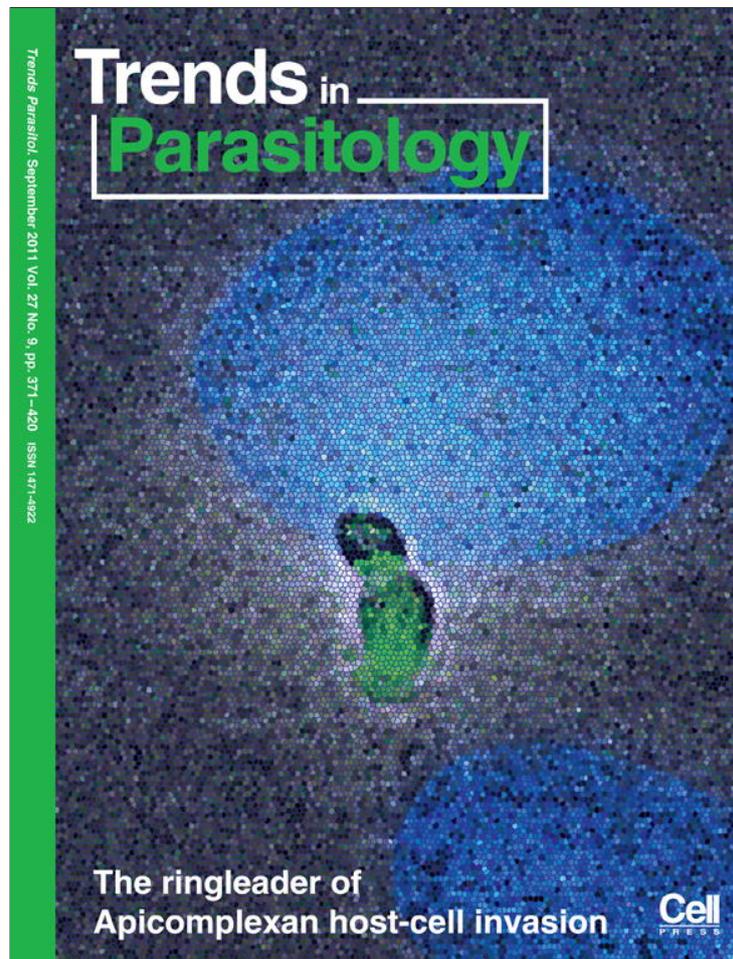


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The economy of inflammation: when is less more?

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In ecology, tolerance of parasites refers to host mitigation of the fitness costs of an infection. This concept of parasite tolerance contrasts with resistance, whereby hosts reduce the intensity of an infection. Anti-inflammatory cells and molecules have been implicated as mechanisms of parasite tolerance, suggesting that a major role of tolerance is in minimizing collateral damage associated with inflammation. A framework is proposed here in which the cost–benefit outcome of an inflammatory host-response is hypothesized to be dependent on host life-history, parasite virulence, and the efficacy of a current inflammatory or anti-inflammatory response. Testable predictions, both within and among host species, are presented for this hypothesis.

Inflammation promotes resistance but reduces tolerance to parasites

In modern immunology the term ‘tolerance’ refers to the ability of the immune system to avoid self-reactive components that can cause autoimmune disease (i.e. self-tolerance). More recently, parasite tolerance (Glossary) has been emphasized [1,2], with particular attention to the mechanisms by which hosts minimize the fitness costs of a particular parasite burden [1,3–6]. Parasites, a term which refers to any infectious organisms that exact fitness costs on a host, can be coped with in two ways: (i) resistance, whereby hosts reduce parasite burden by preventing infection or clearing parasites that do infect, and/or (ii) tolerance, whereby hosts mitigate the deleterious effects of a particular burden of parasites that have infected. Whereas resistance reduces the cost of an infection by minimizing parasite exploitation of host resources, tolerance can minimize costs by repairing tissue damage or immunopathology resulting from the resistance responses of the host. Ecologists increasingly appreciate that parasite tolerance is an important component of host–parasite interactions and disease outcomes [1,7], but mechanisms of parasite tolerance are still poorly understood relative to our understanding of resistance. However, a central theme that emerges from recent studies by both groups [3–6] is that inflammation is a major mediator of resistance but also a perpetrator of immunopathology and, therefore, a depressor of tolerance.

