Immunity by equilibrium

Gérard Eberl

Abstract | The classical model of immunity posits that the immune system reacts to pathogens and injury and restores homeostasis. Indeed, a century of research has uncovered the means and mechanisms by which the immune system recognizes danger and regulates its own activity. However, this classical model does not fully explain complex phenomena, such as tolerance, allergy, the increased prevalence of inflammatory pathologies in industrialized nations and immunity to multiple infections. In this Essay, I propose a model of immunity that is based on equilibrium, in which the healthy immune system is always active and in a state of dynamic equilibrium between antagonistic types of response. This equilibrium is regulated both by the internal milieu and by the microbial environment. As a result, alteration of the internal milieu or microbial environment leads to immune disequilibrium, which determines tolerance, protective immunity and inflammatory pathology.

On the basis of immune equilibrium, it can be assumed that the immune system is able to distinguish between ‘good’ and ‘bad’ — for example, between mutualistic and pathogenic microorganisms — and develop either anti-inflammatory or pro-inflammatory immune responses. However, how it would be able to distinguish good from bad is still an open question. In fact, there are three, possibly four, types of immune response that are mutually inhibitory. These include type 1 responses against intracellular threats (such as viruses, intracellular bacteria and tumours), type 2 responses against large extracellular threats (such as helminths) and type 3 responses against extracellular microorganisms (such as extracellular bacteria and fungi). Activation of one type of response inhibits another type, and the immune equilibrium is maintained by the competing immune responses. This principle forms the basis of the equilibrium model of immunity. In contrast to earlier immunological principles, the equilibrium model of immunity does not predict how an immune response is triggered (as all types of immune response are already active during the steady state) but instead predicts how this active immune system behaves when facing new threats, which are almost always present in combination. I believe that the equilibrium model of immunity provides a broad but simple and testable framework to explain complex immune phenomena such as tolerance, autoimmunity, allergy and resistance or susceptibility to secondary infections. It might also open up new approaches for immunotherapy.

The equilibrium model of immunity

The foundations of immunology are rooted in the work of Metchnikoff (1845–1916) and Paul Ehrlich (1854–1915), who drew on the discovery by Louis Pasteur (1822–1895) and Robert Koch (1843–1910) of the pathogenic potential of microorganisms. Therefore, the immune system is primarily viewed as a system that opposes pathogens through elaborate mechanisms of recognition and destruction. However, the realization that the immune system is in a constant state of activation, even in the absence of pathogens, indicates that the immune system does not react only to...
In the context of the immune network theory, which was first proposed in the 1970s by Niels Jerne, Heinz Kohler and Geoffrey Hoffmann, the equilibrium between effector T cells and Treg cells is central to the concept of ‘milieu intérieur’, defined by Claude Bernard (1813–1878), and by Richard Gershon in the context of the suppressor T cell theory. Negative regulation has now become an immunological paradigm through the characterization of Treg cells, the absence of which leads to dramatic inflammatory pathology. It is generally agreed that a healthy immune system, as well as a healthy immune response, is based on an equilibrium between effector T cells and Treg cells, and that it involves regulation through a variety of molecules, such as interleukin-10 (IL-10), transforming growth factor-β (TGF-β), and programmed cell death 1 (PD1) or programmed death ligand 1 (PD-L1). CTLA4 and CD25 (PD1; also known as PDCD1), cytotoxic T lymphocyte antigen 4 (CTLA4) and CD25 (also known as high-affinity IL-2 receptor (IL-2RA))

Type 1 and type 3 responses are induced by pathogenic microorganisms, and they fit the original defensive role that was assigned to the immune system by Metchnikoff and Ehrlich. Type 1 responses are shaped by the production of IL-12 by dendritic cells (DCs) and macrophages, which lead to the activation of natural killer (NK) cells and group 1 innate lymphoid cells (ILC1s), followed by the activation of ILC3s and eosinophils, which destroy microorganisms by ingestion. Paul Ehrlich (1854–1915), a close friend of Koch, showed the role of humoral immunity, conveyed by antibodies, in the defence against microorganisms and bacterial toxins.

A century of immunology research followed to try to understand how the immune system recognizes the enormous diversity of microorganisms, and how it destroys pathogens without destroying the organism that it means to protect. Paradigms emerged, such as the self–non-self discrimination principle proposed by Frank Macfarlane Burnet (1899–1985) and Niels Jerne (1911–1994). More recently, Polly Matzinger formulated the danger model, which proposes that the immune system is triggered not only by the recognition of invading microorganisms (non-self), but also by the danger associated with these microorganisms and, more generally, by injured tissue. Finally, Thomas Pradeau, Sébastien Jaeger and Eric Vivier proposed that the immune system is fundamentally activated by a change in normality or discontinuity.

