We review the current literature and suggest that Th2 immunity is an evolutionarily appropriate response to metazoan invaders both in terms of controlling parasites and repairing the damage they inflict. However, successful parasites induce regulatory responses, which become superimposed with, and control, Th2 responses. Beyond helminth infection, this superimposition of response profiles may be the norm: both Th1 and Th2 responses coexist with regulatory responses or, on the contrary, with the inflammatory Th17 responses. Thus, typical responses to helminth infections may differ from Th2-dominated allergic reactions in featuring not only a stronger regulatory component but also a weaker Th17 component. The similarity of immune response profiles to phylogenetically distinct helminths probably arises from mammalian evolution having hard-wired diverse worm molecules, plus tissue-damage signals, to the beneficial Th2 response, and from the convergent evolution of different helminths to elicit regulatory responses. We speculate that initiation of both Th2 and regulatory responses involves combinatorial signaling, whereby TLR-mediated signals are modulated by signals from other innate receptors, including lectins.

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Introduction: Are type 2 responses appropriate to deal with helminths?

Helminths are parasitic worms that belong to two distant animal taxa: the phyla nematoda and platyhelmintha. Infection of mammals by these fellow animals typically induces a type 2 immune response, broadly characterized by the activation of eosinophils, basophils and mast cells, the production of IgE, and the proliferation of T cells that secrete IL-4, IL-5, IL-9, IL-10 and IL-13 (Th2 cells). In contrast, type 1 responses are characterized by T cells that secrete IFN- γ (Th1 cells) and activate

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Abbreviations: **CLR:** C-type lectin receptor · **PAMP:** pathogen-associated molecular pattern · **PRR:** pattern recognition receptor · **SEA:** (*Schistosoma*) soluble egg antigen

macrophages to become fully anti-microbicidal. Type 1 responses are comfortably placed in current immunological models, and are well understood in molecular terms: they are a host adaptation geared to the control of intracellular pathogens, and are triggered by various pathogen-associated molecular patterns (PAMP) engaging pattern recognition receptors (PRR), such as the Toll-like receptors (TLR), present on dendritic cells (DC). In contrast, it has been more difficult to place type 2 responses in an evolutionary framework, and consequently in a clear immunological model. Also, until recently little was known regarding the molecular mechanisms that trigger these responses. Recent experimental and conceptual advances (reviewed in [1, 2]) are changing this situation.

Parasite immunologists have long oscillated between considering type 2 responses the result of immune manipulation by the parasites or the evolutionarily selected response against worms. The observation that almost all worms elicit these responses argued for the latter option. However, the first possibility was supported by the fact that parasitic worms establish chronic infections in the face of a type 2 immune response and was fostered by the type 1/protection–type 2/evasion dichotomy established in the *Leishmania major* model. The consensus now emerging is that type 2 responses are indeed the immune system's adaptation to dealing with worms. This consensus incorporates powerful evidence that type 2 responses are protective in many situations particularly against gastrointestinal nematodes (reviewed in [1, 3]). In addition, this new consensus incorporates two important lines of reasoning, outlined below and in the following section.

First, appropriate responses to multicellular invaders cannot be geared solely to the destruction of the pathogen. Live helminths, their eggs, and even their corpses, have enormous potential for direct as well as indirect (*i.e.*, through host reactions) tissue damage. Some examples are gut wall damage caused by schistosome eggs or hookworm bites, pulmonary hemorrhage brought about by lung migratory stages, and liver damage by migrating juvenile liver flukes. Therefore, the appropriate responses to helminths may be those that contain the parasites (through expulsion or encapsulation) while rapidly repairing damaged host tissues [4, 5]. The tissue-repair element present in the type 2 response is best illustrated by alternatively activated macrophages, which are central downstream effectors of this response. Their most abundant products during helminth infection (Ym1, RELM- α and arginase 1) are proteins induced in response to injury [5]. Further, mice deficient in alternatively activated macrophages fail to repair schistosome egg-induced gut wall damage and die from sepsis [6]. This wound healing function in turn needs to be finely tuned, or the outcome

can be destructive tissue remodeling or fibrosis [4]. Indeed, alternatively activated macrophages and their type 2 cytokine-dependent products are strongly associated with type 2-mediated pathologies such as allergy and fibrosis (reviewed in [7]).