Inflammation is a particularly important mediator of resistance because of its rapid and broad efficacy in clearing infections. The majority of immune responses begin

with the induction and propagation of inflammation by a series of positive-feedback loops (Box 1). These processes thwart the establishment or persistence of diverse parasites (i.e. viral, bacterial, and eukaryotic), even novel parasites for which a host has no immune memory. However, immunopathology can be a major cost of infection [8]; the pathogenicity of a parasite, also defined as ‘virulence’ [9,10], can be due to both host and parasite [11]. For example, intestinal helminths can cause tissue damage directly by burrowing into the epithelium, but the host can also cause damage by launching an inflammatory response in the mucosa. For this reason, high levels of inflammation can eventually lead to downregulation of inflammatory cells and cytokines (Box 1). Given both the protective and self-damaging capacity of inflammation, a central issue that remains to be reconciled is: how does a host determine the magnitude and duration of an inflammatory

Glossary

Danger-associated molecular patterns (DAMP): extracellular signals indicating a general state of danger to the host, such as necrotic cells.

Effector cells: immune cells which respond to directly to parasite stimuli through pathogen recognition receptors (innate), or indirectly through cytokines produced by lymphocytes that recognize parasite antigens (adaptive).

Immunological privilege: particular tissues (e.g. brain, mucosa, placenta) are privileged in that the presence of an antigen does not elicit an inflammatory response. This privilege prevents inappropriate responses to environmental antigens (e.g. intestinal mucosa) or potentially lethal immunopathology (e.g. placenta, brain).

Immunopathology: self-damage caused by non-specific immune responses.

Fast pace-of-life: organisms that mature rapidly and reproduce prolifically; because of their prolific reproduction each offspring constitutes a relatively small portion of the total investment in reproduction.

Pace of life: timing, rate, and overall investment in production of offspring

Parasite tolerance: ability of an organism to reduce the fitness costs of a particular parasite burden.

Pathogen-associated molecular pattern (PAMP): molecules characteristic of parasites, such as the cell-wall component of Gram-negative bacteria, lipopolysaccharide (LPS).

Pathogenicity: the ability of a pathogen or parasite to cause disease in a host.

Regulatory phenotype: a refractory phenotype in which immune cells (including macrophages, T cells and B cells) do not respond to antigenic stimuli and alter the cellular milieu to induce regulatory phenotypes in other nearby cells.

Regulatory T cell (Treg): T helper cells specialized to promote immune quiescence by downregulating effector T helper cells (Th1, Th2, and Th17).

Resistance: ability of an organism to prevent or reduce the intensity of an infection.

Self-tolerance: the ability of the immune system to prevent or halt responses against self-antigens; in other words, the prevention of autoimmunity.

Slow pace-of-life: organisms that mature slowly and produce only a few offspring; each offspring represents a large portion of the total investment in reproduction.

Transforming growth factor beta (TGFβ): a cytokine which, in large quantities, promotes T_{reg} recruitment and proliferation.

Virulence: pathogenicity of a parasite, or its ability to cause disease in a host.

