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Infectious (Non)tolerance—Frustrated Commensalism Gone Awry?

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Despite advances in medicine, infectious diseases remain major causes of death and disability worldwide. Acute or chronic infectious agents mediate host tissue damage and cause a spectrum of disease as diverse as overwhelming sepsis and shock within hours to persistent tissue inflammation causing organ failure or even cancer over years. Although pathogen exposure can cause disease via host-derived inflammation, pathogens share recognized elements with harmless human commensals. Mouse models and organisms with simpler flora are revealing the dialogue between multicellular hosts and commensal flora. In some instances the persistent inflammation associated with pathogens can be interpreted within a framework of frustrated commensalism in which the host and pathogen cannot complete the requisite dialogue that establishes homeostasis. In contrast, coevolved commensals interact cooperatively with the host immune system, resulting in immunotolerance. Attempts to more thoroughly understand the molecular nature of the dialogue may uncover novel approaches to the control of inflammation and tissue damage.

Trends over the past century have shown both the power of humankind to conquer disease and the limitations of that power. In the developed world, advances in sanitation, antimicrobial therapeutics, and vaccination campaigns have dramatically reduced the rates of disability and death due to infectious diseases. In 2008 the World Health Organization announced that for the first time, noncommunicable diseases such as heart disease and stroke caused more deaths than infections (WHO 2008). However, in too many parts of the world political and economic challenges of the 21st century result in public health conditions more reminiscent of the pre–antibiotic era, and more than one-quarter of deaths worldwide are still caused by infections like pneumonia, diarrheal disease, tuberculosis, and malaria (Khabbaz et al. 2010).

In both the developed and the developing world, ecological and social factors have conspired with host and pathogen factors to promote the emergence and reemergence of infectious diseases (Smolinski et al. 2003). The confluence of the human immunodeficiency virus (HIV) and tuberculosis epidemics and the rise of multidrug-resistant tuberculosis illustrate how culture, politics, and economics can fuel a public health crisis. In the United States, which spends more money on healthcare and biomedical discovery than any other country,

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pneumonia remains one of the leading causes of death in the elderly (National Center for Health Statistics 2011). Chemotherapy, antimicrobials, catheters, and ventilators have increased life expectancy and reduced morbidity, but have also brought increasing rates of healthcare-associated antibiotic resistance and opportunistic infections (Klevens et al. 2007; Hidron et al. 2008; Scott 2009).

What do these statistics reveal about our evolution? Throughout human history social and ecological factors have given rise to endemic and pandemic infections (Morens et al. 2008), although humans and pathogens coevolved in relative equilibrium without antibiotics or vaccines. Pneumonia, malaria, and diarrheal diseases have killed countless children, and malaria continues to cause nearly 2000 childhood deaths per day (Mulholland 2007). High birth rates have compensated for high child mortality, and natural selection by childhood infections contributed to our immune evolution (Greenwood et al. 2005; Finch 2010). Indeed, genes related to immunity are among the most polymorphic in the mammalian genome, and more human gene mutations have been linked to resistance to malaria than to any other single infectious disease (Murphy 1993; Hill 2010).

From a microbial parasite's perspective, pathogenicity can be a detriment. When "parasite" is broadly defined to include viruses, mathematical models and empirical evidence suggest that virulence is only beneficial inasmuch as it maximizes parasite survival within a host and/or transmission to a new niche (Anderson and May 1982). Over time host and parasite populations coevolve to balance tolerance and transmissibility such that the most injurious pathogens tend to be recent arrivals to a new host species, whereas in their native host they cause mild or no disease (Read 1994). As extreme examples, Ebola hemorrhagic virus and avian influenza, which have only recently been described in humans, have case-fatality rates of >60%; in contrast, human herpesvirus 6, which has an ancient relationship with humans, latently infects >95% of adults and results in little pathology (Braun et al. 1997; Nichol et al. 2000). In highly pathogenic infections, host and microbial factors trigger overwhelming inflammation, whereas milder infections are controlled and tolerated. Experiments in mice suggest that highly adapted latent DNA viruses can even *protect* hosts from subsequent infectious challenges by altering the thresholds for activation in response to microbial invasion (Barton et al. 2009). In this setting latent lifelong infection may in fact enhance the host's fitness.