The superimposition of regulatory responses onto type 2 responses

The second and crucial element underlying the view that type 2 responses are host-protective is a fine-tuning of definitions: the responses usually observed in chronic helminth infections are not merely type 2. They are rather type 2 responses that include an anti-inflammatory component. While the type 2 profile reflects the immune system's recognition of worms, the down-regulatory component likely reflects the parasites' adaptation to immune evasion. The resulting composite response profile has been recently named as “modified type 2” [2]; it is characterized by diminished IL-5 and IL-13 secretion, increased secretion of anti-inflammatory cytokines such as IL-10 and/or TGF- β , and in many cases, parasite-specific immune suppression (reviewed in [1, 2]). In the new view, a type 2 response less subject to regulatory control is observed in the allergic response of atopic individuals (reviewed [8–10]), as well as in helminth infections in which the adaptation of parasite to host is poor. In agreement, there is evidence from both experimental models [11–13] and clinical human studies (reviewed in [8, 10, 14]) that helminth infection ameliorates rather than exacerbates type 2-mediated inflammation associated with allergy. This has led to a reformulation of the 'hygiene hypothesis', which originally stated that type 1 response-inducing infections antagonized allergic responses, but now posits that allergy is held back by any infection that stimulates regulatory responses [14].

Although helminths are known to suppress host immunity through blockade of specific host mediators or functions [15, 16], they also co-opt host down-regulatory circuits. This includes the stimulation of regulatory phenotypes of myeloid cells [17–20], IL-10-secreting B cells [12, 13] and critically, the stimulation of regulatory T cells (T_{reg} cells) [20–25]. In a model of filarial infection [22], reduction of worm burdens was observed after a treatment that removed T_{reg} cells and augmented type 2 cytokine responses; this suggests that type 2 responses can control helminths (including tissue-dwelling ones), if released from the restraint imposed by regulatory responses.

In sum, this new scenario implies that the immune system has evolved to recognize helminths as such, and to react to them with a type 2 profile. It also implies that parasitic worms have not evolved away from this

recognition – at least not along the type 1–type 2 axis, probably because the type 1 response was no less restrictive to them. This is particularly true for tissue-dwelling helminths, where killing in some settings involves type 1 immunity [26–28]. Rather, helminths have developed the capacity to stimulate the host's endogenous immunoregulatory mechanisms.

A 2-D immunological map with inflammatory–regulatory and type1–type2 axes

The evidence for T_{reg} cell responses is strong in infection with many pathogens that typically induce type 1 responses (reviewed in [29]). Therefore, both type 1- and type 2-inducing pathogens capable of chronic infection superimpose an anti-inflammatory component on the basic response pattern that they elicit. This takes us from a one-dimensional map of immune responses, defined by the type 1–type 2 axis, to a two-dimensional one, in which an “inflammatory–regulatory” axis transverses the first one (Fig. 1a). In this map, four major response arms can combine in pairs, giving immune response profiles that may be summarized as: type 1-inflammatory (acute bacterial infections and classical autoimmunity), type 1-regulatory (chronic protozoan and mycobacterial infections), type 2-inflammatory (allergic and fibrotic reactions), and type 2-regulatory (or “modified type 2”; helminth infections). Response arms that are mutually antagonistic (type 1 and type 2; inflammatory and regulatory) are not shown to overlap, although real-life responses may well fall between them. The map accommodates not only the prevention of allergic pathologies by worm infections, but also the prevention of type 1-dominated autoimmune diseases by diverse pathogens capable of stimulating anti-inflammatory circuits (reviewed in [30]). Presumably, such circuits cannot be done away with by the host because they are needed for tissue-maintenance functions [29, 31].