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Box 1. Activation and resolution of inflammation

Wounding results in immediate inflammation, which creates positive-feedback loops that perpetuate and amplify inflammation (Figure 1a). First, the release of neuropeptides recruits mast cells to the site of injury, which release the inflammatory cytokine $TNF\alpha$. Simultaneously, PAMPs are phagocytosed by DCs and macrophages; macrophages kill the parasite with ROS and RNS (abbreviations: Figure 1 legend). DCs present parasite antigen to T helper cells, including Th1, which induce hyperactivation in macrophages by secreting $IFN\gamma$; macrophages, in turn, release IL-12, which promotes more Th1 activity. Hyperactivated macrophages also produce $TNF\alpha$, which promotes $IFN\gamma$ production by NK cells and further macrophage activation. Macrophages activity

recruits neutrophils from circulation, which phagocytose small parasites or degranulate near large parasites, releasing RS.

However, high levels of inflammation eventually downregulate further inflammatory processes (Figure 1b). High levels of $TNF\alpha$ cause neutrophils to become apoptotic; if a macrophage ingests the apoptotic neutrophils it induces a regulatory phenotype in the macrophages, which produces the anti-inflammatory cytokine IL-10. Similarly, high levels of ROS and LPS cause DCs to become apoptotic, which, when ingested by iDCs, arrest maturation of the iDC and cause it to produce $TGF\beta$, which contributes to the induction of potentially anti-inflammatory T_{reg} cells.

