Th1–Th2: reliable paradigm or dangerous dogma?

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The identification of crossregulating T helper (Th) cells has revolutionized current understanding of the immune response to infection. While paying tribute to this revolution, Judith Allen and Rick Maizels argue that the paradigm can be dangerously oversimplified and that the interaction between host and pathogen cannot always be addressed in the context of Th1 and Th2 cells.

In 1986, Mosmann and colleagues[1] started a conceptual revolution in immunology by dividing T helper (Th) cells into two populations with contrasting and crossregulating cytokine profiles. This new paradigm was enthusiastically taken up in every area of immunology and infectious disease. Studies of *Leishmania* infection in mice were instrumental in establishing the functional relevance of these Th subsets. From these studies, and the many that were to follow, immunologists saw the relevance and value of using infectious disease models to study fundamental pathways. Similarly, microbiologists, parasitologists and virologists were able to make sense of the immunological phenomena they observed during infection.

These past 11 years have been exciting times as the Th1–Th2 paradigm has been applied to infectious disease, cancer, transplantation, neonatal tolerance, autoimmunity and more. However, as influential as this process has been, it is time to question its universality and to identify the pitfalls of over-simplification as some seek to allocate every phenomenon in immunology to one Th subset or the other. To a significant extent, the role of Th1 and Th2 cells has become dogma, with categorical statements now appearing in immunology textbooks that Th1 responses mediate killing of intracellular parasites and Th2 responses eliminate extracellular ones. The inherent danger in such strong preconceptions is that they threaten the process of discovery.

We have been drawn to this perspective by considering infectious diseases, which have arguably been the driving force behind the evolution of the immune system. The existence of multiple overlapping mechanisms for immune defence against infectious diseases has become starkly apparent, more so than in any other area of immunology. Pathogens themselves have evolved startlingly sophisticated means of immune subversion, such that their survival depends on a series of fine-tuned interference mechanisms rather than a generic ability to ignore 'Th1' or 'Th2'-type responses.

Dogma 1: Th1 responses protect against intracellular pathogens

The archetypal 'Th1' response revolves around the production of interferon γ (IFN-γ) and the subsequent activation of macrophages. While these features of cell-mediated immunity are certainly important for the resolution of intracellular infections, the role that T cells, cytokines and other effector cells play in disease outcome may not always fall easily into the discrete Th1–Th2 pattern (Box 1).

Leishmaniasis

The protozoan parasite *Leishmania major* infects macrophages and causes lethal infection in BALB/c mice but a self-limited infection in most other mouse strains. The susceptibility of BALB/c mice has been shown to be dependent on the production of interleukin 4 (IL-4) early in infection, while control of infection and resistance to reinfection in other mouse strains is dependent on IFN-γ) (Refs 2–4). This excellent model for the differential development and function of T-cell subsets gave immediate relevance to the Th1–Th2 paradigm. Equally, these studies enhanced understanding of the mechanisms and pathways that lead to inflammation, as well as the importance of inflammatory mediators such as nitric oxide in the destruction of many pathogens.

An apparently crystal-clear picture of the role of Th1 cells in disease resolution and Th2 cells in disease exacerbation has been painted by the *L. major* model. However, there are key data that cannot be explained simply in terms of Th1- and Th2-cell subsets. Despite the consistent observation that neutralizing antibodies to IL-4 save susceptible mice from fatal infection, Noben-Trauth *et al.*[5] found that IL-4-knockout (IL-4$^{-/-}$) BALB/c mice, which do not develop Th2 responses, are as susceptible as wild-type BALB/c mice. By contrast, Kopf *et al.*[6] found the same transgenic IL-4$^{-/-}$ BALB/c mice exhibited the expected resistant phenotype. While these contrary results may be attributed to strain differences in virulence, or other subtleties of experimental protocol, the original paradigm cannot entirely account for the true complexity of the *in vivo* situation.

The critical role of IL-4 in disease susceptibility has also been challenged in earlier studies in which direct administration of IL-4 has reduced both lesion size and parasitaemia, and rendered animals resistant to reinfection[7,8]. This may be explained by the ability of IL-4 to act synergistically with IFN-γ to activate murine macrophages to kill *L. major* amastigotes[9]. Paradoxically, the transfer of IFN-γ-producing, *L. major*-specific Th1 cells can exacerbate cutaneous leishmaniasis in

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Box 1. Are polarized T helper (Th)-cell responses beneficial to the host or parasite?