An alternative view of immune reactivity, known as the immune network theory, was proposed in the 1970s by Jerne, Heinz Kohler and Geoffrey Hoffmann. According to this theory, the immune system is composed of a network of cells and antibodies, recognizing both non-self antigens and new self-antigens (such as hyper-variable regions of antibodies). This network of recognition includes both activators and suppressors that maintain the system in a state of equilibrium during homeostasis. Disturbance of that equilibrium by a new antigen induces a response, which is followed by a gradual return to homeostasis. Although this theory has been generally abandoned by the immunological community, the idea of an equilibrium within the immune system that is maintained by a network of activators and suppressors is a concept that is supported by more recent studies, and encapsulated by the view that an equilibrium between pro-inflammatory and anti-inflammatory immune responses is required to maintain health.
role in type 2 responses during tissue repair \(^{46,47}\) and were originally described by Metchnikoff as the phagocytes that eliminate abnormal cells during fetal development \(^{48}\).

Mixed type 2 and type 3 responses may occur during allergic responses, possibly induced by concomitant tissue damage and the presence of extracellular microscopic particles \(^{49}\).

A type 4 immune response has also been proposed \(^{38,40}\). This response does not develop against microorganisms or parasites that infect or injure tissues, but rather aims to block microorganisms and parasites before they reach sensitive tissues. For example, in the eye, inflammation is poorly tolerated and causes irreversible damage \(^{40}\), and in the intestine, the extensive microbiota must be kept away from the epithelium to avoid the induction of tissue-damaging chronic inflammation \(^{49,50}\). Type 4 immunity requires secretory IgA, which is released in large quantities into the intestinal lumen, and is also released in tears, saliva, sweat and secretions from the genitourinary tract and the respiratory epithelium. IgA has a broad ‘anti-inflammatory’ effect \(^{40}\), partly because it neutralizes microorganisms before they reach the host tissues where they would induce type 1 or type 3 immune responses \(^{38,40}\). Other elements of the proposed type 4 responses include the production of mucus \(^{49}\) and AMPs, which are also secreted in substantial amounts by epithelial cells \(^{49}\).

So, do \(T_{reg}\) cells constitute a separate type of response that is dedicated to suppressing all other responses? \(T_{reg}\) cells have been described that express the signature transcription factors of \(T\_1\) cells (T-bet; also known as TBX21) \(^{51}\), \(T\_2\) cells (GATA binding protein 3 (GATA3)) \(^{52,53}\) and \(T\_17\) cells (retinoic acid receptor-related orphan receptor-\(y\) (ROSY)) \(^{54,55}\), as well as chemokine receptors that are associated with these \(T\_1\) helper cell subsets. It has been suggested that the cytokine environments that induce type 1, type 2 or type 3 responses also promote a partial differentiation of \(T_{reg}\) cells into these types, allowing them to migrate to effector sites and to efficiently regulate the associated \(T\_1\) helper cell functions \(^{56}\). In addition, the generation of \(T_{reg}\) cells, in particular, type 3 \(T_{reg}\) cells, is induced at the expense of the associated effector cells \(^{49,50}\). Nevertheless, this does not occur during inflammation \(^{22}\), and type 3 \(T_{reg}\) cells do not regulate \(T\_1\) cells, but instead regulate \(T\_2\) cells, in accordance with the equilibrium model of immunity \(^{49}\). The inverse situation is also true: type 2 \(T_{reg}\) cells regulate \(T\_1\) cells \(^{49}\).

Finally, and importantly, although one type of immune response is dominant at one site at a particular moment, different responses can simultaneously develop at different sites or sequentially develop at the same site. For example, a type 3 response that is induced by symbiotic microbiota in the intestine does not preclude the presence of a type 2 response in adipose tissues \(^{50,56}\), at least in the steady state \(^{41}\). Furthermore, destructive type 1 and type 3 responses must be followed by repair-associated type 2 responses to restore homeostasis in the affected tissue \(^{40,62}\).