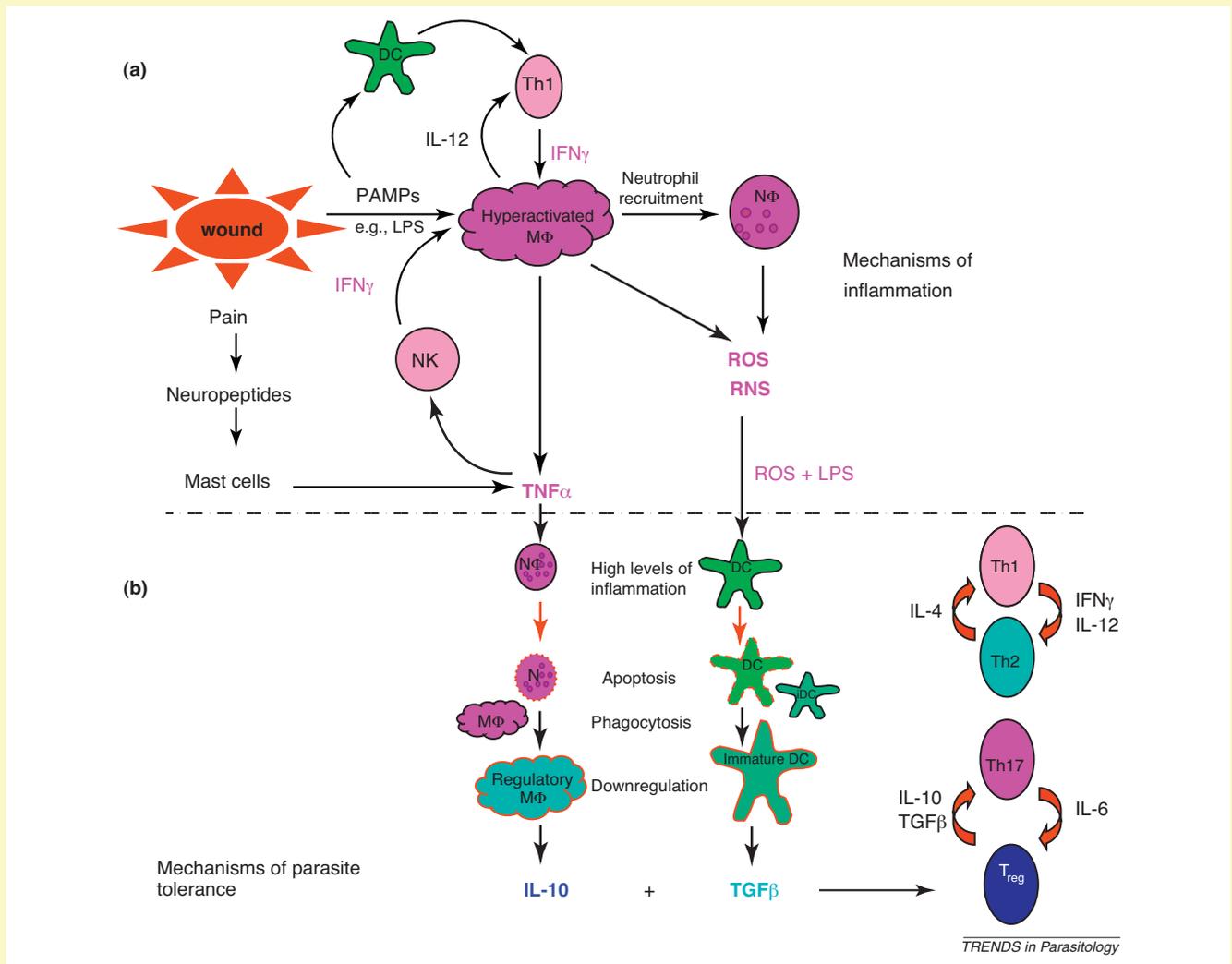


Figure 1. Regulation of inflammation. (a) Positive feedback promotes inflammation. (b) Negative feedback eventually suppresses inflammation, promoting parasite tolerance. Pink-colored cells refer to inflammatory capabilities, with deep pink being more inflammatory than light pink; blue-colored cells and cytokines refer to anti-inflammatory cells and cytokines that probably contribute to parasite tolerance, particularly those below the dashed line. Red arrows and outlines indicate downregulation of a cell type, with dashed red outlines indicating apoptotic cells. Abbreviations: DCs, dendritic cells; $TNF\alpha$, tumor necrosis factor alpha; PAMPs, pathogen-associated molecular patterns; ROS, reactive oxygen species; RNS, reactive nitrogen species; Th1, type 1 T-helper cell; iDCs, immature dendritic cells; $IFN\gamma$, interferon gamma; IL-12, interleukin 12; M ϕ , macrophage; N ϕ , neutrophil; NK cells, natural killer cells; LPS, lipopolysaccharide; $TGF\beta$, transforming growth factor beta; T_{reg} , regulatory T cell.

response? Here, it is hypothesized that hosts use inflammation in a manner that minimizes infection intensity until the cost of the immune response is larger than the cost of the infection in the absence of inflammation. Thus, with information about hosts and parasites, the duration and magnitude of inflammatory responses – and when to favor tolerance over resistance – should be predictable.

The goals of this Opinion are threefold. First, in light of the costs and benefits of resistance versus parasite tolerance, the impact of host life-history upon inflammatory responses is outlined. Second, the costs and benefits of inflammation are reviewed; specifically, that parasite pathogenicity and the location of host infection are determinants of much of the variation in inflammation between

hosts. Third, how a host might switch the character of its response from resistance to tolerance (or vice versa) is explored. Finally, relevant under-studied research areas are identified, particularly putative molecular and cellular mechanisms of parasite tolerance and shared mechanisms of self- and parasite-tolerance. The motivation is not to unequivocally support these hypotheses, but instead to promote ecological and evolutionary investigations of inflammation [12].

Ecology of resistance and tolerance

Host and parasite life-histories should impact strongly upon the balance of resistance and tolerance and, hence, variation in inflammation. Variations in life history will have consequences at three different time-scales (Figure 1): (i) before parasite exposure, (ii) at the time of exposure, and (iii) over the duration of an infection.

Before parasite exposure: host life-history

Life-history theory suggests that variation in the timing of and investment in reproduction is due to selective pressure to maximize the fitness of an organism (i.e. the production of offspring that produce offspring). Life-history 'strategy', which refers to a web of adaptations that dictates the allocation of reproductive effort over the lifetime of an organism [13], is a concept which has been applied to all multicellular taxa. Life-history strategies tend to fall along a fast to slow pace-of-life continuum, with fast-paced species maturing rapidly and reproducing prolifically, whereas slow-paced species are slower to mature and produce fewer offspring per unit time [14]. Because host life-history strategy will impact upon both parasite exposure and the resources available to mount immune responses, in-

flammatory responses are probably under evolutionary pressure such that the pace of life is an important determinant of the magnitude of inflammation.