Despite the prevailing maxim that Th1 responses protect against intracellular pathogens and Th2 responses protect against helminth parasites, exceptions are more numerous than examples:

- In murine *Leishmania* infection, interleukin 4 (IL-4) can accelerate or delay clearance depending upon the time of administration[7,8]
- In human leishmaniasis, Th1 responses are deficient in systemic visceral and chronic mucocutaneous disease; however, Th1 cells are dominant in localized lesions, while healthy cured individuals show strong reactivity in both Th1- and Th2-type compartments[72]
- In murine malaria and toxoplasmosis, unrestrained Th1 responses are deleterious, while a degree of Th2 responses may be required to prevent autodestruction[22,23,26]
- In leprosy, polarized Th1 and Th2 responses can each lead to disease, but of different form – tuberculoid and lepromatous, respectively[36]
- In the human helminth diseases filariasis and schistosomiasis, the most heavy and chronic infections are in patients with the strongest Th2 responses[73]
- In murine schistosomiasis, IgE-depleted mice are more resistant to infection than are controls[60]

some circumstances[10]. Significantly, using T-cell-chimaeric mice, Shankar and Titus[11] demonstrated that high levels of IL-4 can accompany cure and that non-T-cell factors may be as important as T-cell factors in the resistance to *L. major* infection. These studies, often ignored, suggest that the critical functions attributed to IFN-γ and IL-4 in leishmaniasis may be influenced by a vast array of factors such as parasite strain, other cell types present, and additional cytokines that contribute significantly to the outcome of *L. major* infection [including granulocyte–macrophage colony-stimulating factor (GM-CSF), IL-3, IL-10, transforming growth factor β (TGF-β), tumour necrosis factor α (TNF-α) and IL-12][12,13].

On a wider scale, the findings with *L. major* cannot readily be applied to other *Leishmania* species, let alone other intracellular parasites. In *L. donovani* infection of mice, differential production of Th1 and Th2 cytokines does not control the rate of cure: although production of IFN-γ correlates with resistance to infection, Th2 cytokines do not determine susceptibility[14,15]. Consistent with this, IL-4-deficient mice are slightly more susceptible to infection with *L. donovani* than their wild-type counterparts, suggesting that IL-4 may be protective in some circumstances[16] and indeed can promote resistance rather than susceptibility to intracellular pathogens.

Malaria

Malaria stands as an interesting contrast to the *Leishmania* system since not only are multiple cell types required to eliminate infection[17,18], but also different mechanisms act against different life-cycle stages of one species, and against the same stages of different species. The protozoan *Plasmodium* initially infects liver cells, before establishing its major asexual reproductive cycle within red cells. There are brief periods of extracellular life during transit between hepatocytes and/or erythrocytes. The intracellular liver stage can provide a target for $CD8^+$ cytotoxic T lymphocytes (CTLs), but there is controversy as to whether this is the most important pathway in natural malaria[19]. Infection with liver-bound sporozoites is prevented by IL-12 and IFN-γ (Ref. 20). IFN-γ inhibits the growth of the parasites within liver cells, by activating Kupffer cells, as well as by inducing other cytokines such as IL-6 that restrict parasite development. Together, these data argue for a critical role of IFN-γ rather than an absolute requirement for any one of the cell types that can produce this cytokine.

In contrast to the liver stage, eliminating infection at the blood stage requires $CD4^+$ T cells[17]. Following *P. chabaudi* infection in mice, Th1-type cells are needed to control the acute peak of parasitaemia, while antibodies produced with the help of Th2 cells are required for clearance of parasites[17,18]: thus, vaccination protocols that amplify both Th-cell types are successful[21]. Moreover, it appears that an exclusive Th1 response is more likely to have detrimental consequences for the host, because the pathogenesis of fatal cerebral malaria is Th1 dependent[22] and excess IL-12, which drives Th1-cell responses, can kill a mouse that would otherwise have survived infection[23]. Perhaps, therefore, the subsequent Th2 response serves both to eliminate residual parasites and to moderate any pathological consequences of the earlier Th1 response.

