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Two ways to survive an infection: what resistance and tolerance can teach us about treatments for infectious diseases

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Abstract

A host can evolve two types of defence mechanisms to increase its fitness when challenged with a pathogen – resistance and tolerance. Immunology is a well-defined field in which we dissect the mechanisms behind resistance to infection, but we tend to look at the ability to tolerate infections in a less methodical manner. In this Opinion article, we present the argument that animals have a specific suite of tolerance mechanisms (distinct from their resistance mechanisms), and highlight evidence for these defensive measures and discuss their potential clinical impact. It is important to distinguish between these two defence mechanisms because they have different pathological and epidemiological effects. Increased understanding of these defences could lead to more efficient treatments for infectious diseases and a better description of host–parasite interactions.

Introduction

When we study infections, we often consider the body's defence strategy as involving mechanisms that directly attack the pathogen to block invasion or eliminate the invading microorganism; however, our bodies can also defend themselves by limiting the damage caused by the infection. Resistance is defined as the ability to limit pathogen burden while tolerance is defined as the ability to limit the health impact caused by a given pathogen burden. The sum of these two mechanisms defines a host's defensive capacity. Tolerance includes all of the mechanisms that regulate the self-harm (bystander damage). Although we know a great deal about the molecular mechanisms that are used to kill pathogens and prevent infection, we do not have a systemic understanding of how the body regulates the production, repair and avoidance of the damage accumulated during an infection. We typically describe our immune response as a system and we suggest here that tolerance can also be described as a series of systems. By simply broadening the scope of our studies, we will be able to identify more of these tolerance mechanisms that could potentially help us to diagnose and treat patients. We suggest that we can provide a structure for this emerging field, if we borrow some concepts from evolutionary biology.

Resistance and tolerance in plants

The concept of a two-component defence response — involving resistance and tolerance — is well described by plant ecologists to assess plant health in parasite–plant interactions^{1–5}. This model has much to offer for our understanding of animal defence mechanisms against pathogens. In vertebrate models of infectious diseases, we rarely carry out such analyses and

it is practically impossible to do this for actual patients. However, the logic behind this type of analysis could be useful, because resistance and tolerance, as defined in this manner, have exciting ecological and biomedical implications.

Reaction norms are a measurement of the phenotypes for a given genotype across a range of environments and they are used in the fields of ecology and evolutionary biology to measure how an individual responds to a range of environmental conditions (Figure 1). Plant ecologists adapted this method to assess the fitness of a plant (for example, seed production) in response to some measurement of parasite load, be it damage induced by the parasites/host response or the actual number of parasites⁶. In this context, resistance is defined as the inverse of the parasite burden; when resistance increases, the level of pathogen will decrease. Tolerance is defined by the slope of the reaction norm; the more tolerant the host, the flatter the slope will be⁷⁻⁸. In other words, more tolerant plants will exhibit a smaller decrease in their overall health as parasite burden increases compared with non-tolerant plants. By using the slope of the relationship between health and pathogen load it is relatively simple to compare populations that may differ in their health before they were infected (a property defined as vigor).

This definition of tolerance is not new to vertebrate immunity but it is certainly under-represented. In this Opinion article, by discussing known examples of tolerance in animals, we hope to re-ignite interest and encourage a broader application of the concept of tolerance to vertebrate models of infectious disease. First, we speculate on the types of physiologies that might be involved in tolerance mechanisms in animals and discuss evidence that these defensive measures are important in defining the overall health of a host with various types of infection. We then discuss how the concept of tolerance can be studied systematically and how it can be integrated into our medical practices.

What are the mechanisms of tolerance?

