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Editorial Open Access

Potlatch in the Gut - Immunomodulatory Molecules of Potential Therapeutic Benefit from the Commensal Microbiota

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Mutualism between members of the gut microbiota and their mammalian host offers several advantages to both. As revealed by recent research, the co-evolution of specific microbial species with their particular mammalian host directs the maturation of the host's immune system in a way that enables it to respond to infectious or inflammatory challenges appropriately. In addition, changes in microbial species with the host's age, sex, diet, and other variable conditions allow beneficial adjustments. The effect of the gut microbiota on the immune system is not limited to gut tissue but also extends to peripheral sites. Thus the gut microenvironment can be viewed as a specialized immunologic sensor responsible for maintaining the general health of the host.

Very little is known, however, about the ability of specific molecules from the commensal microbiota to effect changes in the host's immune system. Molecules from the human gut commensal *Bacteroides fragilis* have been studied more extensively than molecules from other commensal microorganisms and can be described as "torch bearers" in the field. Two broad types of *B. fragilis* molecules have been determined to be immunomodulatory: polysaccharides and sphingolipids. Polysaccharide A (PSA), a zwitterionic capsular polysaccharide, is the best studied with regard to its presentation by the major histocompatibility class II (MHCII) pathway, its stimulation via the Toll-like receptor 2 (TLR2) pathway, its role in the maturation of the host's immune system, and its immunoprotective role in murine models of colitis, multiple sclerosis, and surgical fibrosis. Our recent studies have shown that antigen-presenting cells of a particular subset i.e., plasmacytoid dendritic cells (PDCs)- are necessary for mediation of PSA's immunoprotective function in murine models of chemically induced colitis and antigen-induced multiple sclerosis. PDCs are stimulated by PSA in a TLR2-dependent manner; this pathway had not previously been recognized in such cells. Molecules on antigen-presenting cells known for cognate interaction with CD^{4+} T cells, such as MHCII and co-stimulatory molecules, are enhanced in PDCs following PSA stimulation and help generate production of the potent anti-inflammatory cytokine interleukin-10 by CD^{4+} T cells. Interestingly, important pro-inflammatory cytokines are not produced by PDCs upon interaction with PSA; these pro-inflammatory cytokines could have altered the anti-inflammatory properties of the molecule through its PDC interaction. This atypical interaction of a commensal molecule with PDCs illustrates how tolerogenic or immunoregulatory dendritic cells can be generated and opens the field for further investigations with other commensal molecules.

Sphingolipid molecule(s) from *B. fragilis* have an immunomodulatory mechanism distinct from that of PSA. They are essentially inhibitory molecules, suppressing the expansion of pathogenic invariant natural killer T (iNKT) cells in the colon at the neonatal stage of development. *B. fragilis* sphingolipids significantly protect mice challenged with oxazolone, which otherwise induces colitis (mimicking ulcerative colitis in humans) through the action of iNKT cells and antigen presentation by the CD1d mode. Thus *B. fragilis* employs a two-pronged strategy to maintain homeostasis in the intestine with two distinct types of molecules.

In general, other major classes of molecules, such as nucleic acids and proteins, are better recognized as immunomodulators. Whether commensal molecules use these well-known immunomodulators will be determined definitively in the future. Research on the microbiome provides a holistic approach to elucidation of the gut ecosystem. However, the clues obtained from microbiome research must be verified experimentally in the design of novel therapeutics. Also needed is an understanding of the metabolites (e.g., butyrate) that are produced by interaction of commensal microbes with the mammalian host and that then modulate the host's immune system. An enormous repertoire of immunomodulatory molecules provided generously by our guests, the commensal microbes, awaits therapeutic exploitation.

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