Each of the response arms on the map axes has innate and adaptive components. However, the four major CD4 T cell subsets, namely Th1, Th2, Th17, and T_{reg} , can be conceived as central elements of the four response arms in the map, type 1, type 2, inflammatory, and regulatory, respectively (Fig. 1b). Classing the newly described Th17 cells (reviewed in [32]), and not Th1 cells, into the “inflammatory” arm of immunity is consistent with compelling recent evidence that the former rather than the latter are primarily responsible for immunopathology in autoimmune conditions (reviewed in [33]). Th17 responses appear to combine with Th1 responses also in mycobacterial [34] and protozoan [35] infections. Information on Th17 responses in

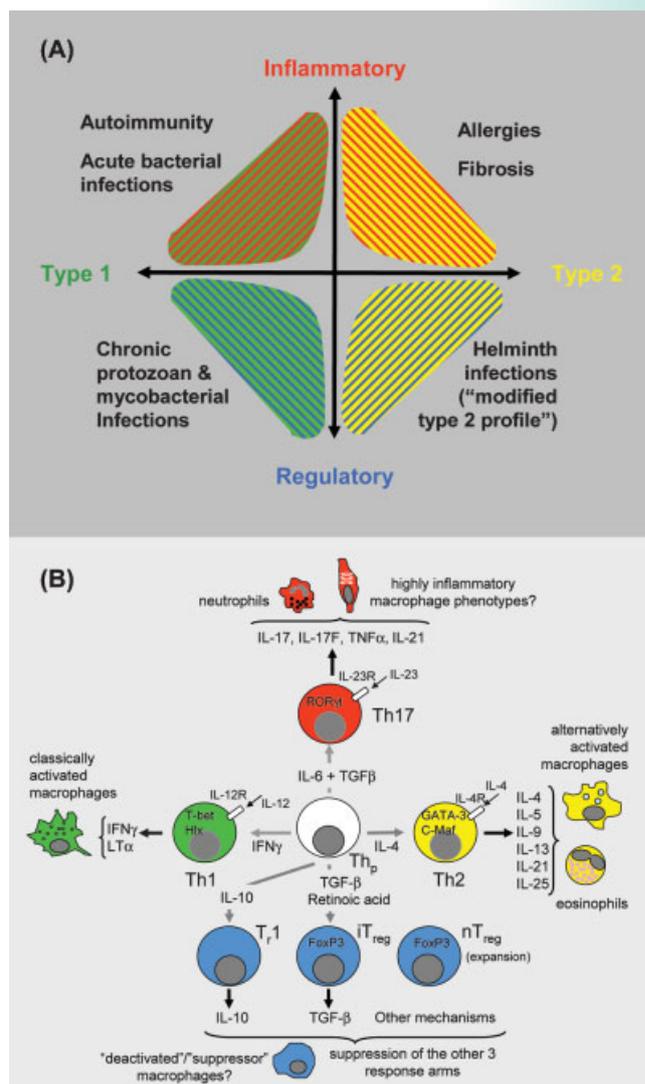


Figure 1. A two-dimensional map of immune responses, and major cellular and molecular elements of the four major response arms. It is proposed that immune responses can be summarized in a two-dimensional “map” defined by type 1–type 2 and inflammatory–regulatory axes (A). Thus, both type 1 and type 2 responses can combine with regulatory or inflammatory responses. Each response direction can be targeted to foreign as well as self antigens, but the responses to self in healthy individuals are mostly regulatory. The central elements of type 1, type 2, inflammatory and regulatory responses are Th1, Th2, Th17 and T_{reg} cells, respectively; each of these is driven by a particular set of signals from innate immunity, and recruits a characteristic set of effector cells (B). Th1, Th2, Th17 negatively regulate each other, and T_{reg} cells suppress all other three subsets (reviewed in [29, 32]). Hence counter-regulation occurs not only between CD4⁺ T cell subsets in opposite poles of the same axis but also between those in perpendicular axes, as reflected in the shape of the areas in each quadrant in (A). In spite of the counter-regulation, the different T cell subsets coexist in real-life responses. The idea of two axes was previously proposed by Yazdanbakhsh et al. [14].