In summary, the four arms of the immune system are balanced in the healthy state. The normal microbiota induces all four types of response and thereby establishes a healthy balance. During infection or injury, one arm of the immune system is stimulated that represses the others until the infection is cleared. By contrast, following a decrease in one type of trigger, for example, during antibiotic therapy to eliminate extracellular bacteria that induce type 3 responses, the other types of response are dysregulated and exacerbated to levels that may lead to pathological inflammation. I propose that the original and intuitive concept of equilibrium — the basis of Claude Bernard’s (1813–1878) principle of ‘milieu intérieur’, and of Walter Cannon’s (1871–1945) concept of homeostasis \(^{49}\) — is a core principle of immunity (Box 1).

**Evidence for the equilibrium model**

**Inflammatory pathologies.** Type 2 responses drive allergic and pro-fibrotic pathologies through the production of IL-4, IL-5 and IL-13 (REF. 64). By contrast, type 3 responses are involved in autoimmune inflammatory diseases, such as inflammatory bowel disease, rheumatoid arthritis and multiple sclerosis \(^{49,60,61}\), through the production of IL-17, granulocyte–monocyte colony-stimulating factor \(^{49}\) and lymphotoxin \(^{49}\), whereas type 1 responses are involved in systemic lupus erythematosus (SLE) and type 1 diabetes (T1D) through the production of IFNs \(^{49}\). In industrialized nations, the decreased incidence of infectious diseases thanks to better hygiene, vaccines and antibiotics, is associated with an increase in the incidence of allergic and autoimmune inflammatory diseases — an association that is described by the hygiene hypothesis \(^{10}\). I propose that inflammatory pathologies may not only be a consequence of exacerbated type 1, type 2 or type 3 responses, but may also be a consequence of diminished type 1, type 2 or type 3 responses.

Epidemiological and experimental data show that a loss of exposure to microorganisms (not necessarily pathogens) leads to an increased susceptibility to allergic responses \(^{69}\). For example, children raised on farms are less susceptible to developing allergies than those not raised on farms \(^{39}\). Conversely, children who are treated at an early age with multiple doses of antibiotics are more susceptible to allergies than those who are not exposed to repeated antibiotic therapy \(^{71,72}\). The same effect is found in mice treated early in life with antibiotics \(^{73}\) or maintained in germ-free conditions until weaning \(^{41}\), and germ-free mice also develop high levels of serum IgE \(^{44}\). Several mechanisms have recently been reported to explain how the microbiota inducing type 3 responses represses pro-allergic type 2
responses. First, exposure of pre-weaned mice to the microbiota leads to long-term epigenetic modification of the gene encoding CXC-chemokine ligand 16 (CXCL16), which recruits invariant NKT cells that produce IL-13 and increase susceptibility to type 2 inflammation74. Second, we showed that the microbiota induces T$_\text{H}17$ cells and RORγt$^+$ T$_\text{reg}$ cells that inhibit the generation of type 2 T cell responses96. Third, it has been shown that B cells respond directly to bacterial signals to limit serum IgE levels and basophil numbers75. In addition, type I IFNs that are induced by murine norovirus (MNV) block the elevated type 2 response that is found in germ-free mice76, and IFNs directly block ILC2s77,78.

Another case of pathological interference between type 2 and type 3 responses involves fat metabolism, and the regulation by AAMs of blood glucose consumption to generate heat79. Monocytes that are recruited to fat are converted to AAMs by IL-4 that is produced by eosinophils80, which are themselves recruited by IL-5 that is produced by ILC2s81,82. However, type 3 responses are enhanced if the adipose tissue is inflamed — for example, after a diet- and inflammation-induced increase in intestinal permeability that causes microorganisms and microbial products to access the circulation and to reach fat tissues61,83,84. As a consequence, type 2 responses are inhibited and blood glucose levels rise, increasing the risk of type 2 diabetes.

Type 3 immunity is regulated by viral and bacterial infections that induce type 1 responses85. In particular, IL-17 production that is required against bacterial IFNs that are induced by murine norovirus (MNV) block the elevated type 2 response that is found in germ-free mice76, and IFNs directly block ILC2s77,78.