Immunologists often describe resistance mechanisms in an organized fashion; we begin with an immune recognition event to effectors and then build up interactions between immune cells. In contrast, though immunopathology is a well-known result of an immune response, its discussion is organized around either the resistance mechanisms that generate the pathology, the organisms responsible for the diseases or the organs that are affected. This can make it difficult to find commonalities that exist among the immunopathological mechanisms that define tolerance. To begin to overcome this, we have organized our discussion of tolerance mechanisms by considering the effects a mechanism has on tolerance and resistance. We define three classes of mechanism that cover a spectrum of effects starting with those in which resistance and tolerance are absolutely linked to a set where they are completely separable. We consider a mechanism to affect tolerance if it is predicted to decrease or increase the slope of the tolerance curve; it is important to understand how to reduce mechanisms that increase the slope of the tolerance curve as well as to augment those mechanisms that flatten the curve.

The distinguishing characteristic of our first class is that it is comprised of effector molecules and that resistance and tolerance effects are absolutely linked and are opposite.

Over evolutionary time, we expect that there has been a selection of non-toxic effectors and receptors in the immune system; during evolution, hosts have probably evolved effector molecules, such as antimicrobial peptides (AMPs) that are less toxic to self than invaders⁹. Likewise, a similar selection must have occurred for receptors, such as the Toll-like receptors (TLRs) that trigger immune responses, such that they have a higher affinity for pathogen-associated molecules¹⁰. This also happens at an individual level over one lifetime, in animals that have an adaptive immune response. What most immunologists call “tolerance” — the elimination of self-reactive T-cell receptors and antibodies — should also increase tolerance according to the ecological definition of this word. Effector mechanisms that are induced during an immune response and can cause self-harm could decrease tolerance. For example, reactive oxygen species produced during an immune response are important for fighting infections, but their activity can also induce severe pathology and even death in some cases, resulting in a decrease in tolerance^{11, 12}. In all of these examples, the factor that is required to reduce pathogen load (and thus increase resistance) is the same factor that causes immunopathology and increases the slope of the tolerance curve.

In the second class, we placed regulators that control both resistance and tolerance. We separated these from resistance effectors because these signaling molecules do not cause pathology directly and it thus may be possible to separate their effects on resistance and tolerance by selectively blocking some signaling pathways or signaling in specific tissues. TNF provides an example of such a molecule; TNF is critical for fighting some infections because it activates immune cells and thus has a pro-resistance function¹³. At the same time, the damage induced by immune effectors as well as additional pathology caused by other targets of TNF will reduce the health of the host and thus increase the slope of the tolerance curve. We consider it to be a tolerance factor because its activity alters the tolerance curve. These first two classes provide examples of factors that are predicted to show a tradeoff between resistance and tolerance.

We placed tolerance mechanisms that can be easily separated from resistance in our third class. We suggest that this group of mechanisms will provide the most useful candidates when searching for new drugs and treatments that modulate tolerance. We describe five mechanisms below. First, during an immune response to infection, toxic compounds can be produced by the host or pathogen that must be dealt with to prevent damage to the host. For example, the destruction of red blood cells during a malaria infection causes free heme, which is toxic to the host, to enter the circulation. Heme oxygenase-1 acts as a detoxifying enzyme of heme¹⁴ and defects in this pathway should cause a decrease in tolerance. Second, resistance responses can be expensive in terms of energy expenditure and appropriate energy management will be required to fuel these responses without causing irreparable damage to other systems and leaving enough energy left for repair. As we discuss in more detail later, the fruit fly *Drosophila melanogaster* exhibits altered energy use and wasting when infected with *Mycobacterium marinum* and this seems to be due to decreased tolerance¹⁵. Third, we propose that processes that prevent physiological damage will also affect tolerance. Some immune responses can induce physiological changes that are deleterious for some organs. For example, sepsis can induce fatal changes in cardiovascular physiology including hypercontraction of the heart and altered vascular tone, which must be counteracted to

prevent damage and increase tolerance¹⁶. The fourth class, repair, is related to the third; repair of tissue damage is necessary if pathology can not be entirely prevented. For example, infections with the helminth, *Nippostrongylus brasiliensis* in mice cause severe damage to the pulmonary environment during larval migration and triggers a number of factors that are key to lung repair including elastin, procollagen, matrix metalloprotease and others, resulting in rapid resolution of the damage^{17, 18}. We propose a fifth group, which is a catch-all of ad hoc evolutionary solutions to infection, which affect tolerance in a pathogen-specific manner. These will probably involve a large variety of mechanisms. Such evolutionary solutions can be seen in terms of the genetic traits that offer increased defences against malaria^{19–23}. We discuss these examples in more detail later. Of course, we expect more examples to be revealed as tolerance mechanisms in animal defences are explored further.

