Role of the innate immune system in the development of chronic colitis

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Based on Pasteur's work on the microbial nature of fermentation, it was widely believed that the presence of bacteria in the intestine was essential for the life of the host. It has also been known for decades that gut commensal microbes effect the activation and development of the systemic immune system through gut-associated lymphoid tissues (GALT). Recent extensive studies have shown that recognition of microbes is mediated by a set of germline-encoded receptors, Toll-like receptors (TLRs), in mammals. This article reviews the role of the innate immunity system in the development of GALT and the pathogenesis of inflammatory bowel diseases (IBD).

Key words: Peyer's patch, innate immunity, Toll-like receptor, MyD88, inflammatory bowel disease

Gut-associated lymphoid tissues and innate immunity

It has been known for decades that gut commensal microbes colonizing the neonatal mammal effect the activation and development of the systemic immune system, in particular by increasing circulating specific and natural antimicrobial antibodies. In contrast to peripheral secondary lymphoid organs that obtain antigens from afferent lymphatics or blood, gut-associated lymphoid tissues (GALT) collect antigens directly across the specialized follicle-associated epithelium (FAE) in Peyer's patches (PPs) that separate the outside from the inside world. Intestinal microbes are believed to drive the development of GALT during neonatal life, and act to maintain the physiologically normal steady state of inflammation. However, the involvement of intestinal microbial flora in the development of PP and related molecular mechanisms remains unclear.

As a framework for understanding mucosal immune responses, it is useful to divide GALT into inductive and effector sites. The primary inductive sites are organized lymphoid aggregates present in the walls of the small and large intestines. In the small bowel, these collections are referred to as PPs. These organized lymphoid structures are composed mainly or solely of spherical B-lymphoid follicles, including B lymphoblasts embedded in a meshwork of follicular dendritic cells. The organogenesis of PPs has recently been clarified in studies of the function of lymphotixin αβ (LTαβ) and TNFα/LTα by removing the genes encoding these cytokines and their respective receptors from mice. It was also reported that LTβ-deficient mice display neither PPs nor LN. As LTα and LTβ form a heterotrimer that binds LTβR, these results support the idea that this heterodimer plays an essential role in the induction of PPs and LN.

It is now well known that CD4+ T cells can follow different functional pathways. Th1 cells secrete proinflammatory cytokines such as IFN-γ and TNF-α. In contrast, Th2, Th3, and Tr1 cells have all been ascribed various immunoregulatory functions. Th2 cells secrete IL-4, IL-5, IL-10, and IL-13, and drive antibody responses. Th3 cells secrete TGF-β, and Tr1 cells predominantly secrete IL-10. There are many examples in rodents that show a Th1-biased immune response to fed antigens in the gastrointestinal tract, and this Th1 bias is even more pronounced in humans.

In contrast, the apparent bias of mucosal immune responses toward the Th2 pathway has an interesting background. It was recognized about 25 years ago that IgA plasma cells in the small intestine were largely T cell-dependent. At about the same time, in a landmark paper by Craig and Cebra, PPs were shown to be an enriched source of precursor cells that could seed the...
mucosa with IgA plasma cells. In the late 1970s and early 1980s, the cellular basis for the bias towards IgA in the gut was partially explained by the fact that murine PP T cells preferentially supported IgA responses. In addition, murine B cells incubated in vitro with B cell mitogens and other cytokines secreted IgA in varying amounts. Depending on the cytokine studied, IL-4, together with IL-5, IL-6, and IL-10, effectively increased IgA production by cells expressing membrane IgA. The only cytokine capable of switching B cells from IgM to membrane IgA in the absence of dendritic cells was TGF-β. Subsequent studies have clearly indicated an important role for all of these factors, as well as antigen binding to the B cell receptor and CD40L-CD40 interactions, in IgA responses.

According to the described cytokine profiles of Th1 and Th2 cells, it seemed most likely that Th2 cells provided help for IgA responses in PPs. It was then suggested that the phenomenon of systemic unresponsiveness following the oral administration of antigen, termed oral tolerance, was a further consequence of the Th2 bias of the mucosal immune system. Indeed, many studies have clearly demonstrated that prophylactic or therapeutic feeding of self-peptides to rodents could prevent experimental autoimmune diseases of various kinds. Th1 cells, induced by antigen feeding, that prevented these autoimmune diseases were generated in PPs and had the characteristics of Th2 cells or Th3 cells. Functionally, these cells downregulated the activity of tissue-damaging Th1 cells by secreting cytokines such as TGF-β.

The highly specific adaptive immune system requires days or weeks to refine Igs and cell-mediated immune recognition systems to eliminate invading pathogens. In contrast, genome-encoded innate immune systems target structurally conserved pathogen-associated molecular patterns (PAMPs), thereby allowing immediate, and in most cases sufficient, responses to limit or eradicate invading microbes.

Toll receptors are type 1 transmembrane proteins that are evolutionarily conserved between insects and humans. Toll was first identified as an essential molecule for embryonic patterning in Drosophila, and was subsequently shown to be vital in antifungal immunity. A homologous family of Toll receptors, the so-called Toll-like receptors (TLRs), exists in mammals (Fig. 1). Based on the similarity of the cytoplasmic portions, TLRs are related to IL-1 receptors (IL-1Rs). However, the extracellular portions of TLRs and IL-1Rs are quite different; the extracellular portions of TLRs contain leucine-rich repeats, whereas IL-1Rs contain three immunoglobulin-like domains. More than ten members of the TLR family can be found in a search of human and mouse public databases.

TLR2 has been reported to signal the presence of bacterial lipoproteins and lipoteichoic acids. TLR4 is a signal-transducing receptor for LPS, and TLR4-deficient mice are hyporesponsive to LPS. TLR9 detects unmethylated CpG motifs that occur in microbial DNA and act as immune activators. MyD88 is an adaptor protein that links the IL-1R family to IL-1 receptor-associated kinase (IRAK)

**Fig. 1.** Toll-like receptors (TLRs) and their ligands. TLRs recognize pathogen-associated molecular patterns (PAMPs) that often represent molecular signatures of a particular pathogen class. TLR recognizes a variety of microbial products. TLR4 is essential for signaling via lipopolysaccharide (LPS) from Gram-negative bacteria. TLR5 is a signaling mediator of bacterial flagellin. TLR9 detects unmethylated CpG motifs that occur in microbial DNA and act as immune activators. MyD88 is an adapter protein that links the IL-1R family to IL-1 receptor-associated kinase (IRAK).