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# Disease tolerance: concept and mechanisms

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Two distinct defense strategies provide a host with survival to infectious diseases: resistance and tolerance. Resistance is dependent on the ability of the host to kill pathogens. Tolerance promotes host health while having a neutral to positive impact of pathogen fitness. Immune responses are almost inevitably defined in terms of pathogen resistance. Recent evidence has shown, however, that several effects attributed to activation of innate and adaptive immune mechanisms, cannot be readily explained with the paradigm of immunity as effectors of microbial destruction. This review focuses on integrating the concept of disease tolerance into recent studies of immune system function related to the regulation and resolution of tissue damage, T cell exhaustion, and tolerance to innocuous antigen.

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## Introduction

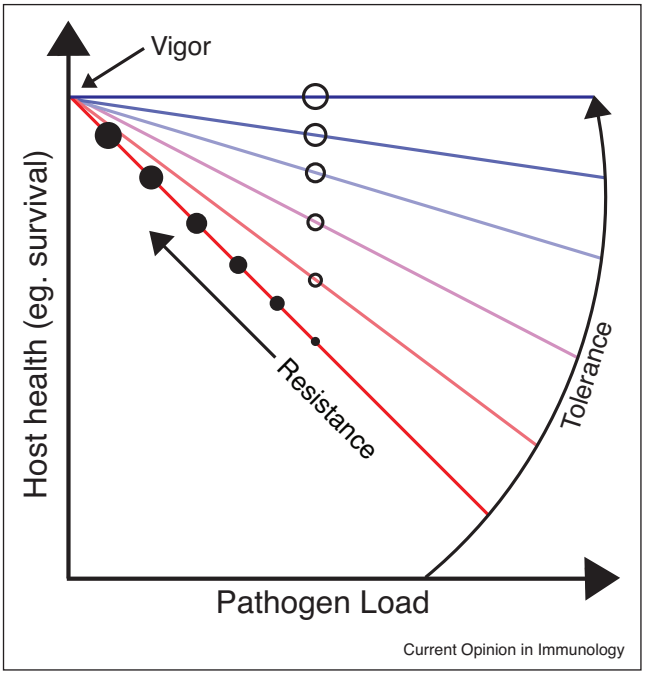
Survival of infectious diseases has traditionally been thought to be entirely dependent on the ability of the host to kill an invading pathogen through the execution of resistance mechanisms [1–3]. In the past decade, a distinct defense strategy called disease tolerance has been recognized as an essential component of the host defense response to infections [1–3,4•]. Disease tolerance is distinct from resistance because it protects the host by promoting host health while having a neutral to positive effect on pathogen fitness. Disease tolerance is not to be confused with immunological tolerance, which involves the elimination of self reactive T cells, although in certain disease contexts immunological tolerance can be considered a disease tolerance mechanism. Experimentally, the contribution of resistance and disease tolerance to any host–microbe system can be distinguished by measuring a parameter of host health (e.g. survival or tissue damage) and examining its relationship to pathogen burden in the relevant tissues (Figure 1) [5]. The past fifty years of immunology have done an excellent job of dissecting the mechanism of resistance. An understanding of the basic mechanisms and contributions of disease tolerance to host defense is a necessary facet for current and future immunological research.

Mechanisms that mediate resistance are well described and involve the response of the immune system and downstream events leading to the execution of microbial killing. The underlying mechanisms that mediate disease tolerance are just beginning to be discovered. While a common assumption is that the mediators of tolerance will be distinct from those that control resistance, recent evidence suggests that functions of the immune system cannot be ascribed to only microbial killing mechanisms and rather also contribute to disease tolerance defenses. In this review, we will discuss recent work suggesting that molecular and cellular components of both the innate and adaptive immune systems are critical regulators of disease tolerance defenses and discuss how these recent advances may shape future research.

## Regulation and resolution of tissue damage

An inevitable consequence of host responses to inflammatory stimuli such as pathogens or physical injury is immunopathology of host tissues. Host encoded mechanisms preventing the onset or supporting resolution of immunopathology in host tissues are components of the disease tolerance defense system [1]. Recent studies have demonstrated that cellular components of the immune system are essential for mediating these health promoting effects. Amphiregulin is an epidermal growth factor receptor ligand (EGFR) that is important for regulating tissue damage induced by viral infections. Earlier work demonstrated that amphiregulin prevented viral-induced lung pathology in mice and suggested that amphiregulin is produced largely by innate lymphoid cells (ILCs) 2 in an IL-33-dependent manner [6]. More recent work has identified an alternative source for amphiregulin in the lung. Arpaia *et al.* demonstrated that amphiregulin from T regulatory (Tregs) cells prevents lung immunopathology induced by influenza infection. Interestingly, amphiregulin was efficacious independent of influencing the suppressive capacity of Tregs (T cell receptor (TCR)-independent) [7••,8]. Further, they confirmed that IL-33 is critical for amphiregulin induction, along with IL-18 [7••]. In immunocompromised hosts ($Tlr2^{-/-}Tlr4^{-/-}$) administration of amphiregulin to animals co-infected with Influenza (LP02ΔdotAΔflaA) and *Legionella pneumophila* alleviated lung damage and promoted host survival