A recurring observation is that fast-paced species tend towards inflammatory responses, whereas slow-paced species produce anti-inflammatory responses [15–17] (Figure 1a). These patterns could result from heritable differences, in which fast-paced hosts are genetically predisposed to respond with proinflammatory responses relative to slow-paced hosts, and/or they could be due to heritable behavioral differences that predispose hosts to be exposed to antigens in a particular order or with a particular frequency; in the latter case the immune cells of the host would be 'educated' to acquire parasite tolerance much as T and B cells are educated during the maturation of the immune system (e.g. [18]). Nonetheless, these events need not be exclusive; acquired parasite tolerance influenced by environmental exposures could eventually become heritable through genetic assimilation [19].

Within species, fast and slow pace-of-life can also be assigned to individuals. Fast and slow paces are often assigned to males and females, respectively, owing to the generally shorter life spans of males and more frequent mating opportunities. Indeed, male mammals consistently exhibit a greater inflammatory bias than do non-pregnant females [15,20,21]. Pregnant females have an even more pronounced anti-inflammatory bias, characterized by a regulatory T cell (T_{reg}) skew that could prevent maternal immune responses against the fetus [22]. Fast and slow pace of life can also be attributed to temperate and tropical individuals in broadly distributed species. Based on body size, clutch size, and average number of clutches per year, Martin *et al.* [23] describe neotropical populations of house sparrows (*Passer domesticus*) as slow-paced relative to temperate populations; neotropical house sparrows are also immunologically slow-paced, demonstrating stronger antibody-based responses to a novel antigen than temperate individuals [17]. If tropical animals are generally slow-paced and parasite-tolerant, it could explain the general tendency of tropical host species to harbor more parasites than temperate hosts [24].

Eco-evolutionary theory makes sense of these patterns. First, fast-paced species and individuals are relatively short-lived, and are therefore less likely to encounter a parasite repeatedly. This lower chance of re-exposure would minimize the relative value of investing in a developmentally expensive adaptive immune system [15]. Second, the short lives of fast-paced animals could prevent them from experiencing the long-term costs of inflammation that long-lived, slow-paced animals endure; strong inflammatory responses are more likely to be beneficial to fast-paced animals because cumulative damage is relatively less likely to compromise fitness in a short-lived organism. Third, the time required to involve the adaptive immune system in an infection (~10 days) could impart opportunity costs (e.g. missed matings) during an illness that are incompatible with a fast pace of life. In summary, we hypothesize that, for a fast-paced host, the benefits of a strong inflammatory response result in resistance-type responses to infection; for slow-paced hosts, the costs of inflammation outweigh the benefits of such a response,