Understanding the evolutionary drive from pathogenicity to latency is essential because insights into contrasting patterns of host–microbial interaction may uncover new treatments for human disease. Specifically, microbial products evolved to induce immunotolerance could be used to treat conditions characterized by inappropriately robust inflammation. In this review we first describe immune recognition pathways responsible for host morphogenic changes that are conserved across beneficial and pathogenic host–bacterial interactions in plants, invertebrates, and mammals. We then hypothesize that because bacterial mutualism implies that symbionts provide their hosts a selective advantage, a key difference between human pathogens and commensals is our immune recognition of commensal factors that provide a homeostatic and/or metabolic benefit.

RECOGNITION OF MICROBIAL PATTERNS

Recognition of microbes by vertebrate cells is initiated through sensing of constituents, absent in vertebrates but conserved among microbes, which contribute critical roles to their structure and viability. For example, cell wall components of bacteria (such as peptidoglycan [PGN] and lipopeptide fragments and the core conserved lipopolysaccharide [LPS]) or of fungi (such as β-glucans, mannoproteins, and chitin) are present in high copy number in these organisms. Because disruption of the enzymatic pathways that engineer the microbial cell wall is usually lethal, microbes must conserve these enzymes and structures, making them conspicuous ligands for host pattern recognition receptors (PRRs). Indeed, all vertebrates have conserved PRR families, including

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Toll-like receptors (TLRs), Nod-like receptors (NLRs), and C-type lectin receptors (CLRs), and all are tuned to activate upon sensing of their corresponding microbial products. Additional mechanisms exist in the plasma membrane and within the cytosol to detect ectopic microbial RNA and DNA fragments that manifest inappropriately in these compartments. (Beutler et al. 2006; Medzhitov 2007; Kawai and Akira 2008). The conserved microbial ligands for PRRs are commonly denoted MAMPS, or microbe-associated molecular patterns, and vertebrate PRRs are unable to distinguish whether core elements, such as the lipid A core binding motif of LPS that interacts with TLR4, in fact originate from a commensal or a pathogen.

There is, however, considerable diversity in bacterial LPS and PGN structures such that the strength or quality of PRR signal activation can vary (Hornef et al. 2002). Bacterial "modifications" that result in reduced MAMP–PRR interaction are common among pathogens and are frequently characterized as an immune-evasive strategy, but this classification makes a fundamental assumption about the role of PRRs in host survival: Immunologists often ascribe PRRs as having evolved specifically to provide immune protection from invaders, but it is clear that their role in controlling access to host cells is quite complex. Studies in germ-free mice show that some degree of MAMP–TLR interaction is necessary for intestinal homeostasis. For example, removal of either the host signaling pathway or the microbial flora caused marked susceptibility to gut injury (Rakoff-Nahoum et al. 2006). The polysaccharide A produced by the commensal *Bacteroides fragilis* signals through TLR2 to decrease interleukin-17-induced inflammation and allow the commensal to adhere to and populate the colonic crypts (Round et al. 2011). Furthermore, pathogens can exploit the PRR pathways: *Salmonella* organisms use TLR binding to traffic into endosomal compartments, where they can sense acidification, activate escape genes, and break free into the nutrient-rich cytosol and replicate. In the absence of TLRs, survival of this pathogen in mammalian cells is attenuated (Arpaia et al. 2011).

In recognition that MAMP–PRR interactions alone cannot discriminate pathogen from commensal, it has also been suggested that the innate immune system uses criteria beyond the classical MAMPs to gauge the "pathogenicity" of microbes. These criteria are established correlates of virulence, including replication, cytosolic access, and conscription of host cytoskeletal machinery (Vance et al. 2009). Yet symbionts that associate with plants and animals use these same strategies to establish intimate host niches without inflicting disease (Table 1). Indeed,

Table 1. Patterns associated with viable pathogens are also present in symbionts[a]

PAMP-PV signals	Pathogen examples	Symbiont examples
Growth	PGNs/TCT	Vibrio-Squid diurnal replication
	Quorum regulators	Wolbachia in arthropods
	Pyrophosphates-c-di-GMP	
Cytosolic access	AB toxin (*Bacillus anthrax*)	T3SS (Sodalis, Hamiltonella, Rhizobia spp.)
	T3SS	T4SS (Wolbachia, Rhizobia spp.)
	T4SS	
	T6SS	
Cytoskeletal alteration	Actin-based motility	Sodalis SSR-1 effector genes
	Phagolysosome fusion blockade	Wolbachia ANK genes
	Disruption of Rho family GTPases	Rhizobial NF genes