As with *Leishmania*, different species of malaria vary in their requirements for effective control. In mice, *P. yoelii* can be controlled by passive antibody transfer but *P. chabaudi* cannot[24], reinforcing the tenet that each successful parasite has found a particular combination of evasion mechanisms that operate in a particular host (neither species is a natural parasite of mice). Equally important, the host immune system has evolved counterbalances to maximize survival in the face of potentially lethal levels of inflammatory mediators; in some cases, such downmodulation is well measured, but in other cases it fails[22,23].

Other intracellular pathogens

During intracellular infections with *Listeria monocytogenes* (bacterial) and *Toxoplasma gondii* (protozoal), the dependence upon IFN-γ for protection is so profound that administration of IL-12 to severe combined immunodeficiency (SCID) mice counters infection[25,26]. Thus, it is not Th1 cells *per se* that are required but IFN-γ, which is produced by natural killer (NK) cells in SCID mice. In apparent contrast, survival of normal mice infected with *Toxoplasma* also requires IL-4 since IL-4 $^{-/-}$ mice show greater mortality than do wild-type mice[27,28] (Fig. 1a). This is not due solely to unrestrained production of proinflammatory cytokines, as the IL-$4^{-/-}$ mice have significantly higher parasite numbers[28]. During acute infection, IL-4 may prevent mortality by limiting inflammation but, later in infection, may enhance IFN-γ production and thus parasite killing. The effects of IL-4

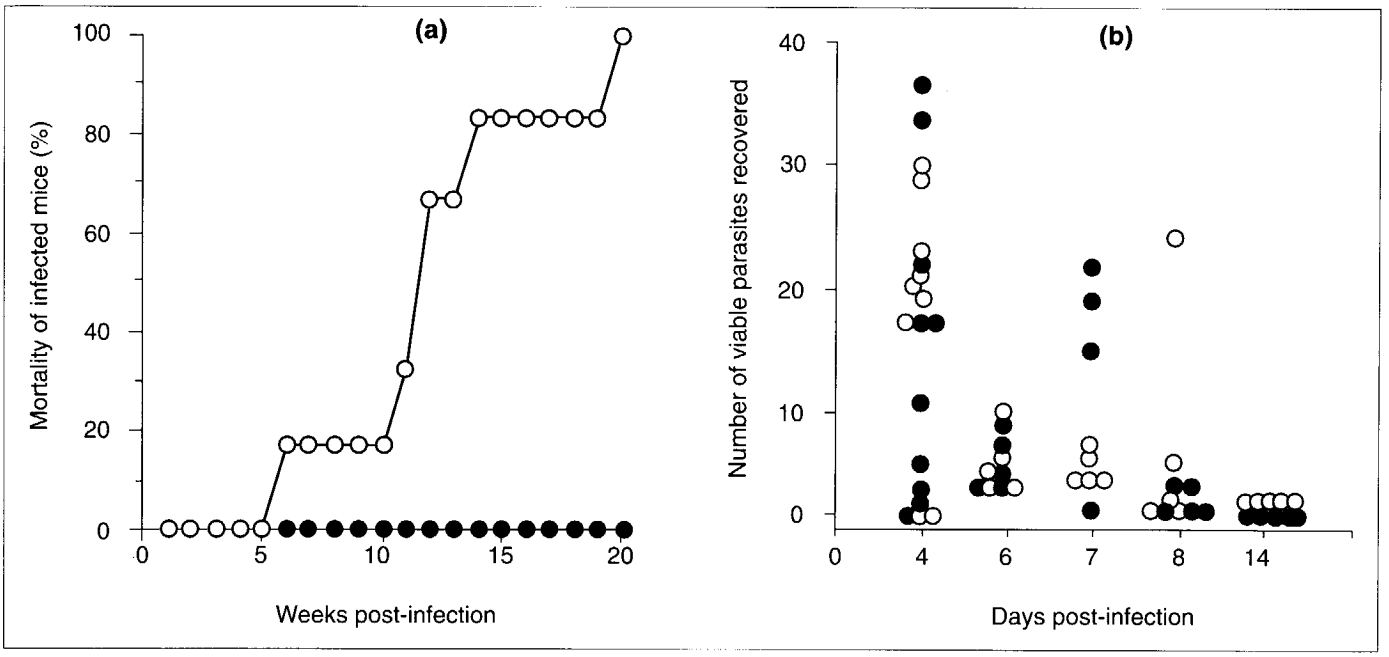

Fig. 1. *Examples of experimental outcomes that counter assumptions that T helper 1 (Th1) cells protect against intracellular pathogens, and Th2 cells protect against extracellular parasites. (a) Interleukin 4 (IL-4)-knockout mice (open circles) die following a* Toxoplasma gondii *infection, which is not lethal for controls (closed circles)[28]. (b) IL-4-knockout mice (open circles) do not differ from wild-type controls (closed circles) in their ability to kill infective larvae of the filarial nematode* Brugia malayi[53].