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**Figure 1 | The equilibrium model of immunity.** a) The equilibrium model of immunity is based on the idea that the immune system is never at rest but instead relies on a dynamic equilibrium between four types of competing and mutually inhibitory immune responses. Type 1 responses are directed against intracellular threats, such as viruses, some bacteria and tumours, whereas type 3 responses are directed against extracellular microorganisms, such as most bacteria and fungi. Type 2 responses are directed against large parasites, such as helminths, which cannot be destroyed by type 3 responses but that can be kept at bay by the construction of barriers through the production of mucus and collagen. Finally, type 4 responses develop to exclude microorganisms and to protect sensitive tissues from potentially destructive inflammation, through the secretion of, for example, large amounts of IgA and antimicrobial peptides into the gut lumen or eye secretions. b) Health is determined by an equilibrium between these four types of response. Following an infection that induces one type of response, the other types of response are inhibited. Conversely, the absence of one type of response leads to the exacerbation (red) of the other types, potentially leading to inflammatory pathologies, such as autoimmunity and allergy. IFNγ, interferon-γ; IL, interleukin; sIgA, secretory IgA; TGFβ, transforming growth factor-β.
infections is inhibited by type 1 and type 2 IFNs. Furthermore, helminth-induced type 2 responses limit autoimmunity inflammation, at least in rodent models. These mechanisms might explain the increased incidence of arthritis, multiple sclerosis and inflammatory bowel disease in industrialized countries, where there is a decreased incidence of infections by helminths, viruses and intracellular bacteria such as Mycobacterium tuberculosis. Conversely, a loss in the diversity of bacterial symbionts, as a consequence of increased antibiotic use, may lead to a loss of type 3 responses and, therefore, to an increase in autoimmunity that is driven by type 1 responses, such as SLE and T1D. In support of this mechanism, segmented filamentous bacteria, intestinal symbionts and potent inducers of type 3 responses, are associated with protection from T1D in mice.

**Infectious pathologies.** Recent data have provided evidence to explain how a pre-existing infection can influence the outcome of a second infection (or superinfection). For example, mice that are latently infected with a y-herpesvirus develop increased resistance to superinfection by the bacteria Listeria monocytogenes. Both microorganisms elicit a type 1 response by the host, and the increased level of IFNγ that is induced by the latent (symbiotic) virus confers protection against L. monocytogenes. However, the presence of a virus can also increase susceptibility to superinfection by a microorganism that is controlled by a different type of response. For example, a previous infection with lymphocytic choriomeningitis virus (LCMV) increases the susceptibility of mice to a subsequent infection with L. monocytogenes or Staphylococcus aureus through a mechanism that involves the type 1 IFN-mediated apoptosis of granulocytes. In this case, the type 1 response that is induced by the virus blocks the type 3 response that is mediated by the granulocytes to limit the early spread of bacteria. Similarly, a previous infection with influenza A virus or respiratory syncytial virus renders mice highly susceptible to superinfection with pneumonia-inducing bacteria, such as Neisseria meningitides, Streptococcus pneumoniae, Haemophilus influenzae, Streptococcus pyogenes and S. aureus. These viruses may also induce type 2 repair responses during later stages of infection that further interfere with the antibacterial type 3 response.

Conversely, helminths that induce type 2 responses impair antiviral type 1 responses. Mice that are infected with MNV develop virus-specific CD8+ T cell and Treg1 cell responses. However, pre-infection with the helminth Trichinella spiralis blocks the generation of virus-specific T cells and leads to increased viral loads. Microbiota-induced type 3 responses also block antiviral type 1 responses. Mice treated with antibiotics resist MNV infection through the production of IFNα by epithelial cells and the activation of the transcription factors signal transducer and activator of transcription 1 (STAT1) and interferon-regulatory factor 3 (IRF3), which are mediators of type 1 immunity. However, in untreated mice, the microbiota induces type 3 immunity and blocks this type 1 response. Finally, infectious microorganisms or helminths can manipulate the immune system for their own benefit. For example, the fungus Aspergillus fumigatus induces a potent pro-allergic type 2 response in the lungs, but neutrophils and IL-17-mediated type 3 responses are required for its efficient elimination.

**Tumours.** Type 1 cytotoxic responses, which involve CD8+ T cells and NK cells, are most effective for fighting tumours. However, tumours induce several responses that inhibit antitumour type 1 responses. Tumour-induced type 3 responses favour tumour growth through the activation of the anti-apoptotic transcription factor STAT3. In a mouse model of spontaneous breast cancer, tumour-infiltrating macrophages produce IL-1β, which induces the production of IL-17 by γδ T cells and the recruitment of neutrophils. The neutrophils inhibit the activation of tumour-specific CD8+ T cells and thereby facilitate tumour metastasis.

Tumours also induce TGFβ-driven ‘anti-inflammatory’ responses, which inhibit tumour-specific CD8+ T cells by promoting the generation of Treg cells (which type of Treg cells remains to be determined). TGFβ also promotes the generation of IgA+ B cells, which are the proposed main effectors of type 4 responses. Recently, IgA+ B cell responses were found in the tumour microenvironment of mice treated with the chemotherapeutic drug oxaliplatin. The generation of such B cells was dependent on TGFβ receptor signalling and led to the expression of IL-10 and PD1 ligand 1 (also known as CD274), which inhibited the cytotoxic T cell-mediated response against the tumour.