[a]Growth, cytosolic access, and cytoskeletal alteration have been proposed as "PAMP-PV signals," molecular patterns and processes that herald live pathogenic organisms and trigger an inflammatory response (Vance et al. 2009). However, organisms employ the same mechanisms to establish mutualistic symbioses (Dale and Moran 2006), which argues that, for the ancient immune systems of these hosts, PAMP-PV patterns do not strictly delineate harmful vs. commensal organisms.

Abbreviations: c-di-GMP, cyclic-di-guanosine monophosphate; T3SS, T4SS, T6SS, Type III, IV, VI secretion systems; SSR-1, *Sodalis* symbiosis region 1; ANK, ankyrin repeat.

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symbionts of insects use these strategies to *benefit* their host by increasing survival and/or reproductive fitness (Dale and Moran 2006).

Studies of anciently evolved symbioses reveal that acquisition of a beneficial partner involves elements of the classical inflammatory cascade (van Rhijn and Vanderleyden 1995; Dale and Moran 2006; McFall-Ngai et al. 2010). Information from MAMP engagement with the host cell is relayed through conserved signaling modules (homologs of NF-κB, mitogen-activated protein kinase [MAPK], and interferon regulatory factor [IRF] family members, along with their associated cofactors), generating a stereotypical inflammatory cascade. The production of biologically active lipids, antimicrobial peptides, cytokines, and chemokines, as well as oxidative and nitrosylated moieties, is essential for microbes and host cells to form a symbiosis. If PRR pathways that existed long before vertebrate immunity evolved to detect and nurture symbionts, might our own PRRs share elements of these primary functions? To better understand pathogen/commensal discrimination, we will first consider how symbionts are specifically selected and fostered by plants and invertebrates.

ESTABLISHING COMMENSALISM THROUGH MUTUAL RECOGNITION AND SIGNALING

The conserved PRRs and downstream inflammatory signals often described to be essential for elimination of harmful pathogens may have evolved as a means of cross talk between microbial commensals and their eukaryotic hosts. Plants and invertebrates have ancient mechanisms that recognize and regulate microbes. In many cases these mechanisms allow commensals and multicellular eukaryotes to form partnerships for their mutual nutritional and/or reproductive benefit. The host species harbor bacteria that aid in metabolite acquisition and stimulate the host's growth and maturation. In turn microbes are provided nutrients, an anatomically protected niche, and the potential for transmission to new hosts (McFall-Ngai 2002; Dale and Moran 2006). Mutual metabolic benefit drives the relationship.

Multicellular organisms encounter an enormous range of microbial agents in their environment but house only a limited selection of commensals or symbionts. Below we describe some examples in which the absence of a single microbial species induces a significant survival defect in the host species. The selection of specific commensal microbes is accomplished by specialized anatomic adaptations and cellular responses, both of which are directed by PRRs and classical inflammatory mediators. Here we summarize three examples of eukaryote–bacterial interactions in which classical inflammatory cascades linked to host defense, namely PRR signaling and oxidative radicals, are necessary for establishment of homeostatic mutualism.

Legume–Rhizobia Symbiosis

Plants form well-described partnerships with bacterial and fungal symbionts. Legumes have a particularly intricate relationship with rhizobial bacteria, which induce nodulation on the roots or stems of their hosts for nitrogen fixation (van Rhijn and Vanderleyden 1995; Desbrosses and Stougaard 2011). The symbiosis starts when soil rhizobia sense flavonoids secreted by a potential host. The bacteria respond by transcription of *nod* genes, encoding lipo-chito-oligosaccharides (Nod factors or NFs), i.e., the MAMPs that induce root nodule morphogenesis (Timmers 2008). After nodule formation the rhizobia thrive inside their niche, replete with nutrients and oxygen supplied by the host legume, and convert nitrogen into the ammonia necessary for plant amino acid synthesis.

