Understanding Immune-Microbial Homeostasis in Intestine

Abstract
The mechanisms concerning how the immune system is able to deal with the massive antigen challenge represented by the commensal bacterial flora have been a mystery. Recently a number of animal models with impairment of these mechanisms have been identified. One of these is the C3H/HeJBir mouse, which, under certain environmental conditions, can spontaneously develop colitis, which later remits. These mice show increased B cell and T cell reactivity to antigens of the enteric bacterial flora. CD4+ T cells from this strain cause colitis, when activated by enteric bacterial antigens and transferred to histocompatible severe combined immunodeficiency recipients. This colitis is mediated by CD4+ Th1 cells and requires a sustained mucosal production of interleukin-12, which, in turn, is dependent on CD40L-CD40 interactions in the gut. Regulatory T cells that appear to limit the colitis have been identified and have the properties of the T-regulatory-1 subset. Functional Tr1 activity for bacterial antigens is present in the lamina propria CD4+ T cells. These Tr1 cells may exert their effects by inhibition of dendritic cell function in the mucosa, rather than by direct effects on Th1 cells. Many questions remain to be answered, including, How do the enteric bacterial-host interactions shape the immune system for abnormal responses such as inflammatory bowel disease, autoimmunity, and allergy?

Key Words
T cell
Th1
Tr1
Bacterial
Intestine
Mucosal
B cell
Antigen
Antibody

Introduction
The interaction between the microbial flora in the host has a profound impact on the intestine in many ways. One is to drive the development of the mucosal immune system, which is quantitatively the largest immune compartment in the body. This impact has been demonstrated by reconstituting adult germ-free animals with the bacterial flora. Such animals have little or no mucosal lymphoid tissue or cells, but these greatly expand and S-IgA is
produced in quantity following reconstitution (1). Such reconstitution can also dramatically alter gene expression of the epithelium (2), which may have a secondary effect on the mucosal immune system because the epithelium and lymphoid cells are in dynamic communication. There are undoubtedly many other ways in which this interaction impacts the host, but, as yet, these remain unknown. A major puzzle has been how the immune system coexists with such a huge quantity and diversity of microbes in the intestine without the development of marked inflammation. One concept that has been advanced to explain this paradox is that there may be a state of immunologic tolerance toward the commensal flora. For example, intestinal lymphocytes from mice have been shown to proliferate when stimulated by antigens of intestinal bacteria isolated from other mice, but not with antigens isolated from their own intestine (3). Similar data have been reported in humans using lamina propria lymphocytes (LPLs) cultured from either the same biopsies or the biopsies of other individuals (4). These reports are intriguing and support the idea that there may be immunologic tolerance to at least some antigens of the enteric bacterial flora. However, these data were derived using undefined mixtures of bacterial strains and antigens, and the definitive answer to this area of question will require testing with defined purified antigens derived from the enteric bacterial flora.

Insights into the mechanisms by which the immune system manages such intimate contact with such an abundance of commensal bacterial have been provided by a number of experimental models, many of them induced mutants, in which these mechanisms have been impaired (5) (Fig. 1). There are quite a number of such models, reflecting the diversity of mechanisms maintaining intestinal homeostasis, and these have been reviewed elsewhere. The focus of the present brief commentary is on one of these, the C3H/HeJBir mouse. This mouse is a substrain of the C3H/HeJ inbred mouse strain and was generated by selective breeding based on a clinical phenotype of perianal ulceration in soft feces (diarrhea). This clinical phenotype was in turn due to the presence of an inflammatory bowel disease predominantly in the cecum and right colon that developed as early as 2 wk of age, which coincides with bacterial colonization, and largely resolved by 8–12 wk of age (6).

Systemic and Mucosal Immune Function

Analysis of systemic immunity in colitic C3H/HeJBir mice vs the parental C3H/HeJ strain has revealed no differences in immune cell populations or their functions. There were no shifts in total number of B cells, T cells, or the ratio of CD4+ : CD8+ T cells in peripheral blood, lymph nodes, or spleen, nor was there any difference in proliferative responses to various polyclonal cell activators between the two strains. Both strains are deficient in Toll-like receptor-4 (Lpsd), which renders them resistant to the effects of bacterial endotoxin. Some differences have been found between the two strains in the mucosal immune system. For example, the C3H/HeJBir substrain has increased IgM B+ cells in Peyer patches, increased levels of S-IgA in the intestine, the presence of high-titer serum IgG antibodies to commensal bacterial antigens, and increased T cell responses to orally delivered antigen (7). These differences are compatible with a defect in mucosal immune regulation in the C3H/HeJBir substrain.

C3H/HeJBir B Cell Reactivity to Antigens of Commensal Flora

C3H/HeJBir mice have no detectable serum IgG reactivity to food or epithelial cell antigens but have high-titer antibodies to antigens of the commensal bacterial flora, as detected