**Figure 1**




Overview of host tolerance and resistance measurement. A dose dependent curve can be generated from the relationship between host health (e.g. survival) and pathogen burden, where vigor represents uninfected hosts. Host resistance (closed circle) is defined as a decrease in pathogen burden as host health (e.g. survival) increases (linear relationship). Increases in host resistance are represented by increasing circle size. In comparison, host tolerance (open circle) is defined as an increase in host health (e.g. survival) independently of pathogen burden. Increases in host tolerance are represented by increasing circle size and slope color (red = low tolerance, blue = high tolerance).
Adapted from [1,4•].

without influencing viral or bacterial load [9]. Interestingly, disease tolerance mediated by amphiregulin may extend beyond protection from respiratory challenges. Administration of dextran sulfate sodium (DSS) to mice induces mucosal erosion and intestinal injury resulting in a 'colitis' like disease. Monticelli *et al.* showed that amphiregulin can also alleviate DSS-induced colitis. The intestinal microbiome contributes to the pathogenesis of DSS-induced colitis and without measurements of the microbiome composition and levels, it remains unclear if amphiregulin is mediating resistance or disease tolerance in this context [10].

The mechanisms that regulate amphiregulin induction, apart from IL-33 and IL-18, remain unclear but recent work suggests that proresolving lipid mediators, molecules that possess both resistance and disease tolerance traits, may be one such mechanism [11]. One way in which proresolving lipid mediators may support tolerance mechanisms is through the *de novo* generation of forkhead box P3 (FoxP3)-expressing Tregs [12,13]. The proresolving lipid mediator maresin-1 promoted the generation of Tregs and regulated cytokine production from ILC2s including increased amphiregulin production in the murine lung [13]. Although amphiregulin contributes to disease tolerance and survival of infections, it remains to be formally tested if the proresolving lipid mediators themselves mediate disease tolerance through their regulation of amphiregulin.

Pattern recognition receptors of the innate immune system are traditionally appreciated for their role in executing antimicrobial responses during challenge. However, several studies over the past decade have extended the function of these sensors to resolving immunopathology through tissue repair functions, suggesting that they are important for mediating disease tolerance. Beneficial microbes, including those of the intestinal microbiome, encode microbial associated molecular patterns (MAMPS) that activate innate immune receptors. In a DSS colitis model, recognition of commensal microbiome derived ligands by Toll-Like Receptors (TLRs) was critical for mediating tissue repair in the colon [14]. More recent studies have shown that the various inflammasomes can also promote tissue repair. Inflammasomes are cytosolic multiprotein complexes that are required for the activation of Caspase 1 protease and subsequent maturation of inflammatory responses. Casp1−/−, Asc−/− and Il18−/− mice exhibited greater disease severity, barrier permeability, microbial translocation and defective cell proliferation when treated with DSS. Administration of recombinant IL-18 to Casp1−/− mice reduced disease severity, supporting a role for IL-18 in promoting repair of the gut epithelium. Thus, activation of the inflammasome and other innate immune receptors in the intestine may promote disease tolerance through tissue repair, alleviating dehydration, electrolyte imbalances and anemia that could be caused by gut damage. An important caveat of these studies is that the levels and composition of the microbiomes were not appropriately evaluated and thus it remains to be formally tested whether the effects of these receptors on tissue repair promote disease tolerance or resistance against the microbiome [14–19]. In addition to the role of these receptors at mucosal surfaces, the role these sensors play in tolerance and resistance to disease beyond the gut are being explored [20,21••].

## Organismal metabolism and immune crosstalk

Infections lead to profound changes in host metabolism that affect the outcome of the host. For example, many types of infections lead to the sickness induced anorexia that is mediated by the actions of the innate immune system on the central nervous system and brain. In 1979, Murray and Murray showed that blocking the anorexic response was detrimental for host survival of a systemic bacterial infection [22]. In a fruit fly model, Ayres and Schneider showed that any benefits of the anorexic response for host outcome were context-dependent [23]. In