Each rhizobial and legume species has a narrow range of partners that can induce nodulation, and this specificity is determined in part by the NF MAMPs (Geurts et al. 2005). Host-specific NFs are composed of modular chito-oligosaccharide backbones, the substituents of which are recognized by host LysM-type transmembrane PRRs analogous to TLRs. Together, the regulation of NFs in rhizobia and the recognition of these signature MAMPs by host PRRs

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define the rhizobial host range prior to nodulation (Radutoiu et al. 2003).

Host–rhizobium associations are mediated by reactive oxygen species (ROS), which are generated by an NADPH oxidase common to all eukaryotes as part of the stress response to invading pathogens. ROS are also potent signals that direct a wide range of physiologic functions critical for homeostasis (Wellen and Thompson 2010). Legume roots produce intracellular and extracellular ROS within minutes of encountering either pathogenic microbes or symbiotic rhizobia. In plant–pathogen interactions this is followed by sustained, high-level ROS accumulation at the site of infection, whereas in plant–symbiont interactions the initial oxidative burst is followed by suppression of ROS synthesis and production of plant hormones, such as cytokinins, necessary for nodule organogenesis. For a successful symbiotic infection, the rhizobium must be capable of antioxidant defense and its NF MAMPs must be recognized by the host roots as a signal to reduce ROS production (Pauly et al. 2006; Nanda et al. 2010). The NF provided by the symbiont is essential for the PRR signaling that establishes a habitable niche.

Squid–*Vibrio fischeri* Symbiosis

The nocturnal squid, *Euprymna scolopes*, burrows into the sea floor during the day and at night emits counterillumination ventrally to obscure its moon shadow. Unlike autobioluminescent species that generate their own light, *E. scolopes* houses a luminous bacterial symbiont, *Vibrio fischeri*. Within hours of hatching, the immature light organs of juvenile squid are monocolonized by *V. fischeri* in epithelium-lined crypts. In the process of differentiation, the squid epithelium undergoes apoptosis, halting further colonization, and the surrounding tissues form into a lenslike structure that focuses light intensity and direction (Nyholm and McFall-Ngai 2004; Tong et al. 2009).

Of all the bacteria encountered in the ocean, only luminescent *V. fischeri* achieve the light organ niche. Squid resist colonization by any other species, even in the absence of *V. fischeri*, and the mutual specificity of *E. scolopes*–*V. fischeri* symbiosis is accomplished by host–microbial interactions at each stage of morphogenesis. Even before contact with squid tissues, *V. fischeri* displays a tropism for components of the mucus secreted over the light organ pores. The Syp exopolysaccharide enables symbiont aggregation around the pores (Mandel et al. 2009), and after several hours the bacteria migrate through the pores into the deep crypt spaces despite toxic concentrations of host-derived oxidative radicals, first generated by nitric oxide synthase (NOS) and then by halide peroxidase (Nyholm and McFall-Ngai 2004). *V. fischeri* encounters NO in the mucus layer, which induces expression of the flavohemoglobin NO scavenger *hmp*, protecting the bacteria from oxidative damage (Wang et al. 2010). Three PRR classes have been identified in *E. scolopes*: TLR, PGN-recognition protein (PGRP), and LPS-binding protein (LBP). As *V. fischeri* infection of the crypts progresses, LPS and tracheal cytotoxin (TCT), a cell wall PGN fragment released during the process of peptidoglycan recycling, are sensed by squid PRRs (TLR, PGRP, and/or LBP) that attenuate the activity of host NOS. The *V. fischeri* inhibition of NOS is necessary to allow host cell apoptosis and light organ morphogenesis to proceed (Goodson et al. 2005; McFall-Ngai et al. 2010; Altura et al. 2011). As in human neutrophils, squid myeloperoxidase catalyzes the production of hypohalous acids. The squid peroxidase is also found in gill tissue, where it nonspecifically eliminates pathogenic bacteria filtered through the circulatory system. That the same enzyme is found in symbiotic light organs argues that it may produce ROS as a signal to select or limit bacterial symbionts (Small and McFall-Ngai 1999).

Once the symbiosis is established in the mature light organ, the squid and *Vibrio* continue to exchange metabolic signals that coordinate growth of the bacteria with the needs of its host. This cross talk is mediated by the host's restriction of nutrients within the light organ, supplying the bacteria primarily with glycerol or chitin substrate in a diurnal pattern, to ultimately regulate aerobic versus anaerobic growth of the bacteria, respectively (Wier et al. 2010). In

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this way the host limits growth of the commensal during the day when the light organ is unnecessary and promotes growth at night when the light organ is essential.