helminth infections is so far very limited but is consistent with IL-17 as a mediator of inflammatory pathology [28, 36–38]. In mouse models of asthma, a type 2-dominated pathology, Th17 responses are needed for the full deployment of inflammation [39, 40]. In one of these works, eosinophil and neutrophil recruitment was shown to depend on Th2 and Th17 cells, respectively, suggesting that the mix of effector cells recruited in each situation may mirror the particular combination of Th cell responses activated. It is therefore likely that Th17 responses will be found to combine with type 2 as well as with type 1 responses, thus mirroring (in the inflammatory direction) the regulatory-type 1 and regulatory-type 2 responses outlined above. Hence, the separation along the inflammatory-regulatory axis that exists between responses to well-adapted helminths and allergic reactions could be due (at the T cell level) not only to the differential presence of T_{reg} cells but also to differences in the strength of the Th17 response.

How does our innate immune system perceive helminths?

Response profiles are ultimately dictated by the ways in which the innate immune system perceives potential pathogens and their effects on tissues. The size and complexity of helminths and a lack of structural biochemical knowledge has hampered our ability to define their innate recognition. Although this gap is being alleviated by transcriptomic and, to some extent, proteomic data, the glycoconjugates in particular still represent a daunting frontier.

A second difficulty arises in the superimposition of immune response profiles discussed above: the innate immune system's perception of helminths surely involves the parallel decoding of type 2 and regulatory signals (and possibly also Th17 signals). In practice, the quests for signals that drive type 2 and regulatory responses have been largely indistinguishable until now. For example, helminth products have frequently been shown to inhibit IL-12 and TNF- α secretion by APC (reviewed in [1, 41]), but this can be interpreted as favoring type 2 responses, regulatory responses, or both. Conceptually, the type 2 profile is widely described as anti-inflammatory, and the regulatory cytokine IL-10 (recently found to be produced by Th1 cells as well [42]) is usually thought of as typical of Th2 cells. A conceptual separation between type 2 and regulatory responses is needed, even if worm-derived molecules are capable of inducing both.

Focusing on type 2 responses, a further hurdle is that the signals from DC that instruct Th2 cell development are not known. Type 2-inducing preparations such as *Schistosoma* soluble egg antigen (SEA) typically induce

feeble DC responses, with few if any signs of activation. Rather, they tend to antagonize type 1-inducing TLR agonists (reviewed in [41]). MyD88 is the central adaptor for most TLR and relays signals that instruct type 1 and suppress type 2 responses. In its absence responses shift to type 2 [43], an observation that led to the hypothesis that a lack of TLR-derived maturation signals on DC leads to type 2 responses. At the extreme, this “default hypothesis” implied that type 2 PAMP were defined merely by the absence of type 1 PAMP. This hypothesis fails, because DC co-pulsed with type 1- and type 2-inducing pathogens can induce both response types in parallel [44]. Also, SEA induces up-regulation of OX40L in DC, and blocking of OX40L–OX40 interaction attenuates the Th2 response elicited [45]. It is worth considering that the weak responses of DC to helminth products (*in vitro*) might reflect that tissue-to-DC signals are particularly important for the instruction of type 2 responses. A cytokine signal from intestinal epithelial cells to DC is needed for type 2 responses to *Trichuris* infection [38], and as discussed below, signals of tissue injury likely contribute to type 2 responses [5].