are critically time dependent: if given in the first seven days of infection, neutralizing anti-IL-4 antibodies can protect mice and prevent death[29]. Thus, IL-4 can both exacerbate disease and protect the host, depending on the levels of expression and the time point of infection. Investigations of the Th2-type anti-inflammatory cytokine IL-10 further demonstrate that it is not possible to generalize about whether Th1 or Th2 responses are beneficial to host or parasite. In a *Toxoplasma* model, mice lacking IL-10 die due to unrestrained inflammatory responses[30]; whereas, following infection with *Trypanosoma cruzi*, another intracellular protozoan, the lethality of IL-10 responses is presumably due to the inhibition of macrophage killing capacity[31].

The distinction between Th1 and Th2 cells first emerged in mouse models, and was found to be applicable to the human immune system[32,33], although with important differences such as the ability of both human Th1 and Th2 cells to express IL-10 (Ref. 34). Intracellular infections in humans, as in mice, frequently elicit Th1-type responses but these are not necessarily sufficient for disease control. In leprosy, for example, responses that are dominated by Th1-type or Th2-type cytokine profiles are associated with tuberculoid and lepromatous disease, respectively[35,36]. Thus, although macrophage activation and other features of the 'Th1' response are certainly critical components in the control of most intracellular pathogens, cytokines other than those produced by Th1 cells can mediate these responses, and Th1 responses are not by themselves inherently 'protective'.

Viral infection

CTL killing of infected cells is undoubtedly the single most important feature in the control of viral infection[37] and, despite the role of antibody and Th cells in immunity, virology has been less dominated by the Th1–Th2 paradigm. A prominent exception to this has been the case of human immunodeficiency virus (HIV) infection, which provides a unique scenario because the virus infects the cells that are primarily responsible for the control of Th cytokine responses ($CD4^+$ T cells and macrophages) and thus cytokine regulation is likely to be a critical feature of disease progression. A progressive switch from Th1-type to Th2-type cytokine profiles has been observed during HIV infection[38], leading to the hypothesis that the former may protect while the latter allows progression of disease. Numerous studies provoked by this suggestion have provided conflicting data, with many laboratories reporting stable cytokine patterns *in vitro* or in direct *ex vivo* samples[39], and even a trend towards Th0 cells rather than Th2 cells in patient-derived clones[40]. As yet, the case for the Th1–Th2 dichotomy being a central feature of HIV infection is far from persuasive, and the key question of whether the switch itself is the cause or effect of overt disease remains open.

Dogma 2: Th2 cells protect against extracellular parasites

The paradigm that Th2 cells protect against extracellular parasites arises in part from the established role of antibodies in the control of many extracellular pathogens and the role that the Th2-type cytokines IL-4, IL-5 and IL-6 play in the generation of an effective antibody response. However, there are many situations in which antibody is ineffectual or nonessential for the control of extracellular parasites. In syphilis, for example, chronic infection with *Treponema pallidum* is accompanied by high levels of specific antibody, and macrophage activation is the primary defence mechanism against infection[41]. This is also true of extracellular yeast infections where antibody and Th2 responses are correlated with disease progression[42]. Furthermore, although antibody appears to be the most important effector mechanism in Lyme disease, clearance of the *Borrelia* spirochete occurs in μ-deficient

mice given IL-4 and thus antibody-independent mechanisms can suffice in the absence of immunoglobulin[43]. In helminth systems, IL-4 is a critical component in controlling infections with the intestinal nematodes *Trichuris* and *Nippostrongylus* yet animals lacking any antibody response are fully able to control infection[44,45].

Helminth infection

Infection by helminths is universally associated with high levels of IgE, eosinophilia and mastocytosis: all responses that are associated with Th2-type cytokines. Demonstrations that eosinophils and IgE can kill parasites *in vitro* has led to the widespread belief that these Th2-dependent responses are primarily responsible for the destruction of large extracellular parasites. However, a striking contradiction occurs *in vivo*. In most helminth infections, heavy parasite burdens occur despite abundant Th2 responses and direct *in vivo* evidence for the role of eosinophils, IgE or mast cells controlling helminth infection remains scarce.