Nematode–*Xenorhabdus* Symbiosis

Another host–bacterial relationship in which chitin metabolism figures prominently is that between the insect-parasitic nematode *Steinernema carpocapsae* and *Xenorhabdus nematophila* bacteria. The nematodes rely on *Xenorhabdus* for their life cycle; these bacteria colonize juvenile worms in the soil and are then released upon parasitism of insect larvae. They suppress insect immunity, kill the insect, and degrade its carcass into nutrients that feed several rounds of nematode reproduction. When the insect nutrients are depleted, juvenile worms are recolonized with *Xenorhabdus* as they leave to hunt for new insect prey (Goodrich-Blair and Clarke 2007). Worm-derived nutrients are required for subsequent bacterial growth and survival, and bacterial products enable entomoparasitism, maturation, and reproduction.

Xenorhabdus bacteria are carried inside the nematode gut in a specialized vesicle structure that is covered in mucus and rich in *N*-acetylglucosamine (GlcNAc), which is a by-product of chitin degradation (Martens and Goodrich-Blair 2005; Chaston and Goodrich-Blair 2010). Similar to the squid light organ, the worm's niche structure contains bacteria from only one or two clones, which means that one or two bacteria find the structure, initiate the colonization, and then divide to fill the niche. Chitin and GlcNAc are prevalent throughout eukaryotes, yet *Steinernema* and *Xenorhabdus* genera show marked mutual specificity such that some nematode species can only be colonized by their single cognate species of bacteria.

A number of regulatory and amino acid biosynthesis proteins enable *X. nematophila* to colonize *S. carpocapsae* (Heungens et al. 2002), but two bacterial genes in particular are required for these species' mutual specificity, *nilB* and *nilC*, both located in the *nilABC* locus (Cowles and Goodrich-Blair 2008). By sequence homology these are presumed to encode outer membrane proteins, but aside from their role as MAMPs, their precise function is unknown. Moreover, little is known about the specific nematode PRRs that have evolved to recognize *Xenorhabdus* as a beneficial partner and the downstream signals that mediate colonization. However, a related nematode, *Caenorhabditis elegans*, has a TLR, Nod-like genes, and CLRs, which, along with G-protein-coupled receptors, are believed to contribute to microbial recognition (Schulenburg and Ewbank 2007).

CONSERVED SIGNALS PROMOTE MAMMALIAN–COMMENSAL MUTUALISM

In these examples of mutualism, microorganisms release biochemical elements that signal the host to curtail MAMP-induced inflammatory activation and undergo host niche morphogenesis. As suggested above, in analogous fashion, a major driving force for the evolution of mammalian PRRs may have been the colonization of mucosal surfaces with organisms that optimize nutrient extraction and promote surface epithelial homeostasis rather than immunity against invaders per se. Unlike invertebrates, which have a limited range of microbial commensals, vertebrates harbor trillions of bacteria from thousands of different species. Still, evolution dictates that hosts will be selected whose flora confer the greatest fitness, whether it be through provision of rare nutrients, by protection from more virulent invaders, or by addition of biochemical pathways that allow scavenging of otherwise indigestible dietary substances (Ley et al. 2008). For example, recent studies comparing the fecal flora in different human populations have revealed how different dietary fiber sources can enrich for intestinal bacteria with the capacity to digest these polysaccharides into usable sugars for the host (De Filippo et al. 2010; Hehemann et al. 2010).

An advantage of maintaining such vast and diverse microflora populations is that the host benefits from the commensals' collective capacity to synthesize vitamins and digest polysaccharides (Xu et al. 2007; Martens et al. 2008; Hooper and Macpherson 2010; Sonnenburg et al. 2010; Maslowski and Mackay 2011).

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Studies in germ-free and genetically manipulated mice and zebrafish suggest that host-genetic and micronutrient factors specify the diverse flora composition (Rawls et al. 2006; Turnbaugh et al. 2009; Spor et al. 2011). Further, highly adapted speciation is apparent even among related families of bacterial colonizers, revealing an evolutionary process driving host specificity (Frese et al. 2011). Although the bacterial biochemical pathways that promote mucosal homeostasis in vertebrates may be conserved, the complex flora necessary to achieve a "metabolome" may be assembled differently in different species, or even in different individuals. Studies in humans have begun to suggest the presence of dominant "enterotypes" that combine to satisfy requirements for intestinal homeostasis (Arumugam et al. 2011). The composition of our intestinal microbiota closely resembles that of other omnivorous primates, which argues that nutrient extraction is the driving force behind selection of our flora (Ley et al. 2008).