If we consider only pathogenic interactions between bacteria and hosts we risk missing important host-microbe interactions; we have an enormous number of non-pathogenic interactions with bacteria every day. Interactions with mutualistic and even commensal bacteria may reveal more examples of tolerance mechanisms. A simple one might be that our guts do not normally raise pathological immune responses to the grams of LPS in our intestinal lumens. Our body plan, which sequesters microbes to certain regions of our body could be considered to be a tolerance mechanism. We argue that our native microbiota form an integral part of our resistance and tolerance mechanisms. If we have a normal flora, we can endure a certain level of pathogens in our guts and this tolerance drops if we alter our flora with antibiotics.

All of these examples we listed consider the host and pathogen as independent and consider resistance and tolerance to be host properties. In bacterial pathogens, we know of many virulence factors that affect resistance; are there also there tolerance factors? A good place to look for these might be in mutualists or in pathogens that cause chronic infections.

Tolerance mechanisms in invertebrates

Studies examining immune-defence systems in invertebrates commonly estimate genetic contribution to immunity by measuring a single parameter of immuno-competence; for example, parasite load or antimicrobial activity are used to represent the effects of infection on host fitness^{24–26}. This has been a successful approach and studies such as these led to the dissection of the Toll and Imd signalling pathways in *D. melanogaster*^{27–36}. Such studies also led to the observation that flies lacking these two pathways can not produce AMPs and therefore have high bacterial loads and die rapidly after infection. This approach was based heavily on dissecting the mechanism (NF- κ B-mediated regulation of AMPs) and measured phenotype (survival) as a secondary characteristic^{36–40}.

Approaches that look primarily at phenotypes tell a different story; to better understand the relationship between disease resistance and host fitness, Corby-Harris *et al.* infected eleven different genotypes of *D. melanogaster* with the insect pathogen *Pseudomonas aeruginosa* and asked whether parasite burden was positively correlated with host survival. Significant variation was found between genotypes in terms of both bacteria titers (a measure of

resistance) and survival, yet no positive correlation was found between these two parameters. In other words, those genotypes that had low bacteria titers were not necessarily the healthiest. This suggests that processes other than resistance are used by *D. melanogaster* to cope with the stresses of infection and that tolerance, not resistance, is a crucial determinant of host survival during this type of infection. Furthermore, these results suggest that genetic variation for tolerance exists in invertebrates⁴¹.

Dionne *et al.* examined the mechanism by which *M. marinum* kills *D. melanogaster* and found that *M. marinum* infection leads to wasting, with a progressive loss of fat and glycogen. It seems that *M. marinum* infection causes a decrease in the activation of the insulin effector kinase AKT, which results in increased FOXO transcriptional activity, driving the wasting process in flies and ultimately leading to death. The authors showed that this wasting could be suppressed by decreasing FOXO activity in the fly. This had no effect on microbial number but increased survival of *D. melanogaster*; therefore, protection against *M. marinum* infection was not a resistance effect, rather it altered tolerance. This is an example of tolerance being based on altered energy use by the host. This is one of the few examples of a *D. melanogaster* infection for which the cause of death is known, and it seems to be due to a problem with tolerance, rather than increased susceptibility to infection or proliferation of the pathogen¹⁵.

The detection of tolerance mechanisms during pathogenic infections in a genetically tractable organism such as *D. melanogaster* offers promising potential to identify pathways involved in regulating these tolerance properties, which might ultimately be translated into biomedical practices.

