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Perspective

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Cooperative Microbial Tolerance Behaviors in Host-Microbiota Mutualism

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Animal defense strategies against microbes are most often thought of as a function of the immune system, the primary function of which is to sense and kill microbes through the execution of resistance mechanisms. However, this antagonistic view creates complications for our understanding of beneficial host-microbe interactions. Pathogenic microbes are described as employing a few common behaviors that promote their fitness at the expense of host health and fitness. Here, a complementary framework is proposed to suggest that, in addition to pathogens, beneficial microbes have evolved behaviors to manipulate host processes in order to promote their own fitness and do so through the promotion of host health and fitness. In this Perspective, I explore the idea that patterns or behaviors traditionally ascribed to pathogenic microbes are also employed by beneficial microbes to promote host tolerance defense strategies. Such strategies would promote host health without having a negative impact on microbial fitness and would thereby yield cooperative evolutionary dynamics that are likely required to drive mutualistic co-evolution of hosts and microbes.

Introduction

Our interactions with microbes are primarily thought of as antagonistic. This perspective is not limited to professional pathogenic microbes. The emerging interest in the intestinal microbiota—the trillions of microbes inhabiting the intestine that are essential for our health—has been accompanied by a rise in the perspective that these microbes are the cause of diseases of interest in the developed world (Longman et al., 2013). Thus, understanding how these microbes may cause disease has taken priority over understanding how our health may benefit from these microbial interactions. A consequence of this perspective is that it has biased our view of host defense strategies against microbes. Traditionally, the defense response in animals against microbes has been most often thought of as a consequence of the immune response, the primary function of which is to sense and eradicate microbes through the engagement of microbial killing pathways, collectively referred to as "resistance mechanisms." In this perspective, I consider evidence that the response to microbes is not exclusively antagonistic. Beneficial microbes can induce host defense responses that promote both host and microbe fitness and will lead to mutualistic host-microbe interactions.

An examination of the evolutionary implications that resistance mechanisms have on host-microbe interactions reveals an important complication of this antagonistic perspective. Resistance protects the host by having a negative impact on microbial fitness and leads to the coevolution of antagonistic traits in both the host and microbial populations (Svensson and Råberg, 2010). Negative selective pressures placed on the host population by microbes drives the selection for adaptive defense strategies, which places selective pressures on the microbe population to drive the selection for counterattack defense strategies, which in turn leads to "new" selective pressures on the host population. These interactions have the potential to lead to open-ended evolutionary dynamics causing the oscilliation of resistance alleles in both populations, called the Red Queen effect (Figure 1) as well as the selection of new resistance traits. Many host-viral interactions provide excellent examples of these principles (Daugherty and Malik, 2012). For example, tetherin blocks the release of HIV-1 virions from infected cells and is a target of several viral factors. This antagonistic trait has driven the evolution of a mutant tetherin, resistant to these viral antagonists, which has then driven the evolution of an alternative method to antagonize tetherin (Daugherty and Malik, 2012).

Considering only pathogenic host-microbe interactions, these evolutionary dynamics may make sense. However, our microbial interactions that yield pathogenic outcomes make up only a small fraction of our total interactions with microbes, which are largely benign and often beneficial. The best example illustrating this principle is the microbiota, which performs essential functions for host physiology, including shaping the immune response, harvesting energy, and sustaining brain health. While it is established that resistance mechanisms help to shape the microbiota ecology (Strowig et al., 2012), there is little evidence to suggest that a loss of resistance mechanisms *alone* can trigger pathogenicity by the microbiota. It would be maladaptive to mount unnecessary resistance responses to our microbiota, as this would result in pathological consequences for the host. Thus, there must be other mechanisms in addition to killing mechanisms that enable a host to co-evolve beneficial microbial relationships.

Several models have been proposed to explain how we can have mutualistic microbial relationships with the microbiota while still responding to pathogenic threats. Originally, it was thought that the microbiota remains sequestered within the intestinal lumen with minimal interaction with the host. However, it is now

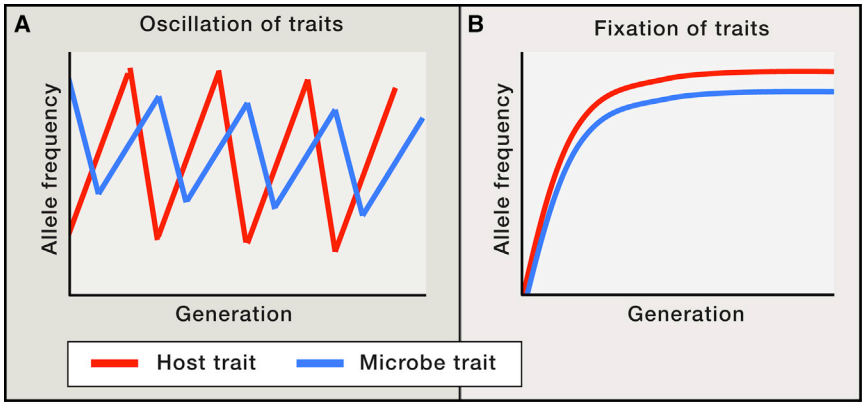

Figure 1. Evolutionary Dynamics of Host-Microbe Interactions

(A) Resistance traits in the host population place negative selective pressures on a microbial population, leading to selection of a counter-attack strategy in the microbial population. This response places a new selective pressure on the host population, driving the selection for a "new" resistance trait and a decline in the presence of the previous resistance trait. An oscillation of antagonistic traits in both host and microbe population, or the Red Queen Effect, results. Graph adapted from Svensson and Råberg, (2010).