How are the human microflora selected from among the myriad bacteria encountered by an individual? Few of the signals that constitute the human–commensal dialogue have been definitively elucidated, but because nutrient extraction has driven specific intestinal colonization throughout evolution, one clue may be the effects of innate inflammatory genes on the risk of obesity in humans (Chen et al. 2008; Emilsson et al. 2008). Both Gram-positive and Gram-negative bacteria in the normal human flora can modify their cell wall PGN elements, and some of these alterations suppress host inflammation (Shimada et al. 2010; Davis and Weiser 2011). Recent reports have highlighted the capacity of discrete metabolic signals to affect mucosal integrity. For example, certain orphan G-protein-coupled receptors can sense short-chain fatty acids generated by intestinal microflora (Tazoe et al. 2008; Oh et al. 2010), and acetate produced by intestinal bifidobacteria, which consume fucosylated glycans supplied by enterocytes, can protect the epithelium from toxins produced by enteropathogenic bacteria (Fukuda et al. 2011). These examples reflect ways that mammalian innate immunity might recognize and accept commensals, but as noted below, human genetics and infectious disease susceptibility provide further hints of this process.

INFORMATIVE HUMAN MUTATIONS IN MICROBIAL RECOGNITION PATHWAYS

A landmark study from Denmark published in 1988 examined the causes of death among members of 960 families with children adopted at an early age, allowing a comparison of causes of death in the children and in their unrelated adoptive parents and genetically related biologic parents (Sørensen et al. 1988). Unexpectedly, deaths due to infectious diseases showed a substantial genetic influence; the relative risk of death from infectious diseases that adopted children shared with their biologic parents but not their foster parents was greater than that due to vascular diseases or cancer, each of which has established genetic components. The fact that genetic variants in the population contribute significant infection susceptibility underscores the impact of infectious diseases on survival and longevity in early human populations (Finch 2010).

Although innate immunity is often described as recognizing a broad range of pathogens, each signaling pathway may in fact have evolved to detect and accommodate a specific coadapted taxon or species. With enhanced genomic sequencing, combined with awareness and epidemiologic networks that identify rare mutations, there are increasing reports of human mutations that predispose to infectious diseases. Curiously, mutations in genes anticipated to have broad effects in innate microbial recognition have been associated with susceptibility to a surprisingly narrow spectrum of infections (Netea and van der Meer 2011). For example, MyD88 and IRAK4 mutations result in increased infections with only pyogenic bacteria, although both molecules are central adaptors in PRR/NF-κB signaling. Mutations in terminal complement components specifically lead to recurrent invasive *Neisseria* infections. Similarly, TLR3, TRAF3, and UNC93B mutations are independent components in the

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double-stranded RNA sensing pathway, and mutations in each predispose to severe herpes simplex virus encephalitis. These and other examples underscore a recurrent theme: In humans, genetic mutation of what has been described as a critical mammalian immune pathway commonly results in susceptibility to one or a few specific infections.

This forces a rethinking about the evolutionary selection that shaped vertebrate innate immune recognition receptors. We can no longer consider PRRs as broad "modules" necessary for host defense against entire classes of organisms, but rather as specific genes that evolved in stepwise fashion to restrain a relatively small number of microbes. For example, terminal complement components directly or indirectly comprise the host signals that recognize *Neisseria* species and form the host "niche" that ensures it remains a harmless colonizer. In the absence of complement, the signals needed to create and maintain the niche are lost, and the organism's invasion evokes inflammatory pathology. Considered from this perspective, what makes a bacterium potentially pathogenic in an immunocompetent host is not the microbe's expression of virulence factors, but rather its *failure* to identify itself as a niche-worthy partner.

A PROPOSED MODEL: DOES INFECTIOUS INFLAMMATION REPRESENT FRUSTRATED COMMENSALISM?