**Predictions from the equilibrium model**

*Thymus-derived Treg cells and repair responses.* A key principle of adaptive immunity is the clonal selection of immature T cells in the thymus, during which T cells that recognize self-antigens are eliminated (through negative selection). An apparent violation of this rule is the generation in the thymus of Treg cells that react against self. It is generally thought that thymus-derived Treg cells (tTreg) are generated to suppress responses by effector T cells that weakly react to self-antigen; these cells react with self-antigen too weakly to be eliminated during negative selection, but do react strongly enough to have the potential to become autoreactive disease-causing cells during infection. So, tTreg cells are selected in the thymus owing to their intermediate reactivity to self.

The equilibrium model of immunity suggests an alternative explanation for the generation of tTreg cells, as well as a new classification for thymus-derived and peripherally derived Treg (pTreg) cells. We have recently reported that, in the intestine, microbiota-induced pTreg cells express RORγt, which is the marker for type 3 lymphoid cells, and initially differentiate along a pathway that is common to Treg cells and then through a distinct pathway in the presence of retinoic acid. By contrast, Treg cells that express GATA3, the marker for type 2 lymphoid cells, can develop in the absence of the microbiota and constitute another major population of Treg cells in the intestine and adipose tissue. On the basis of these observations, we propose that Treg cells differentiate according to the associated effector T cells into type 1, 2 or 3 Treg cells, and thus determine the level of the local immune response. This suggests that recognition of self by developing tTreg cells, which occurs in the absence of microbiota-derived antigens, should lead to the generation of type 2 Treg cells, which may contribute to tissue repair when activated in the context of sterile tissue injury. During the late stages of an infection that require tissue repair, type 2 Treg cells may also contribute to the inhibition of type 1 and type 3 responses. This idea could be tested by assessing the expression of molecules that are associated with type 2 immunity and tissue repair by tTreg cells.

**Neonatal and oral tolerance.** Immune tolerance is considered to be a general mechanism of immune control that is required to avoid inflammatory pathology.
However, as in the case of T<sub>reg</sub> cells, tolerance may instead reflect an inhibition of one type of immunity by another type<sup>19</sup> (FIG. 2).

For example, neonatal tolerance occurs on the exposure of neonates to antigens<sup>118</sup>. It is commonly accepted that the immature status of the neonatal adaptive immune system leads to the elimination rather than to the activation of T cells specific for such antigens. This view is an extension of the principle, formulated by Frank Macfarlane Burnet (1899–1985), that embryonic antigens are defined as self and should therefore induce tolerance<sup>1</sup>. However, as discussed above for the generation of T<sub>reg</sub> cells, neonatal antigens, as well as embryonic antigens, may induce type 2 cells (T<sub>h</sub>2 cells, type 2 T<sub>reg</sub> cells, ILC2s and AAMs) and thereby induce the repair responses that are required to control developing tissues. Neonatal type 2 responses are predicted to inhibit the type 1 and type 3 responses induced by most experimental challenges<sup>33</sup>. It may also be predicted that an absence of type 2 responses during the neonatal period increases susceptibility to pathological tissue damage and life-threatening organ dysfunction.

Oral tolerance is a mechanism by which antigen delivered through the gastrointestinal tract suppresses effector responses against that antigen throughout the organism<sup>117</sup>. However, although tolerance suggests an absence of response, intestinal responses to orally-delivered antigens are not eliminated but instead comprise type 3 T<sub>reg</sub> cells<sup>46</sup> and the production of IgA<sup>47,118</sup>. Consistent with the equilibrium model of immunity, the induced type 3 response inhibits type 1 and type 2 responses against the orally-delivered antigen. Accordingly, RORγt-deficient mice, which lack type 3 immunity, develop a pathological form of type 1 immunity against intestinal antigens<sup>119</sup>. Similarly, the type 4 response comprising IgA inhibits the other types of response. Oral tolerance can be breached by the administration of antigen together with mucosal adjuvants, such as cholera toxin, which shifts the type 4 IgA response to a local type 3 response<sup>120</sup> or to a systemic type 2 response<sup>121</sup>.