Tolerance properties in vertebrate models

Evidence for genetic variation for resistance and tolerance traits has been shown in mice infected with the protozoan parasite *Plasmodium chabaudi*. Raberg *et al.* reported the first study that applied the statistical framework of reaction norms developed by plant ecologists to an animal model⁴² (Figure 1). To measure the variation of tolerance in animals they infected five strains of mice with *P. chabaudi*. Three different clones of *P. chabaudi* that differed in infection intensity were tested as well as uninfected mice. To measure host health, they recorded the severity of anaemia as well as weight loss in infected mice. These health indicators were then plotted against peak parasite density, which measured parasite burden. As had been noted previously, there was significant variation in the degree of resistance between the mouse strains. Interestingly, the slopes generated from the reaction norms varied between the different mouse strains, which indicates that there is variation in tolerance between the mouse strains tested. In addition, they report that tolerance and resistance are negatively correlated, which indicates that there is a trade off between tolerance and resistance. The mechanism(s) behind tolerance in these mice is unknown⁴².

The tick-transmitted spirochete, *Borrelia burgdorferi*, is the causative agent of Lyme disease in humans. In the mouse model of Lyme disease, *B. burgdorferi* causes a wide spectrum of arthritis severity that depends on the genetic background of the infected mouse. Both resistance and tolerance mechanisms seem to be important in controlling the development of

arthritis, depending on the mouse strain. Ma *et al.* showed that BALB/cAnN mice control the severity of disease by controlling the numbers of spirochetes in tissues, which indicates that this mouse strain uses resistance mechanisms to control the infection⁴³. C57BL/6N mice, by contrast, do not develop severe arthritis regardless of the number of spirochetes found in the tissues, which indicates that these mice are better able to tolerate the pathology of the infection through unknown mechanisms⁴³.

The above examples provide phenotypic evidence of tolerance but are not informative about the tolerance mechanisms driving such phenotypes. Studies of individual mouse mutants have provided some mechanistic insight for tolerance physiologies. For example, mice deficient for an ATP-sensitive potassium (K_{ATP}) channel were found to be more sensitive to lipopolysaccharide (LPS). This channel is expressed in coronary arteries and the mutant mice were found to suffer from heart attacks when challenged with LPS⁴⁴. Additional alleles of this gene were identified in a screen for mice with an altered susceptibility to murine cytomegalovirus. During viral infection of mice deficient for this K_{ATP} channel, cytokine production is lower and mice die rather abruptly with no obvious signs of sickness, but viral titres are comparable to infected wild-type mice, which indicates that this K_{ATP} channel is involved in positively regulating tolerance during infection. The K_{ATP} channel is thought to work by preventing coronary artery vasoconstriction that is induced by cytokines produced in response to TLRs or MDA5 during some types of infection⁴⁵. The tolerance mechanism here seems to fit in the class of damage prevention.

The phenomenon of endotoxin tolerance, which is the transient decreased responsiveness to repeated exposure of LPS, is a well-known example of tolerance^{46–49}. Traditionally, endotoxin tolerance was described as a desensitization of TLRs, resulting in macrophages being hyporesponsive to subsequent exposures to LPS^{50–52}. A report by Foster *et al.* more closely examined the effects of endotoxin tolerance on the expression of genes under the control of TLR signalling⁵³. They hypothesized that because hundreds of genes of many different functions are under the control of TLRs, it seems unlikely that endotoxin tolerance acts at the level of regulating the total signal through a TLR, but rather acts in a gene-specific manner. To test this idea they used an *in vitro* model system for LPS tolerance in mouse macrophages and compared the gene-expression profile of naïve or tolerant macrophages that were stimulated with LPS. They identified two classes of TLR4-induced genes based on their functions and regulatory requirements. The first class, which included pro-inflammatory cytokines, was silenced in the tolerized macrophages. The second class, which included antimicrobial genes, was not silenced in the tolerized cells. Regulation of these classes occurs at the level of gene transcription rather than the upstream TLR signal and involves transient chromatin modifications⁵³. This study shows that the resistance and tolerance properties can occur as separate and distinct mechanisms that are regulated independently of each other.

