Microbiome, Mucosal Immunology, and Immunomodulation

Exogenous Stimuli Maintain Intraepithelial Lymphocytes Via Aryl Hydrocarbon Receptor Activation


Purpose of the Study. Intraepithelial lymphocytes (IELs) are immune cells with unique but incompletely understood properties related to epithelial barrier defense. This study builds off the authors’ previous work with specialized T-cell populations and investigates how these interesting cells develop and function.

Study Population. Studies were performed in mice.

Methods. The authors used gene expression studies and transgenic mouse models to characterize factors involved with IEL development, survival, and function in the gastrointestinal tract.

Results. In contrast to other lymphocyte populations, IELs were found to express high levels of a transcription factor known as aryl hydrocarbon receptor (Ahr). In Ahr-deficient mice, IELs developed and were recruited normally to the intestines and skin, but their survival was markedly diminished and they eventually disappeared as the animals matured. Previous studies had shown Ahr to bind to plant-derived nutrients found naturally in cruciferous vegetables, and therefore the authors investigated whether diet affected Ahr signaling and, consequently, IEL development. Feeding wild-type mice a synthetic diet devoid of Ahr ligands resulted in the disappearance of intestinal IELs similar to that seen in transgenic mice lacking Ahr expression; and the IELs returned when a single specific Ahr ligand was added to the synthetic diet. Finally, IELs appeared to be important for intestinal health, since their absence was associated with increased intestinal bacterial burdens, resulting in abnormal immune activation and increased susceptibility to chemical-induced colitis.

Conclusions. Diet-derived compounds activate Ahr-signaling pathways to maintain proper intestinal immune function.

Reviewer Comments. This article presents another reason to eat your vegetables: proper functioning of the intestinal immune system. The authors demonstrate that specific dietary compounds found in cruciferous vegetables like broccoli, cauliflower, and cabbage are essential for the survival of IELs, which maintain the delicate balance between immune reactivity and tolerance to the intestinal microbiota. These provocative findings provide a potential mechanism by which diets low in fruits and vegetables may predispose people to immune dysregulation and the occurrence of intestinal inflammatory diseases. Furthermore, this article highlights how the environment can have dramatic effects on immune system development and function.

Infant B Cell Memory Differentiation and Early Gut Bacterial Colonization


Purpose of the Study. To determine whether early intestinal bacterial colonization patterns are associated with B-cell activation and maturation.

Study Population. The study evaluated 65 healthy Swedish infants (33 boys and 32 girls) born at term in rural areas in southwest Sweden. These infants were part of a prospective newborn/infant cohort that was followed to investigate the relation between intestinal bacterial colonization and pattern and maturation of the immune system.

Methods. Cord blood samples from newborn children and peripheral blood samples from children at 3 to 5 days, 1 month, 4 months, 18 months, and 36 months of age were obtained. Phenotypic characterization of the circulating B cells by flow cytometry was performed within 72 hours after venipuncture. Fecal samples were obtained at 1, 2, 4, and 8 weeks of age and cultured quantitatively for major groups of aerobic and anaerobic bacteria.

Results. At both 4 months and 18 months of age, children colonized with Escherichia coli and/or bifidobacteria during the first 8 weeks of life had significantly higher numbers of CD27+ memory B cells than did noncolonized children. Early colonization with Staphylococcus aureus was associated with low numbers of CD27+ memory B cells at 4 months of age.
CONCLUSIONS. The results of this study showed that early colonization of the gut microflora with different species of bacteria affects B-cell activation and maturation. *E. coli* and bifidobacteria colonization may lead to more B-cell activation and maturation, whereas *S. aureus* colonization may lead to lower counts of circulating memory B cells.

REVIEWER COMMENTS. This study was the first to demonstrate that gut bacterial colonization may affect B-cell activation and maturation in humans. The study showed that early colonization of the gut with *S. aureus*, which is increasingly common with improved sanitary conditions in the Western world, is associated with lower counts of circulating memory B cells in infants, whereas early colonization with *E. coli* and bifidobacteria is associated with B-cell activation and maturation. The study team suggests that *S. aureus* colonization may reflect low diversity of gut microbiota and *E. coli* and bifidobacteria colonization may reflect greater diversity of gut microbiota. Whether either the gut microbiome or lower levels of B-cell activation and maturation in early life are risk factors for developing allergic disease is unknown, but evidence linking either to allergic disease would support the conduct of prevention studies aimed at increasing the diversity of the gut microbiome.


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Peripheral Education of the Immune System by Colonic Commensal Microbiota

PURPOSE OF THE STUDY. To determine if the gut microbiota is important for the development of regulatory T cells (T_{\text{REG}}), which help maintain tolerance by regulating inflammatory responses in the intestine.

STUDY POPULATION. Studies were performed in mice.

METHODS. The authors evaluated T-cell receptor (TCR) diversity and specificity of T_{\text{REG}} and effector T cells isolated from the gut and peripheral lymphoid tissues. The authors then performed T-cell transfer studies to determine if lymphocytes specific for the gut microbiota had pathogenic potential in mice genetically predisposed for spontaneous colitis.

RESULTS. The authors discovered that the TCR repertoire for colonic T_{\text{REG}} was distinct from that for other effector T cells in the gut and T_{\text{REG}} isolated from other lymphoid tissues. A significant proportion of colonic T_{\text{REG}} were specific for antigens derived from gut bacteria. Unlike conventional T_{\text{REG}}, which are derived in the thymus, colonic T_{\text{REG}} primarily developed from naive T cells in peripheral tissue. The TCR repertoire of colonic T_{\text{REG}} was shaped by the animal’s own unique microbiome, as T_{\text{REG}} from one mouse did not recognize colonic bacteria from another mouse unless they were first co-housed. Finally, the authors demonstrated that in mice genetically predisposed for spontaneous colitis, naive T cells could develop into pathogenic effector T cells rather than T_{\text{REG}}.

CONCLUSIONS. In normal mice, T cells that recognize commensal bacteria preferentially differentiate into T_{\text{REG}} in the colon, thereby promoting tolerance to the gut microbiota and preventing the development of detrimental inflammatory disease.

REVIEWER COMMENTS. The gut microbiome has gained significant attention recently for its putative importance in human health and disease. In experimental animals, it has long been known that homeostasis critically depends on proper bidirectional communications between the microbiota and the immune system. However, little is known about the specific mechanism or mechanisms by which an animal tolerates these trillions of microbes. The studies by Lathrop et al add direct evidence that each animal develops its own repertoire of peripherally induced T_{\text{REG}} that are critically involved in promoting tolerance to foreign antigens in its gut. These findings also infer that alteration of the gut microbiota as seen with indiscriminate antibiotic use could disrupt the development of T_{\text{REG}}, thereby predisposing individuals to developing immunopathology, such as inflammatory bowel disease or food allergies.


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Reduced Diversity of the Intestinal Microbiota During Infancy Is Associated With Increased Risk of Allergic Disease at School Age

PURPOSE OF THE STUDY. To investigate the potential association between the diversity of neonatal intestinal microbiota and the development of atopic disorders in childhood.

STUDY POPULATION. Four hundred eleven infants born in Copenhagen to mothers with a history of asthma were enrolled from the years 1998 to 2001.

METHODS. Infants had an initial visit at 1 month of age and were subsequently seen for a scheduled visit every 6 months until the age of 6 years. Atopic disease was assessed through examination by doctors at the clinical research unit with support from symptom diaries kept by...
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