(B) A tolerance trait in the host population will have a neutral to positive selective pressure on a microbial population. This balance will maintain the presence of the microbe population and associated selective pressures on the host population that will drive the selection and spread of the tolerance trait in the host population, eventually leading to fixation of that trait. In addition to host-encoded tolerance mechanisms, beneficial microbes likely have evolved traits that promote tolerance of their host and are predicted to yield similar evolutionary dynamics.

well established that the microbiota participates in a dynamic dialog with the host. Pathogens can be considered highly adapted organisms that have the capacity to cause disease in their host. In 1989, Finlay and Falkow, (1989) described common "themes" that pathogens have evolved. These themes can be broadly described as behaviors or "patterns of pathogenesis" that pathogens utilize to establish infection (Vance et al., 2009). As both pathogenic and beneficial microbes encode microbial-associated molecular patterns (MAMPs), innate immune recognition of patterns of pathogenesis combined with the recognition of MAMPs has been useful to describe in part how a host can distinguish a pathogen from a beneficial microbe and mount an appropriate response to a microbial threat (Vance et al., 2009).

An issue that further complicates host-microbial relationships is that they are seldom binary. It is rare that a single microorganism, particularly in the case of those composing the microbiota, can be classified strictly as pathogenic or beneficial to the host. Rather pathogenicity or beneficial effects of a single microbe on host health is dependent on individual microbial behaviors and the context in which these behaviors occur. The capacity of microbes to cause disease is dependent on immune status, genetics, and diet of a particular host as well as microbial location within the body. For example, *Bacteroides thetaiotaomicron* is considered a mutualist in most hosts. However, in genetically predisposed immunocompromised animals, *B. thetaiotaomicron* colonization leads to colonic inflammation (Bloom et al., 2011; Hickey et al., 2015). As such, it is likely that the microbial strategies that lead to beneficial outcomes for the host will likely be highly analogous to the ones that result in pathogenic outcomes.

In this perspective, I explore the idea that beneficial microbes have evolved strategies to manipulate host processes in order to promote the fitness of *both* host and microbe, framing the discussion around the intestinal microbiota of mammals. Such strategies would yield cooperative evolutionary dynamics that are required to drive mutualistic co-evolution of hosts and microbes.

Tolerance Defenses in Host-Microbiota Interactions

In a mutualistic relationship, if a microbe can promote its own fitness by *promoting* host health, and thus host fitness, then there must be host-encoded mechanisms that are induced during microbial interactions and that enhance host health without killing the microbe. Such mechanisms were initially described in the plant literature in the context of infections and herbivore interactions. Ecologists have long recognized that, in addition to resistance, plants rely on a distinct defense strategy called "tolerance" to protect against pathogens and pests. Tolerance promotes plant fitness in the presence of given levels of pathogen or herbivore (Bent et al., 1993; Caldwell et al., 1958). In recent years, the concept of tolerance defenses has been introduced into the field of animal host-microbe interactions (Ayres and Schneider, 2012; Medzhitov et al., 2012; Råberg et al., 2007; Schneider and Ayres, 2008). In this context, tolerance is a defense strategy that minimizes the physiological damage that occurs during interactions with microbes without having a negative impact on microbial numbers. Thus, tolerance protects the host during microbial interactions by promoting health (and fitness) while having a neutral to positive impact on microbial fitness, suggesting implications for the co-evolution of host-microbe interactions that are distinct from resistance. The example of *B. thetaiotaomicron* described above provides an excellent example of tolerance defenses in mutualistic interactions. In immunocompromised mice, the loss of IL-10/TGFβ signaling results in colonic inflammation in *B. thetaiotaomicron*-colonized mice (Bloom et al., 2011; Hickey et al., 2015). Thus, the induction of IL-10/TGFβ in immunocompetent mice promotes tolerance of this mutualist. As long as a microbe remains present in the host population, it will drive the selection for tolerance traits to spread in the host population and will go to fixation. Tolerance defenses would therefore yield the predicted evolutionary dynamics required to drive host-microbe mutualistic relationships and can help to explain how we co-evolved with our microbiota (Ayres, 2013) (Figure 1).

The field of disease tolerance in animals is in its infancy and as a result we do not know the full spectrum of the underlying mechanisms; however, tolerance defenses in host-microbiota interactions theoretically fall into four main classes: repair, regulation of inflammation, neutralization of toxins, and metabolic homeostasis (Ayres, 2013). Although the microbiota is beneficial for host health, the close proximity of this abundant microbial community to host tissues poses potential health risks to the host if