Tolerance properties in humans

Malaria puts serious evolutionary pressures on humans, and genetic traits that affect resistance or tolerance — such as sickle-cell anemia (*HbS* gene), α thalassemia and glucose-6-phosphate dehydrogenase (G6PDH) deficiency — have appeared in affected

populations. In the case of α thalassaemia, individuals with the mutation have less severe malaria episodes and this seems to be due to increased tolerance properties because parasite loads are unaffected²². A possible mechanism for the protective effects of α -thalassaemia comes from observations involving the expression of complement receptor 1 (CR1) on α +-thalassaemia red blood cells. Previous work has shown that there is decreased expression of CR1 on red blood cells from individuals with α -thalassaemia. As CR1 seems to be involved in rosette formation of red blood cells, which occurs in severe forms of malaria, α +-thalassaemia cells have decreased rosetting and therefore decreased disease²².

The phenomenon of natural antimalaria immunity, known as premunity, in which infected individuals can withstand the presence of parasites in their blood at levels that would elicit sickness in unprotected individuals^{54, 55}, was first described seventy years ago. We propose that this might be another example of tolerance in that the body is somehow abiding the *Plasmodium* rather than inducing a large immune response that would cause pathology. A recent model to explain this phenomenon involves desensitization of TLR-mediated signalling, which draws a link between anti-malaria immunity and endotoxin tolerance. During a *Plasmodium* infection, the glycosylphosphatidylinositol (GPI) of the parasite, released during lysis of red blood cells, induces a pro-inflammatory response via signalling through TLR2–MyD88, leading to the production of cytokines including TNF, IL-1 and IL-6, which are important for controlling the growth of the parasite. When parasite levels and pro-inflammatory cytokine levels decrease, anti-inflammatory cytokines, including IL-10, are produced. This signalling and cytokine profile is reminiscent of that seen for LPS-induced cellular signalling through TLR4. In fact, more than forty years ago it was shown that experimentally induced malaria infections in human volunteers resulted in cross tolerance to the febrile response caused by endotoxin (LPS) injection. Cross tolerance between TLR2 (activated by GPI) and TLR4 (activated by LPS) has also been shown *in vitro*⁵⁶. This indicates that antimalarial immunity might involve alterations of TLR signalling, as seen with endotoxin tolerance, indicating a common tolerance mechanism.

How can we study tolerance systematically?

We described how the defence response in humans and other animals can be broken down into resistance and tolerance mechanisms, but our impression is that tolerance studies are rare in mammals whereas resistance studies make up most immunological reports. Of the tolerance mechanisms we do know, many seem to be tightly linked with resistance mechanisms. We argue that current immunological studies that focus on effector mechanisms and signalling between immune cells will be able to find only these types of tolerance mechanism that are tightly integrated into the immune signalling web. But, what about proteins such as the K_{ATP} channel, which seem to lie at the periphery of the signalling web? When we limit the scope of our studies to resistance signalling and effector molecules, as we do in our traditional immunological studies, we miss spotting the outlying tolerance mechanisms and these are the ones that will likely prove most useful in medical interventions because they are less likely to affect resistance. We need to broaden the focus of our studies and take a holistic approach to understanding the factors contributing to disease severity. We need methods of identifying tolerance mechanisms that are separable from resistance.