Here we propose three tenets to consider in understanding inflammation and infectious diseases susceptibility. First, recognition of MAMPs by evolutionarily conserved PRRs does not effectively distinguish commensals from pathogens. Second, the signaling pathways induced by PRR–MAMP interactions from commensals and pathogens are similar. Third, the effectors unleashed as part of the immune response to pathogens, including reactive oxygen and nitrogen moieties, antimicrobial peptides, and bioactive lipids, can also be unleashed in response to commensal MAMPS. As discussed in the examples above, these three principles pertain to innate immunity conserved in plants and animals, irrespective of an adaptive immune system.

What then distinguishes the response of the host to commensals as compared with pathogens? We suggest that commensals respond to host signals with their own signals that "retune" the inflammatory response. Commensals that trigger canonical PRR-mediated cascades respond in turn with reciprocal alterations in their MAMPs, including release of recycled or degraded cell wall fragments or biochemical metabolites (Fig. 1). In concert, the microbial products create a nonhostile stance with two effects on the host: First, various changes in the host cells deescalate the inflammatory milieu, and second, the host epithelial constituents adjust to shape a welcoming anatomic and/or biochemical niche. These host changes range from alterations in surface glycosylation, such as release of fucosylated glycans, to a more dramatic morphogenesis such as induction of plant root nodules or squid light organs. The resulting niche nurtures the commensal, thus establishing conditions for healthy mucosal homeostasis. In contrast, noncommensals lack the capacity to return the dialogue, and thus are eliminated from the suddenly unfriendly niche. Those pathogens that evolve the genetic material enabling migration into compartments or tissues where the host response is muted can avoid the initial response and thereafter become virulent agents. Similarly, individual hosts that are genetically deficient in the innate recognition and/or signaling that correspond to a commensal will be incapable of maintaining its niche and therefore become susceptible to invasion by an otherwise benign colonizer.

This model offers a different interpretation of microbial pathogenesis. Like commensals, a pathogen first activates PRRs and triggers the downstream inflammatory host cell response. In some cases pathogens such as *Legionella pneumophila* are poorly recognized due to weak PRR–MAMP binding (Neumeister et al. 1998). In other cases the pathogen's MAMPs are recognized, but it does not reciprocate with the appropriate signal that verifies its identity as a harmless colonizer or a beneficial partner. Thus, although pathogens and commensals compete

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Figure 1. Examples of pattern recognition in ancient symbioses. Cross talk between eukaryotic host cells and bacterial commensals is necessary to establish homeostasis. (*A*) Rhizobial Nod factors (NFs) are recognized by legume PRRs. (*B*) *Vibrio* polysaccharides are recognized by squid PRRs. (*C*) *Xenorhabdus* proteins are recognized by an unknown nematode receptor. In each case signaling down-regulates the classical "inflammatory" pathway and induces anatomic changes that form a symbiotic niche.

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to establish interactions with host cells, pathogen signals are incapable of inducing the necessary changes to make the host compartment hospitable. One of two outcomes ensues (Fig. 2): expulsion of the pathogen out of the niche in favor of an appropriate, fitter commensal (i.e., avirulent "failed infection"), or, for pathogens that have acquired certain virulence factors, invasion and persistence in host tissues. In the latter case, host inflammatory output increases as the host cell continues to probe what it perceives as a wayward commensal, akin to a person shouting louder and louder but receiving no comprehensible reply.

This model can also explain the occasional instance of invasive disease caused by organisms that are members of the mucosal flora. If innate immunity exists to recognize harmless organisms and provide them a niche, the loss of the niche can lead to tissue damage and inflammation. For example, antibiotic exposure increases the risk of infection with colonizers like *Pseudomonas*, *Enterococcus*, *Candida*, and *Clostridium difficile* that are relatively antibiotic-resistant. These organisms are present in low numbers among normal human microflora, but when an antibiotic kills off the more abundant species, it leaves epithelial real estate uncontested and allows overgrowth of these potential pathogens (Sullivan et al. 2001). Conversely, healthy tissue is rich with commensal signals and their inflammatory consequences are suppressed.