There is now little doubt that IL-4 is critical in the control of intestinal helminth infections[46]. *In vivo* experiments with neutralizing antibody to IL-4 have shown that worm expulsion is dependent on IL-4 during infection with *Trichuris muris*. IL-4 is not required for worm expulsion in several other intestinal helminth infections, but does have a major impact on the intensity of infection and the production of eggs[47]. Despite the apparent role for IL-4 in these gut infections, it has been very difficult to demonstrate that the classic phenotype associated with Th2 responses is responsible for detrimental effects on the parasites. It is possible that IL-4 is acting directly on an existing cell population (to induce peristalsis or mucus production, for example) and that the IL-4-driven 'Th2-cascade' is a side-effect of infection. IL-4 administered directly causes worm expulsion in *Nippostrongylus*-infected SCID mice, demonstrating that IL-4 can act independently of the acquired immune response[47]. In addition, there are IL-4-independent mechanisms that can control gut helminth infection[48,49]. Immunocompetent mice treated with anti-IL-4 antibody or lacking a functional IL-4 gene are still capable of eliminating a *Nippostrongylus* infection[47,50]. Immunity may rely on a combination of T-cell factors and non-T-cell factors, the permutation of which differs between different parasites and different hosts. Certainly, the evidence to date, although providing convincing data for the role of IL-4, has not proven that a Th2-type response is the key factor in parasite elimination within the specific environment of the gastrointestinal tract.

Tissue-dwelling helminths

The evidence that IL-4 (and thus, by extension, Th2 responses) plays a protective role in intestinal nematode infection has been rapidly extrapolated to all helminths. In truth, the evidence that Th2 responses are protective against extracellular parasites that reside in the tissues is circumstantial, with a strong body of evidence to the contrary. Furthermore, as with malaria and toxoplasmosis, generalizations about immune mechanisms against one stage cannot be applied across the board to the entire chronology of biological encounters between parasite and host. For example, it has been suggested that Th2 responses are protective against *Brugia malayi*[51] (the lymphatic-dwelling nematode causing filariasis) because survival of the non-infective larval stage (microfilaria) is negatively associated with the presence of eosinophils and IgE (Ref. 52). By contrast, knockout of the gene encoding IL-4 had no effect on the survival of any life-cycle stage[53] (Fig. 1b); and one recent study implicates nitric oxide production as crucial in preventing infection[54]. Moreover, human studies argue that Th1 but not Th2 responses are associated with low or zero infection levels[55–57]. Thus, the question of whether Th1 or Th2 cells are protective against tissue helminth infections is still far from resolved and, increasingly, we feel that the dichotomous form of the question itself may be misleading.

Schistosomiasis

The complexity of the Th1–Th2 paradigm is equally well illustrated in schistosomiasis, where human and mouse studies have come to strikingly different conclusions concerning the role of Th2 responses in protective immunity. In humans, epidemiological correlations suggest that IgE and eosinophils may be the key to protective immunity[58]. In the mouse, however, several studies have indicated that successful vaccination requires IFN-γ-activated effector cells for parasite destruction[59]. Studies in mice have even suggested that Th2 responses and IgE are beneficial to the parasite and actually enhance infection[60–62].

Induction of Th2 cytokines, particularly IL-10, may downregulate Th1 responses that are damaging to the host and to the parasite, thus providing a balance that is favourable to both. However, both subsets have the potential to damage the parasite and cause host pathology. Thus, resistance of the parasite to host killing in schistosomiasis as well as lymphatic filariasis and onchocerciasis is likely to be dependent on the ability of the parasite to downmodulate immune responsiveness in general rather than to control selectively one or the other Th-cell subset. Suppression of both subtypes is supported by the observation in schistosomiasis and filariasis that Th1 and Th2 responses can both be elevated following chemotherapy and removal of live parasites[63,64]. The striking conclusion from the examination of a large body of literature on helminths is that, although Th2-type responses may have evolved as a means to control helminth infection, the parasites now extant have adapted not only to avoid these responses but also, in all probability, to use them to enhance their own survival.