Tolerance traits can be determined genetically and we suggest these properties should be easy to find by broadening the scope of our assays by measuring tolerance directly. For the past decade, *D. melanogaster* genetic screens have concentrated on learning how AMPs downstream of the Toll or Imd pathways are regulated. These types of screens are focused on resistance mechanisms and therefore mutations that affect tolerance mechanisms could be easily missed. We recently published an unbiased forward genetic screen in *D. melanogaster* that coupled the concepts of resistance and tolerance to identify genes involved in defence against *Listeria monocytogenes* infection⁵⁷. In this study, we measured bacterial burden in these mutant flies and found that in two thirds of the mutant lines, increased susceptibility to death was correlated with increased bacterial burden, indicating defects in resistance mechanisms. By contrast, the remaining mutant flies died with comparable levels of bacteria to those seen in wild-type flies, which indicates that these mutants were defective in tolerance mechanisms and were unable to endure the pathological consequences of the infection. Similarly, various candidate knockout studies in mice, in addition to the genetic screen by Croker *et al.*^{14, 45, 58, 59}, showed that by simply studying both disease severity and parasite burden, the involvement of immune responses in tolerance mechanisms can be revealed. Past experience demonstrates that when we focus on our favorite mechanisms we can miss interesting biology – keeping this in mind, we should be broadminded in future screens and be sure to perform our screens so that we can measure both positive and negative changes in tolerance induced by both gain-of-function and loss-of-function mutations rather than stick only with what has worked already. When screening, we should also turn to the microbes for answers; because of the potential benefits tolerance mechanisms may have on pathogen infection and transmission, some pathogens may have evolved mechanisms to enhance the tolerance of their hosts. Pathogens are the best immunologists around and have much to teach us.

Of course, genetics is not the entire story and it is important to remember that tolerance traits are also affected by the life history of a host. For example, fruit flies suffer from immune senescence that occurs during aging and, in one model, this is due to an age-related loss of tolerance⁶⁰. Flies injected with a lethal dose of *E. coli* differ in their death rate depending upon their age, however the growth rate of the infecting bacteria remains constant. This is diagnostic of a change in tolerance. We should pay attention to epigenetic mechanisms for altering tolerance because these may provide the fastest route to developing new treatments.

We stress the importance of testing a variety of pathogens when studying tolerance mechanisms both genetically and epigenetically. In humans, we anticipate that different classes of disease — for example, bacterial diarrhoea, pneumonia or sepsis — will have different sets of mechanisms controlling tolerance. For example, the TNF-family member in *D. melanogaster*, Eiger, has multiple and opposite roles in fly defence that become clear only when a variety of pathogens are tested^{61, 62}. If tolerance is to be modulated medically, we must ensure that while treating one infection we do not make a patient more susceptible to others.

Medicine and tolerance

In current medical practices, doctors can recognize when the tolerance of a patient must be increased for several specific disease types and the tools needed to achieve this are available. For example, the death of patients with cholera is the result of severe dehydration and the first line of treatment for these patients is to give them electrolytes and to keep them hydrated. This increases tolerance by limiting pathology and allows the patients to live long enough to rely on their resistance mechanisms to clear the pathogen. Bacterial meningitis is an example where we assume that we are increasing the tolerance of a patient by directly manipulating the immune response. When administered in combination with the initial antibiotic treatment, corticosteroids significantly decrease the risk of mortality and hearing loss⁶³. The goal of this article is not to highlight tolerance as a new way of treating patients. Instead, by using a different description of our defences against infectious diseases, we hope to encourage new experiments to discover more examples of tolerance mechanisms. Such findings could then be integrated into our current clinical practices to increase the survival of patients.

The reaction norms used by plant ecologists to measure plant health rely on a logic that we propose can be applied to assess patient health. Alas, it is likely impossible to determine a particular patient's reaction norm for tolerance and to use that as a diagnostic tool - but maybe we can make some good guesses - by systemically studying tolerance, we will learn more about the mechanisms that control these properties, allowing us to develop diagnostic tools to monitor relevant mechanisms and gain a better sense of tolerance curves for individual patients. Using this information, doctors could determine if a patient is sick because their resistance is suboptimal or because their tolerance is low and then use this information to choose appropriate treatments.

The intentional manipulation of resistance would increase health by moving the patient up the reaction-norm curve. This can be accomplished with current medical practices, such as vaccination before the patient encounters the pathogen or antibiotics once the patient becomes ill. The manipulation of tolerance would cause the slope of the curve to change. If the patient's tolerance mechanisms are collapsing, then they will have an extremely steep tolerance curve. The physician needs to rotate the reaction norm back up to its normal position by increasing tolerance properties of the patient and by doing this will increase the patient's health. The manipulation of tolerance is already a common practice in medicine, as we described for cholera and meningitis. As our studies examining tolerance mechanisms increase we will be able to develop additional drugs and therapeutics that can be used to manipulate a patient's tolerance and shift their tolerance curve to a healthy range (Figure 3).