A problem related to the identity of DC signals that instruct type 2 responses is the lack of candidate PRR for this arm of immunity. There is a perception that TLR signaling always antagonizes type 2 responses, but this is wrong: although inhibition of type 2 responses is hard-wired to MyD88, in MyD88-deficient settings LPS can promote type 2 responses in a TLR4-dependent manner [46, 47]. Further, TLR4 may act as a PRR for some type 2 pathogens. Two candidate type 2-inducing helminth PAMP, the SEA oligosaccharide lacto-*N*-fucopentaose III (LNFPIII) and certain phosphorylcholine-decorated glycans from filarial nematodes act in a TLR4-dependent manner [48, 49]. Surprisingly, the filarial glycans do not require conventional TLR4 signaling, suggesting that TLR4 may act as co-receptor in that setting [48].

If TLR4 and possibly other TLR participate in type 2 responses, how do type 2 PAMP activate MyD88-independent pathways while not activating dominant MyD88-dependent ones? The answer may lie in combinatorial signaling. Co-ligation of non-TLR PRR can profoundly alter signaling outcomes, certainly in terms of cytokines. This is well documented for TLR2 and the C-type lectin receptor (CLR) dectin-1, both engaged by fungal carbohydrates (reviewed in [50]). Three less well understood CLR bind to glycans in SEA [51, 52]. One of these, DC-SIGN, is specific for the Lewis^x determinant, present in *S. mansoni* LFNPIII [51], and may participate in the observed effects of this carbohydrate. Preferential activation of ERK observed after DC-SIGN cross-linking [53] is also reported for LFNPIII [49] and SEA [54]. Overall, TLR, CLR, and possibly other receptor classes, acting in combination, may convey type 2 signals that bypass MyD88 activation.

Perhaps accordingly, type 2 PAMP are highly diverse, including proteins as well as lipids and carbohydrates (reviewed in [1, 41]).

The identification of helminth-derived signals that induce regulatory responses is additionally complicated by the existence of different (and not fully defined) T_{reg} subsets (Fig. 1b), encompassing naturally occurring T_{reg} , which are instructed in the thymus and T_{reg} induced in the periphery. There is evidence for the expansion of natural T_{reg} by helminth infection [21, 23] as well as for the induction of T_{reg} in response to helminth products [55]. Induction of T_{reg} , which are IL-10-dependent, Tr1-like cells (Fig. 1b), is observed *in vitro* in response to DC exposed to lysophosphatidylserine polar lipids from *S. mansoni*, and is a TLR2-dependent phenomenon [55]. Perhaps accordingly, TLR2-deficient mice infected with *S. mansoni* develop impaired regulatory responses and exacerbated immunopathology [25]. In contrast, MyD88-deficient mice infected with *S. mansoni* do not appear impaired in their regulatory responses, but as expected, are shifted towards type 2 on the type 1–type 2 axis [25]. So, similar to that discussed above, signaling from individual TLR can have effects not predicted from the properties ascribed to MyD88. It seems that we still have things to learn on TLR signaling, and we certainly have much to learn on combinatorial signaling involving non-TLR receptors. Although not yet directly shown, CLR may also participate in helminth-induced regulatory responses, since in other systems, DC-SIGN is associated with anti-inflammatory immune deviation [50, 56], and induction of Tr1 cells [57].

What is the relationship between response profile and pathogen phylogeny?

Although helminths drive broadly similar type 2 immune responses, the search for helminth-specific molecular patterns is misguided. Not only do helminths belong to two distinct animal phyla but type 2 responses can also be induced by products from arthropods [58, 59] (a group that includes ectoparasitic species). Nematodes, platyhelminths and arthropods are all animals, but so are we. And the time those three groups have spent evolving as separated branches is much longer than the time (if any [60]) that their ancestors spent as a single lineage once they separated from our own. The hope for a phylogenetically tied type 2 signature is also undermined by the diversity of the molecules (or molecule classes) that can induce type 2 responses (reviewed in [1, 41]). It is therefore possible that the immune system has, through evolution, come to recognize individual helminths through different molecules, as “type 2 organisms”. In other words, a large set of molecules, subsets of which are associated with each

of the animal taxons that include parasites, would be decoded by a broad set of PRR acting in combination. The translation of many distinct signals to a single response profile may take place mostly at the level of the pathogen-DC interaction, but could also occur at the DC–T cell interaction level [45].