Alternatively, pathogens that are not found in normal flora, such as *Mycobacterium tuberculosis*, avoid shortening the life of their host and thereby increase the odds of horizontal transmission. To limit collateral immunopathology within their "hypoinflammatory niche," these pathogens use molecular mimicry signals that fool the host into believing that commensalism has been established (Schnappinger et al. 2006; Vance et al. 2009). Tuberculosis kills millions of people each year, particularly the elderly, malnourished, and immunocompromised, yet only half of those exposed become infected, and in the majority of infections the bacteria remain latent for decades inside granulomas and never cause disease. Studies in mice and

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Figure 2. Pathogens are unable to engage in host–commensal dialogue. An alternate model of host–microbial interactions. (*A*) Commensals express MAMPs and additional signals in response to host inflammatory mediators that limit inflammation and promote healthy mucosal coexistence. (*B*) Like commensals, pathogen MAMPs signal through host PRRs and trigger inflammatory mediators, but pathogens do not have recognizable commensal signals to complete the dialogue, and inflammation escalates. As a result, the pathogen is either killed or, through various virulence factors, is able to persist in the host by protecting itself from antimicrobial toxins or by invading spaces where it is shielded from immune effectors.

in cultured macrophages show that NO production by NOS is one of the first events that occur after phagocytosis of mycobacteria. Along with interferon-γ (IFNγ), NO, hypoxia, and low pH trigger the *M. tuberculosis* DosR regulon, consisting of ~50 genes controlled by a single transcription factor that accompany the latency phase of infection. Because host deficiency of IFNγ (e.g., due to HIV or immunosuppressive therapy) or pathogen loss of the DosR regulon correlates with rapid progression to disease, it is theorized that these are important components of the host–pathogen dialogue required to sustain latent infection (Schnappinger et al. 2006).

Mycobacterial "reactivation" disease can therefore be considered a breach of the latency agreement, a detente that allows both parties to benefit through limited bacterial growth and limited host inflammatory response. Beyond the advantage of reducing immunopathology, it is conceivable that sequestration of latent *M. tuberculosis* in granulomas, with the accompanying high levels of circulating IFNγ, might endow the host with enhanced immune killing of other infectious agents (Barton et al. 2007). In a *Mycobacterium marinum* granuloma model, superinfecting mycobacteria "home" to preexisting granulomas, suggesting that these are metabolically favorable niches for the organisms within host tissues (Cosma et al. 2004). Unraveling the molecular signals imparted by bacteria to induce hypoinflammatory niches might lead to powerful methods for reducing excessive inflammation.

IMPLICATIONS FOR IMMUNOTOLERANCE AND FOCUS OF FUTURE RESEARCH

The majority of host–microbial interactions in an individual involve the mucosal epithelium and immune system cooperating to provide a relatively permissive environment for microflora while ensuring that they do not trespass into other organ systems. From an evolutionary

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perspective, selection for optimal metabolic fitness has driven the makeup of the intestinal microbiome in cooperative fashion: Our immune system recognizes and harbors bacteria with beneficial properties, and bacterial populations evolve signals that induce an immunotolerant host niche. The specific commensal products that give rise to immunotolerance are a subject of increasing interest (reviewed by Littman and Pamer 2011). In various systems microbial products have been shown to stimulate intestinal myeloid cells, innate lymphocytes, or epithelium. Mediators released by these innate effectors in turn support barrier homeostasis and tune the adaptive immune system, for example by induction of regulatory T cells or IgA-secreting B cells.

Despite these observations, highly coadapted microorganisms that have ancient relationships with humans are studied less intensively than the more recent pathogen arrivals that induce inflammation and disease. Similarly, laboratory infection models often mix mice with pathogens that rarely reflect the adapted organisms that mice encounter in their natural environments. In the model we propose, the disease caused by pathogens can be largely attributed to their failure to convey recognizable commensal signals rather than to their propensity for virulence factors. In other words, the immunotolerance found in barrier tissues exposed to countless microbial antigens might not depend on these organisms lacking pathogenic markers but rather on their possessing markers innately recognized as beneficial. Like all models that seek to simplify complex interactions, this one certainly has its limitations. Nevertheless, we suggest that further study of the host response to coadapted microorganisms may elucidate signals that evolved to enhance selection of beneficial organisms, as opposed to inflammatory responses to less well-adapted organisms. Identification of metabolites and other microbial products involved in the homeostatic dialogue between commensals and hosts may create opportunities to provide exogenous signals that modulate the health of human epithelial tissue through establishment of immunotolerance. Understanding this mutual signaling may not only impact the control of overwhelming infectious diseases, but also provide insights into metabolic dysregulation and other inflammatory syndromes.

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