The Th1–Th2 dogma in other immunological systems

Although this review has focused particularly on infectious diseases, all areas of immune function have been radically changed as a result of the Th1–Th2 paradigm. Perhaps the sharpest delineation has emerged from studying disorders of the immune system itself, such as autoimmune and allergic diseases. The generalization that autoimmune diseases are Th1 mediated[65,66] is supported by experimental work on insulin-dependent diabetes mellitus and experimental allergic encephalomyelitis (EAE), although extrapolation to all forms of autoimmunity is more

problematic. Similarly, IgE-associated allergic disease is closely allied to Th2 responses. However, it may be worth reflecting that the clearest cases of 'pure' Th1 or Th2 responses occur in situations of dysfunctional immunopathology, and not in the normal operation of the immune system in protection against potential pathogens.

Immune defence against tumours is, in some instances, mediated by Th1-type responses; however, tumours of different cytological origin and niche show markedly different immune susceptibilities, and in many experimental systems are cleared by $CD8^+$ cytotoxic cells, or even by Th2-dependent eosinophils[67]. As with infectious disease, protection against cancer is likely to have been an imperative in the evolution of the immune system, and the redundancy resulting from this strong selective force may preclude identification of any one crucial cell type.

Finally, it is interesting to consider T-cell subsets in tissue transplantation, as this is an immunological process for which no evolutionary adaptation has occurred. The general conclusion has been that graft rejection is Th1 mediated and graft acceptance is Th2 mediated. Even here, the stringent delineation into Th1-type and Th2-type cytokine responses has not been sustainable. Th2 responses can accompany rejection, and animals unable to mount a Th1 response can still reject an allograft[68,69]. The lesson from each of these diverse immunological systems is that an exclusive response of a single T-cell subset rarely, if ever, exists *in vivo*.

Conclusion

The study of infectious organisms and their interactions with the mammalian host has provided many fascinating lessons for immunologists, not least of which has been the crossregulatory nature of parasite-specific T cells. However, parasites differ in their predilection for host species and cell type, and defy simplification with respect to their resistance to diverse immune mechanisms. This reflects the degree of adaptation each parasite species has found necessary to survive in any particular host. Although the generalizations of associating Th1 responses with intracellular infections and Th2 responses with extracellular infections may reflect the attempts of the host immune response to clear pathogens, the organisms that survive unscathed have evolved individual solutions to the problem. This exquisite and dynamic adaptation between host and parasite means that immunological phenomena identified in one host–parasite pair cannot always be extrapolated to related organisms.

The Th1/Th2 terminology has proved extremely useful and will continue to be so as it describes a clearly observable phenotype with a particular set of cytokines. However, as infectious disease systems and other immunological phenomena are understood with increasing sophistication, it is important to avoid immediate categorization into Th1-type or Th2-type responses and instead to assess immune responses by the individual cytokines and effector pathways that are induced (Box 2). This more rigorous perspective is further justified by the realization that Th1 and Th2 represent extremes of a continuum of cytokine production profiles, and that many instances exist of cells secreting combinations of cytokines that defy the paradigm[70].

Box 2. Beyond Th1 and Th2

Several findings indicate that it would be more appropriate to define the combinations of cytokine and effector cells required for a successful immune response than to attempt to classify protective immunity as 'Th1-type' or 'Th2-type':

- **In many infectious diseases, both T helper 1 (Th1)-type and Th2-type responses are required for a healthy outcome (e.g. to avoid immunopathology)**
- **Individual cytokines can produce opposing effects depending upon dose and timing of their participation in the immune response**
- **Key cytokines can be made by $CD4^+$ or $CD8^+$ T cells, or by innate immune system cells [e.g. natural killer (NK) and mast cells]; thus, there are redundant pathways to achieve a 'Th1' or a 'Th2' effect**
- **Some cytokines exert their effect through non-adaptive cells (e.g. macrophages and intestinal epithelial cells), thereby bypassing specific T cells**

The immune response has evolved as an integrated whole: innate immunity is an important partner and a frequent predeterminant of the more specific adaptive immune system[71]. In developing a comprehensive defence against ubiquitous pathogens, it seems most likely that different arms of the immune system have evolved to act in concert, and instances where a single T-cell subset is entirely and uniquely responsible for protection are likely to be rare. Perhaps most importantly in the context of infectious disease, it is a balanced immune response and not the induction of a particular Th-cell pathway that leads to disease resolution.

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