In addition to canonical PAMP–PRR interactions, certain molecular-level functional cues might contribute to the type 2 response. One such cue could be extracellular proteolytic activity. Helminths release proteases to aid tissue migration, and proteases from both helminths and arthropods have been identified as type 2 adjuvants or allergens [61]. Further, at least one receptor involved in allergic inflammation is protease activated [62]. Complement activation might be another contributing signal, as C3 deficiency inhibits type 2 responses in schistosomiasis [63]. Such functional cues, proteolytic activity especially, may also arise from damaging effects of helminth activity on host tissues [5]. Although we have argued that type 2 responses lack a phylogenetic basis (*i.e.*, helminth-specific), a contribution from metazoan-‘specific’ molecular signatures cannot be ruled out at this stage. Xenograft rejection tends to be associated with a type 2 bias, resembling eosinophil-mediated helminth killing [64, 65]. It is therefore conceivable that signals broadly associated with animals (including helminths), together with signals of tissue injury, can induce type 2 responses. Indeed, sterile tissue injury alone is sufficient to induce an innate type 2 response but other signals are required to induce full Th2 cell activation [5].

The idea that type 2 responses should not be wired to a “phylogenetic classification” should not surprise us. In fact, type 1 responses are triggered by an even wider spectrum of organisms, encompassing prokaryotes, fungi, and protozoans (Fig. 2). Therefore, the immune system appears to classify “practically” rather than phylogenetically, causing “type 1” and “type 2” organisms to correspond simply to unicellular and multicellular ones. Within unicellular organisms, we may also broadly distinguish between extracellular and intracellular ones, mounting responses that have respectively a strong or a weak Th17 component, in addition to the Th1 element (reviewed in [32]). Such “practical” classifications probably incur considerable levels of “phylogenetic overspill”, as group-common, rather than pathogen species-specific, molecules are often used for recognition. Thus, the responses elicited by a given pathogen are often also triggered by its close relatives, including any non-pathogenic ones, as illustrated by the induction of type 2 signals with extracts of the free-living nematode *C. elegans* [66]. In contrast, pathogen induction of regulatory pathways would have evolved as adaptations to parasitism, and therefore would be absent from free-living relatives. For example, DC-SIGN is engaged by