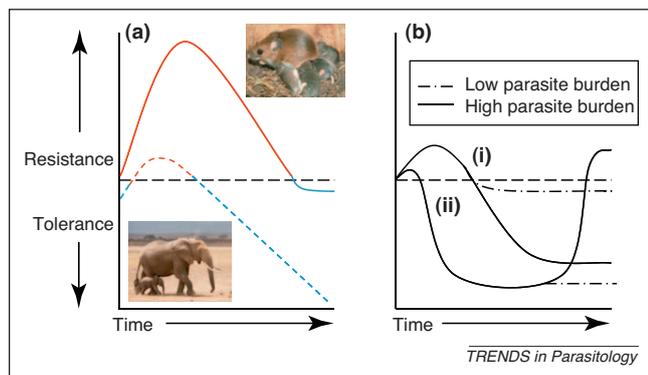


Figure 1. Host and parasite characteristics influence the magnitude and duration of inflammatory responses. (a) Fast-paced hosts or those infected with virulent parasites (solid line) should use inflammatory responses that maximize the likelihood of eliminating an infection (i.e. resistance) so as to survive to one or a few reproductive events. Chronic infections in a fast-paced host will probably slowly transition to tolerance-type responses. Slow-paced hosts or hosts infected with less-virulent parasites (dotted line) probably utilize some resistance initially (due to positive feedback; Box 1), but quickly transition to tolerance to prevent the accumulation of immunopathology. Note also that the character of the constitutive defenses of the host (i.e. the y-intercept) is also likely to differ between hosts, with slow-paced hosts maintaining a less inflammatory state in the absence of infection. (b) Hosts can adopt different strategies during chronic infections, depending on the intensity of infection. (i) A host that initially launches an inflammatory response will return to homeostasis if parasite exposure was modest or the infection is cleared (dot-dash line), or the host can damp inflammation [i.e. favor tolerance; (solid line)] if inflammation fails to clear a high-intensity infection. (ii) A parasite that is initially tolerated, such as a helminth, can eventually elicit inflammation at high burdens (solid line) or damp inflammation (i.e. remain tolerated) at low densities (dot-dash line).

resulting in immune responses that instead promote tolerance to parasites.

At the time of exposure: costs of infection

Host life-history can be important to setting the threshold at which inflammation is used or avoided but, for an individual host, what determines whether a parasite is resisted or tolerated once an infection occurs? The answer probably lies in the potential cost of a specific infection, particularly parasite virulence and the location of the infection. Hosts probably avoid inflammation/resistance in favor of anti-inflammatory processes and tolerance when: (i) the tissue at the site of infection will be compromised by a strong inflammatory response, and/or (ii) when the cost of resisting is greater than the cost of tolerating (i.e. the parasite has low inherent virulence).

In particular tissues, inflammatory processes cannot be engaged continuously without compromising functionality (e.g. mucosal tissue, brain, and placenta); these tissues are subject to immunological privilege, in which immune responses are markedly downregulated and specific effector cells are excluded. Exclusion of immune cells from certain tissues was first described in studies of self-tolerance; however, immunological privilege also appears to extend to parasite-responsive immune cells (Table 1). In the mucosa, for instance, T_{reg} cells produce anti-inflammatory cytokines, such as interleukin 10 (IL-10) and transforming growth factor beta (TGFβ), both of which depress effector T cell actions, including inflammation [25]. To maintain tissue integrity, parasitic infection could initially incite minimal inflammation followed by rapid transition to tolerance-type responses, mediated by cells with regulatory phenotypes (Figure 1b).

Parasite virulence, in the sense of pathogenicity [9], should also impact upon whether resistance or tolerance is favored. A less virulent parasite is, by definition, a lesser threat to host fitness than a virulent parasite, and hosts should engage immune responses appropriate to indicators of parasite virulence (Figure 1a) [26]. Hosts can use pathogen-associated molecular patterns (PAMPs) as traits that offer both specific information regarding a pathogen, as in more- or less-virulent genotypes, and taxonomic affiliation

(i.e. bacteria versus helminth) that might reflect the replicative potential (virulence *sensu lato*) of the parasite [27,28] and, therefore, inform the host of the necessity of employing inflammation. For example, lipopolysaccharide (LPS; a bacterial cell-wall component) and flagellin (a bacterial flagellum protein) variants can offer fine-tuned information regarding the virulence of *Salmonella enterica* genotypes [29]. Similarly, exposed mannan on the cell wall of the commensal yeast *Saccharomyces cerevisiae* distinguishes it from the pathogenic yeast *Candida albicans*, which lacks mannan [30]. In addition, the accompaniment of PAMPs with danger-associated molecular patterns (DAMPs), such as necrotic cells, could indicate a more virulent parasite than PAMPs alone [31], informing the host that a stronger inflammatory response might be necessary to manage the infection.

