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Maintaining Diplomatic Relations Between Mammals and Beneficial Microbial Communities

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Abstract

The first reports of diplomatic relations between human communities date back to the 14th century B.C.E. and the age of the Egyptian pharaohs. However, the evolution of analogous relations between mammals and mutualistic microbial communities is as old as multicellular organisms themselves. A fundamental issue surrounding the biology of these mutualistic relationships is how the immune system recognizes beneficial microbes and tolerates their colonization of barrier surfaces while simultaneously preventing their outgrowth and potentially lethal dissemination throughout the host. New evidence provides insight into the molecular mechanisms that orchestrate diplomacy between the mammalian immune system and bacterial communities in the gut.

Mutualistic or commensal relationships between hosts and microbial communities are a conserved feature of all multicellular life and are important for normal development and physiology in plants, insects, nematodes, fish, birds, and mammals (1-3). In the human intestine, mutualistic relationships have evolved between the host and members of all three domains of life. Bacteria are the most abundant microbial colonizers of humans. For example, an estimated 100 trillion individual bacteria colonize the gut, with a combined microbial genome estimated to be 100 times as large as that of their human host (4).

Some of these bacteria are essential for normal physiologic and developmental processes, whereas others have been implicated in the pathogenesis of multiple inflammatory diseases. For example, dysbiosis or alterations in the composition of microbial communities are associated with several inflammatory and metabolic diseases, including inflammatory bowel disease (IBD), cancer, asthma, diabetes, and obesity (5). In the context of IBD, dysbiosis may be a potential trigger of disease. Genetic predisposition to IBD is associated with mutations in genes that encode factors required for innate immune recognition of microbes and altered innate and adaptive immune responses to intestinal bacteria have been proposed to contribute to inflammation (6-9). Despite the potential impact of microbial communities on human health and disease, our understanding of the molecular mechanisms that maintain and disrupt mutualism between mammals and intestinal bacteria remains incomplete.

Employing selective genetic manipulation of components of the innate and adaptive immune system, Slack *et al.* have demonstrated that both branches of the mammalian immune system act cooperatively and in a compensatory way to manage microbial communities and orchestrate mutualistic relationships (10). Many innate immune responses are regulated by Tolllike receptors (TLRs), a conserved family of innate immune receptors that recognize microbial-derived molecules, including lipopolysaccharide, lipoprotein, RNA, and methylated DNA. Ligation of TLRs results in activation of multiple signaling cascades, including the nuclear factor κ B (NF- κ B) and mitogen-activated protein kinase (MAPK) pathways that control

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expression of a wide range of innate immune response genes (11,12). TLR signaling-deficient mice that lack MyD88 and Ticam1, two important adaptor molecules required for signaling through TLRs, were generated and inoculated orally with a commensal bacterium (*Escherichia coli* K12) to which they had never been exposed. Consistent with a report from Hooper and colleagues (13), TLR signaling-deficient mice exhibited systemic dissemination of commensal *E. coli* that was associated with increased serum concentrations of commensal-specific immunoglobulins (10). The inability of TLR signaling-deficient mice to contain commensal bacteria in the gut lumen was independent of either non-specific defects in intestinal barrier function or impaired production and secretion of immunoglobulin A (IgA). These results highlight the essential role of TLR-dependent pathways in compartmentalization of enteric commensal bacteria (10) (Fig. 1).

Although not addressed by Slack *et al.*, a fundamental question arises regarding the types of mammalian cells that recognize commensal bacteria. For example, intestinal epithelial cells (IECs) are at the interface with commensal bacteria, they express pattern recognition receptors, and IEC-intrinsic innate pathways play essential roles in antimicrobial responses and immune homeostasis (14-16). In addition, distinct subsets of dendritic cells within the gut microenvironment recognize microbial-derived signals and regulate innate and adaptive immune responses (17,18). Therefore, although TLR-dependent pathways are essential in normal microbial containment, the influence of IECs versus dendritic cells and other antigen-presenting cells on commensal-TLR interactions in the gut remains undefined. Nevertheless, the importance of TLR-dependent pathways in bacterial compartmentalization and maintenance of mutualism supports the possibility that, compared with pathogenic microbes, commensal communities may have been an equal or greater selective evolutionary pressure to maintain TLR-associated signaling pathways in the mammalian genome.

In a subsequent series of studies employing colonization of germ-free wild-type and TLR signaling-deficient mice with defined commensal communities, Slack *et al.* went on to show that CD4 T cell-dependent immunoglobulin production was a critical factor in the containment of commensals independently of TLRs (10). Moreover, genetic deletion of all immunoglobulin responses in TLR signaling-deficient mice resulted in stunted growth, protein-losing enteropathy, and early mortality of the host, supporting an essential TLR-independent compensatory function for the adaptive immune system in maintaining mutualism between the host and microbial communities. Glimcher and colleagues reported that disruption of innate immune responses resulted in an outgrowth of “pathogenic” commensal species (19). However, whether simultaneous disruption of TLR signaling and immunoglobulin responses reported by Slack *et al.* results in a dysbiosis similar to that reported by Garrett *et al.*, and whether these changes contribute to disease, remain to be determined.

As discussed above, genetic predisposition to IBD in patients is associated with mutations in innate immune response genes that control microbial recognition. Results presented by Slack *et al.* support a model of IBD etiology in which defects in innate immune surveillance of microbial communities in the gut could allow the outgrowth and dissemination of defined bacterial communities. Subsequent adaptive immune responses to systemic bacteria may have a fundamental influence on disease outcome.

Taken together, these findings indicate that the realpolitik of mutualistic relationships between mammalian hosts and microbial communities relies on complementation between the innate and adaptive immune systems to maintain compartmentalization of commensals. Specifically, T cell-dependent immunoglobulin responses can restore mutualism with microbial communities in TLR signaling-deficient mice. With the growing recognition that signals derived from commensal communities can have both a proinflammatory (20,21) and immunoregulatory (22,23) influence on immune cell function, understanding the complexity

of bidirectional communication between intestinal bacteria and the mammalian immune system could provide new insights into the etiology of multiple human metabolic and inflammatory diseases, as well as provoke the development of new preventive or therapeutic agents.

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Fig .1.

The innate and adaptive immune systems coordinate containment of intestinal microbes. Intestinal microbes are recognized by innate immune cells through TLRs and other pattern recognition receptors. TLR signaling (MyD88- and Ticam1-dependent) directly and indirectly prevents microbial dissemination (denoted by the dashed lines) through antimicrobial peptide and IgA (yellow) production. In the absence of TLR signaling, compensatory T cell-mediated systemic IgG (blue) responses can act as an additional barrier to dissemination.