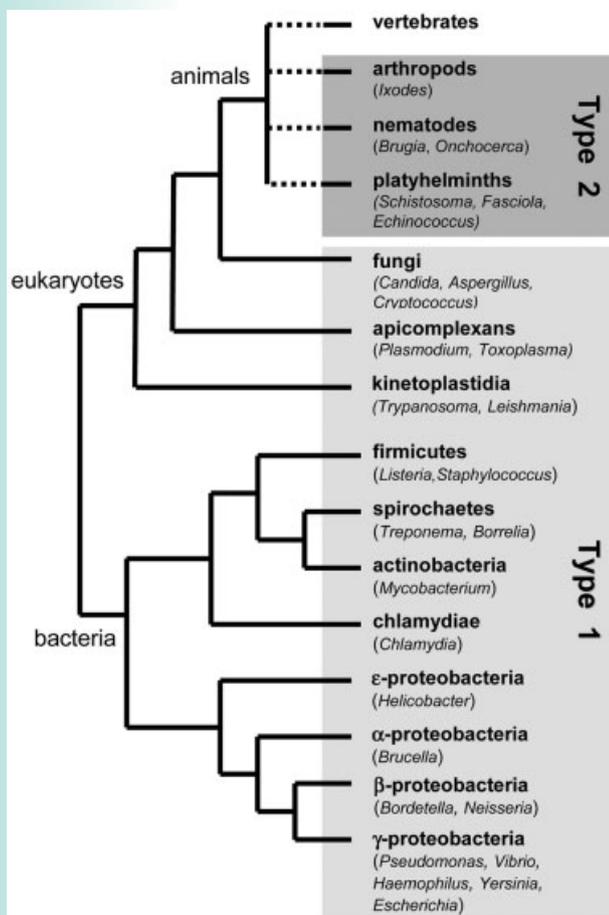


Figure 2. The classification of pathogens by the immune system into type 1 and type 2, mapped onto the tree of life. The classification reflects the major response profile elicited, on the basis of published data but is by necessity a simplification. Immune deviation away from the primary response pattern (e.g. Th2 induction by *Vibrio cholerae* toxin or elicitation of IL-4-secreting T_{reg} by *Candida* hyphae) is not included. The tree shows only topology, and not genetic distances. Topological relationships were taken from [60], except that arthropods, nematodes, platyhelminths, and vertebrates (the relationships among which are currently debated [67]) are represented as if having diverged simultaneously from their common root. Only taxa harboring vertebrate pathogens are represented, the list is not comprehensive, and taxons named do not necessarily have the same hierarchy.

pathogenic mycobacteria, resulting in immune suppression, but not by avirulent mycobacteria [56].

Conclusions

In summary, the stereotyped response pattern that worms usually elicit would have arisen from two processes: the adaptation of the immune system to “class together” organisms dealt with adequately by similar types of responses, and the convergent evolution by helminths to elicit regulatory responses (an adapta-

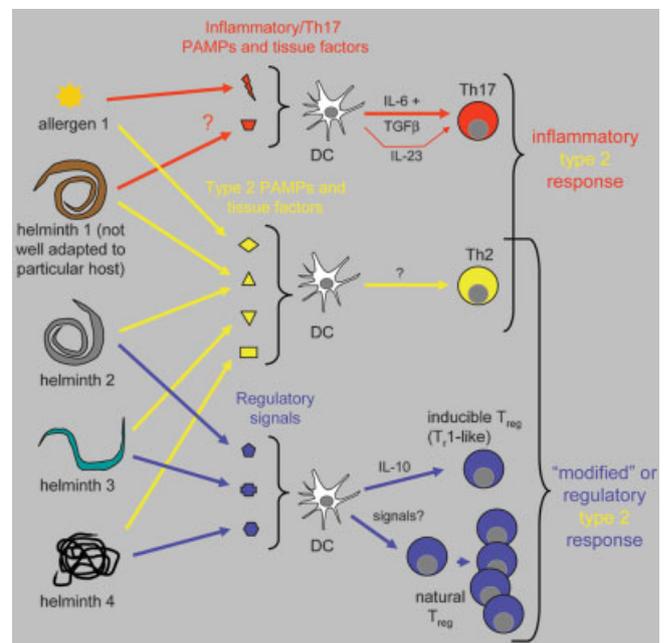


Figure 3. Summary of proposed mechanisms giving rise to the typical responses to helminth infection and to allergic reactions. A range of organisms and environmental agents elicit type 2 responses through a broad set of type 2 PAMP and/or tissue factors released by their activities. Depending on the extent of concurrent induction of regulatory responses, and possibly also inflammatory/Th17 responses, type 2 responses are non-inflammatory or inflammatory. Examples of helminth-host pairs that are not well matched and hence result in inflammatory responses are infection of cattle by the common (sheep) strain of the larva of the cestode *Echinococcus granulosus* and infection of humans with *Anisakis simplex*.

tion common to organisms that establish chronic infections). According to this scenario (Fig. 3), the type 2 component of responses, but not the regulatory one, would be expected to show “phylogenetic overspill”. A failure of regulatory circuits has been strongly implicated in the epidemic rise in allergy and autoimmune disease in the developed world as well as middle-income nations [14, 30]. Thus, understanding the induction of regulatory components by helminths, the most complex endoparasitic organisms, is imperative for the development of new therapeutic approaches for these diseases.

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