Overall, PAMPs and virulence factors both appear to be integral determinants of the magnitude and duration of inflammatory responses because of their propensity to activate the immune system. The manner in which the immune system is activated then influences the recruitment and proliferation of T helper cell subsets, which impacts upon the inflammatory milieu of an immune response. Inflammatory, type 1 T helper cells (Th1) typically promote resistance to intracellular infections, which tend to have high virulence because they cause host cell damage and have high rates of replication. However, Th1 responses can induce marked pathology during infections (e.g. [32]), thereby compromising tolerance. On the other hand, Th2 cells, which are the hallmark response to metazoan infection [33], promote both tolerance and resistance to extracellular parasites. Resistance can occur by flushing out intestinal parasites or encapsulating worms in tissues. Similar mechanistic pathways also mediate tolerance by rapidly repairing damage caused by these metazoan parasites, such as sepsis-inducing breaches to the gut wall [34]. The ability of Th2 responses to promote both resistance and tolerance could help to explain the preponderance of Th2 responses in intestinal tissue, which is sensitive to inflammation. Th2-mediated responses are often associated with the development of fibrosis [35], indicating that the need for rapid repair can be costly.

Table 1. Mechanistic and functional similarities of self-tolerance and parasite tolerance

Description	Self-tolerance mechanisms	Parasite tolerance mechanisms	Refs.
Anergy ^a of over-reactive lymphocytes	Binding of the receptors Fas and PD-1 induces anergy in auto-reactive B and T cells	Binding of the receptors PD-1 and CTLA-4-mediated anergy of repeatedly activated ('exhausted') T cells	[42,46,47]
Overactivation-induced cell death	Binding of the receptors Fas, PD-1, or CTLA-4 induces apoptosis	Binding of the receptors PD-1 or CTLA-4 induces apoptosis	[42,46,47]
Reactive T cells become T _{reg} cells	Generation of natural T _{reg} cells in thymus from self-reactive lymphocytes	During infection, generation of inducible T _{reg} cells from overstimulated Th cells	[46]
Immunologically privileged sites (e.g. brain, mucosa)	Expression of Fas-ligand in privileged tissue instigates apoptosis of Fas-bearing lymphocytes, which enter privileged sites, preventing immunopathology	T _{reg} -populated mucosal tissue, bias toward defense by antibodies (non-inflammatory) rather than effector cells (potentially inflammatory)	[25,42,48]
T _{reg} cells	Decreased activity of self-reactive T cells	Decreased activity of parasite-responsive effector T cells	[25]

Abbreviations: Fas, 'death receptor' CD95; PD-1, programmed cell death-1 receptor; CTLA-4, inhibitory receptor CD152; T_{reg}, regulatory T cells; Th, T helper cell.

^aAnergy, loss of responsiveness.

During an infection: switching strategy from resistance to tolerance

A final factor that might influence the host inflammatory response involves the comparatively shorter generation times of parasites than hosts and the capacity of parasites to exhibit plasticity [36]. As an infection progresses from acute to chronic, or parasite strategies change (such as the switch from dormant to proliferative stages of *Toxoplasma gondii* [32]), it could sometimes be necessary for hosts to transition from a tolerant strategy back to a resistant one or vice versa. Over the course of an infection, tolerance should manifest if the cost of minimizing burden (resistance) becomes greater than the cost of minimizing damage (tolerance); such a situation would probably arise if immunopathology is the chief cost of an infection. Indeed, a switch from resistance to parasite tolerance is typical of many, if not most, chronic intracellular infections such as toxoplasmosis and leishmaniasis. The acute phase of these two infections is characterized by IFN γ -mediated activation of macrophages to resist infection. However, as the infection progresses, increasing amounts of IL-10 modulate this response [37], reflecting a more parasite-tolerant state. If tolerance is ineffective at minimizing the fitness cost of an infection, hosts can shift back to one of resistance (Figure 1b). Such is the case in toxoplasmosis, when the quiescent stage of the parasite periodically reactivates, requiring renewed host resistance [38].

