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 naïve 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, naïve 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 microflora 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
the parents. Investigators conducted interval testing of peripheral blood eosinophil count, skin prick tests, and IgE testing. Infants’ microbiota were assessed through collection of fecal samples at 1 and 12 months of life. Polymerase chain reaction fragments from infant stool separated by DGGE (denaturing gradient gel electrophoresis) provided relative assessment of main bacterial strains and were used in assessing variety and richness in microbial genetic diversity. Cultures were used to identify bacteria, fungi, and yeast present in infant stool.

RESULTS. In looking at trends associated with diversity of microbiota as measured by band richness on DGGE, investigators found that diversity of intestinal flora was inversely associated with allergic rinitis ($P = .007$), allergic sensitization (serum specific IgE, $P = .003$, and skin prick test, $P = .17$), and peripheral blood eosinophil count ($P = .34$). Band richness at 1 month was not predictive of band richness at 12 months, but band richness at each point in time independently was associated with these measures of atopy. No significant association was found between band richness and development of asthma or atopic dermatitis. Particular bands seen on DGGE and specific microbiota isolated by culture were not significantly associated with clinical or laboratory evidence of atopic disease. Interestingly, it was noted that in children with culture positive for staphylococci, there was reduced band richness (14.8 vs 13.8) ($P = .06$). Additionally, risk for development of allergic sensitization was increased in infants with cultures positive for staphylococci at 1 month of age but not at 12 months.

CONCLUSIONS. The authors concluded that increased bacterial diversity in infants’ intestinal flora reduced risk of allergic sensitization, allergic rinitis, and peripheral blood eosinophilia. Although a particular bacterial strain was not found to be protective, results suggest that certain pathogenic bacteria such as *Staphylococcus* may increase risk for allergic disease, possibly through reduction in diversity of intestinal flora.

REVIEWER COMMENTS. This study supports the association between decreased diversity of intestinal flora and development of allergic phenotype, specifically allergic sensitization, eosinophilia, and allergic rinitis. It is interesting, however, that bacterial diversity in the intestinal flora was not associated with the development of asthma and atopic dermatitis. It might have been useful to look at the impact of intestinal microbiota on the development of food allergies. Additionally, the authors mainly focus on outcomes of the diversity of intestinal microbiota, without addressing mechanism or contributing factors. Future studies in this area may include development of food allergy as an outcome and address risk factors and potential interventions that promote or limit the diversity of infants’ intestinal microbiota and subsequent development of atopy.

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### The Antibacterial Lectin RegIII-Gamma Promotes the Spatial Segregation of Microbiota and Host in the Intestine


PURPOSE OF THE STUDY. The mammalian intestine is home to ~100 trillion bacteria that perform important metabolic functions for their hosts. The proximity of vast numbers of bacteria to host intestinal tissues raises the question of how symbiotic host-bacterial relationships are maintained without eliciting potentially harmful immune responses.

METHODS. The authors developed a strain of mice that did not express the RegIII protein (RegIIIγ(−/−)) mice). The authors then tested the effects of the gene deletion on the separation between the small-bowel mucosa and luminal bacterial, and also T-cell, inflammation in the intestinal wall.

RESULTS. RegIIIγ, a secreted antibacterial lectin, was found to be essential for maintaining a ~50-μm zone that physically separates the microbiota from the small-intestinal epithelial surface. Interestingly, colonic mucosa expressed relatively little RegIIIγ, and gene deletion did not affect relationships with bacteria in the colon. Loss of host-bacterial segmentation in RegIIIγ(−/−) mice was coupled to increased bacterial colonization of the small-intestinal epithelial surface and enhanced activation of intestinal adaptive immune responses by the microbiota.

CONCLUSIONS. The authors conclude that RegIIIγ is a fundamental immune mechanism that promotes host-bacterial mutualism by regulating the spatial relationships between microbiota and host in the intestine. These findings could be relevant to the pathogenesis of inflammatory bowel disease and other disorders of chronic intestinal inflammation.

REVIEWER COMMENTS. Have you ever wondered why the mucosal immune system in the intestines can tolerate the huge amounts of bacteria, along with endotoxin and other immunostimulants packed into the intestines? Even a tiny fraction of this material in the peritoneum or bloodstream would cause sepsis and/or shock. This fascinating article illustrates (literally) a mechanism by which an antibacterial lectin known as RegIIIγ maintains a bacteria-free zone next to the small intestinal epithelium that forms a barrier against bacterial invasion of the epithelium and induction of inflammation. The
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