As discussed in BOX 1, ecologists predict that resistance and tolerance will have different evolutionary effects on pathogens. Because host resistance mechanisms place selective pressures on pathogens, the microorganisms will eventually evolve mechanisms to subvert the resistance. We encounter this problem with many of our medical treatments that increase host resistance, for example, antibiotic resistance. Because tolerance mechanisms are not expected to have the same selective pressures on pathogens as resistance mechanisms do, we suggest that new drugs targeting tolerance mechanisms will provide therapies to which

pathogens will not develop resistance. The types of tolerance mechanism that could be targeted for drug manipulation should be chosen with caution. Those tolerance mechanisms that are tightly linked or inversely related to resistance mechanisms might not be the best candidates for drugs as their manipulation could affect both resistance and tolerance in unpredictable ways. Tolerance genes that lie outside immune signalling networks might be better drug targets as their manipulation is not expected to affect central immune signals and effectors.

BOX 1

Evolutionary implications of resistance and tolerance

Resistance and tolerance are predicted to have different evolutionary impacts on the pathogen and host. In the case of resistance, host–pathogen interactions are expected to drive the co-evolution of antagonistic traits^{64, 65}. Because resistance mechanisms act by directly limiting pathogen burden, if a host evolves resistance to a particular pathogen, the microorganism will evolve a method to subvert the resistance. This will drive the selection of more resistant traits in the pathogen population that can overcome the resistant mechanisms of the host, which will then drive the natural selection of more effective resistance mechanisms in the host population. This co-evolutionary relationship prevents a resistant trait from becoming fixed within a host population^{66–68}. That is, this co-evolutionary relationship continues to drive the evolution of host resistance mechanisms.

By contrast, these types of selective pressure are not expected to be placed on pathogens due to the evolution of increased tolerance. As tolerance works by alleviating disease severity, it should have a neutral or possibly positive effect on the pathogen; for example, tolerant hosts might live longer, increasing the prevalence of the disease and potentially altering its spread. Unlike resistance, a tolerance trait will eventually become fixed in a host population because it will be positively selected for in a population. Mechanisms that increase tolerance are not predicted to lead to the development of highly resistant pathogens. Therefore, understanding tolerance mechanisms should provide a good foundation for therapies, because they will remain useful for long periods of time as microorganisms are not anticipated to develop resistance. As we discuss in detail here, several tolerance mechanisms are already targeted in medical practice to help fight infections^{66–71}.

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Figure 1. Definitions and implications of resistance and tolerance

Resistance, which is a measurement of the ability of an individual host to limit pathogen growth, can be interpolated from these graphs as the inverse of the mean of the pathogen load. Tolerance, which is a measurement of the ability of an individual host to survive an infection at a given pathogen load, is the slope of the curve relating host health to pathogen load. Examples of different reaction norms adapted from Raberg *et al.*⁴²

Figure 2. Correlation between resistance and tolerance

This figure shows a core set of mechanisms that are involved in both resistance and tolerance in the fruit fly. As the figure moves into its outer rings, we predict that the tolerance mechanisms will have smaller and smaller effects on resistance. For example, alterations of immune effectors and receptors, on the left, will have strong effects on both tolerance and resistance. Immune modifiers in the center will have an intermediate effect. Outlying tolerance mechanisms will still certainly have effects on resistance but the effects might be smaller than those that modify resistance mechanisms.

Figure 3. Applications of resistance and tolerance to medical treatment

We propose that every patient has an tolerance curve describing the health of that patient in relation to their pathogen load. Health can be increased by reducing pathogen load or by drastically altering the shape of the tolerance curve.