Hosts can also adjust their immune responses during an infection contingent on the initial intensity of an infection. For example, rats infected with low numbers of *Echinostoma trivolvis* rapidly clear all worms, but rats infected with a high dose of *E. trivolvis* do not, maintaining nearly as many worms late in the infection as the initial inoculation [39]. Such a pattern suggests a shift from resistance in low-dose infections to tolerance in high-dose infections, perhaps based on balancing the benefit of clearance of low numbers of parasites against the cost of potential tissue damage in the intestine. Conversely, sheep seem to initially tolerate both low- and high-intensity infections of *Fasciola hepatica*, releasing the Th2-associated anti-inflammatory cytokines IL-4, 5, and 10. However, after 12 weeks of infection, heavily-infected sheep shift to inflammatory responses (by reducing IL-10 and TGF β production) indicative of a shift to resistance [40].

Regulation of inflammation

At the molecular and cellular level, regulation of specific cytokines and particular T cell subsets can mitigate the induction, duration, and resolution of inflammation (Box 1). Th cells have particularly dynamic mechanisms for the downregulation of inflammation. When repeatedly activated, as occurs during an infection, T cells can become refractory to further activation by upregulating the expression of CTLA-4, a molecule that prevents a T cell from responding when it encounters antigen [41] (Table 1). Furthermore, if repeatedly stimulated, Th cells can differentiate into T_{reg} cells [42] or produce downregulatory cytokines [37], which can shut down inflammatory cascades. Therefore, contrary to the many positive feedback loops that initially induce inflammation, long-term inflam-

mation can eventually downregulate the progenitors responsible for its induction [43] (Box 1).

The subset of Th cells responding to a parasite can also play an important role in the degree of inflammation produced. A combination of host life-history and parasite identity are responsible for inducing different types of Th cells, as discussed above. The differing roles of Th cell types in an infection are further polarized by reciprocal negative regulation of Th1 and Th2 cells (Box 1). Likewise, Th17 and T_{reg} cells could have functionally similar inflammatory/anti-inflammatory roles; Th17 cells incite very strong levels of inflammation mediated by the cytokine IL-17 whereas T_{reg} cells are strongly anti-inflammatory and suppress other effector Th cell functions [44]. Th2 cells are also fundamentally anti-inflammatory, which is probably associated with their role in tissue repair, a process that requires an end to the inflammatory cascade [45].

In many ways, the mechanisms of both parasite tolerance and self-tolerance overlap substantially (Table 1). T_{reg} cells play an integral role in promoting immune quiescence in both types of tolerance. Researchers are only beginning to understand mechanisms of parasite tolerance, but we, as researchers, could find other probable mechanisms of parasite tolerance by considering the self-tolerance literature.

Concluding remarks

In an ecological and evolutionary light, the magnitude and duration of inflammatory responses should be predictable based on the costs and benefits of the response in terms of host fitness, although so far these ideas have been only indirectly substantiated. First, the cost-benefit outcome of an inflammatory host response is probably dependent on host life-history, parasite virulence, and the efficacy of a current inflammatory or anti-inflammatory response. Second, whereas inflammation is a key component of resistance to parasitic infection, anti-inflammatory responses and the resolution of inflammation are probably key mediators of tolerance.

Although some tolerance mechanisms might not be directly related to anti-inflammation, investigation of the instigators and resolvers of inflammatory responses could open new doors to immunological understanding. Ecological immunologists can benefit from the mechanistic approach of classic immunology by better appreciating the nuances of immunological processes and the concomitantly nuanced costs of such processes; there is rarely a monolithic 'immunocompetence' to be measured. Likewise, ecological thinking could lend immunology a context upon which to improve human health.

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