**Resistance to infection.** An important implication of the equilibrium model of immunity is that resistance to infection is partly determined by the state of the immune system before infection (FIG. 3). For example, a primary infection confers resistance or susceptibility to a subsequent infection, depending on the types of response that are engaged by the two infectious agents. This idea may be generalized to the modulation of the immune system by the symbiotic microbiota, which includes type 1-inducing viruses, type 2-inducing helminths and allergens, and type 3-inducing bacteria and fungi. Therefore, analysis of the immune state of an organism before infection, in terms of the balance between the different types of immune response, may allow researchers to predict the outcome of an infection or the efficiency of immunotherapy and vaccination.

**Preventive and therapeutic avenues**

On the basis of the equilibrium model of immunity, novel types of preventive and therapeutic strategies may be developed.

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**Figure 2 | Tolerance in the equilibrium model of immunity.** The four types of immune response are mutually inhibitory. Therefore, tolerance, as measured by the elimination of one type of response, may in many cases reflect inhibition by another type of response rather than a total absence of immune responses. For example, measures of the type 1 response against a virus (interferon-γ (IFNγ) levels and antigen-specific cytotoxic T lymphocyte responses) can be significantly decreased by the presence of symbiotic bacteria that induce type 3 responses and helminths that induce type 2 responses. Regulatory T (T<sub>reg</sub>) cells are an important component of mutual regulation, but they do not lack effector functions; thymus-derived T<sub>reg</sub> (tT<sub>reg</sub>) cells react to self-antigens, not only to inhibit type 1 and type 3 responses, but also to promote tissue repair<sup>115</sup>, which is a trait of type 2 responses. GATA3. GATA binding protein 3; pT<sub>reg</sub>: peripherally derived T<sub>reg</sub>; slgA, secretory IgA.
For example, to protect against viruses or tumours type 1 responses need to be induced. This can be achieved either by directly enhancing type 1 responses or by blocking type 2 and type 3 responses. William Coley famously used *S. pyogenes* to treat patients with cancer in the 1890s, a strategy that was later shown to involve either tumour necrosis factor (TNF) or IL-12 [REF. 123]. In addition, one of the most effective treatments against non-invasive bladder cancer is intravesical delivery of *Mycobacterium bovis* bacillus Calmette-Guérin (BCG), which is a strong inducer of type 1 responses[124]. To increase the safety and feasibility of this approach, MAMPs could be used or synthesized to promote type 1 responses. Antibiotic treatment has been shown to prevent persistent infection by MNV, as the type 3 response that is induced by the bacterial microbiota (which is inhibited by the antibiotics) inhibits the production of antiviral IFNα by epithelial cells[101]. Type 2 or type 3 responses can be further targeted using neutralizing antibodies against key cytokines, such as IL-33 or IL-23, or using antagonists against key transcription factors such as RORγt[125,126]. Similar strategies may be developed to enhance antihelminth type 2 responses or antibacterial and antifungal type 3 responses.

Conversely, the immune equilibrium could be manipulated to dampen allergic and autoimmune inflammation. Current strategies for treating allergy and inflammation rely on targeting effectors, such as histamine and TNF, or the use of broad anti-inflammatory drugs. Instead, it might be possible to induce type 1 or type 3 responses using non-pathogenic bacteria, fungi or viruses, or MAMPs derived from these microorganisms[127], that inhibit pro-allergic type 2 responses. Furthermore, the induction of type 1 or type 2 responses using viruses, helminths, allergens or related MAMPs, could be used to inhibit autoimmune type 3 inflammation, an approach that has been investigated using helminths[128,129] and helminth-derived proteins[89,130].

Approaches that are based on the positive manipulation of the immune equilibrium have an important benefit compared with the use of drugs that target microorganisms or inflammation. These approaches re-equilibrate the immune system and strengthen the equilibrium through the presence of ‘regulatory’ microorganisms, rather than weaken it through drugs or losses to the host microbiota.

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Figure 3 | **Microorganisms in the equilibrium model of immunity.** The induction of one type of response by microorganisms or helminths inhibits the other types of response. Thus, viruses are predicted to decrease susceptibility to allergy, but at the same time to decrease tissue repair (a property of type 2 responses) and increase susceptibility to infection by helminths, bacteria and fungi. By contrast, helminths are predicted to increase tissue repair, but at the same time decrease resistance to viruses and bacteria and increase susceptibility to allergy. Following the same logic, most bacteria and fungi are predicted to decrease susceptibility to allergies, but also to increase susceptibility to viruses, tumours and helminths, and to inhibit tissue repair.
PERSPECTIVES


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Competing interests statement

The author declares no competing interests.