EDUCATIONAL COMMENTARY: IMMUNITY OF THE GUT MICROBIOME

Educational commentary is provided through our affiliation with the American Society for Clinical Pathology (ASCP). To obtain FREE CME/CMLE credits, click on Earn CE Credits under Continuing Education on the left side of our web page.

Learning Objectives
On completion of this exercise, the participant should be able to
- identify the gut microbiome and benefits to the host;
- discuss interaction of gut microbiome and immune system; and
- recognize alterations of the gut microbiome and immune system associated with disease.

Introduction
The human gut contains many commensal microorganisms. This group of microorganisms, including their collective genetic material, is also termed the gut microbiome. There is homeostasis between the microbiome and host and the gut microbiome is beneficial to the host in many ways. Alterations in the gut microbiome can lead to disease states. In this commentary, we review the gut microbiome, identify advantages to the host, discuss interactions between the microbiome and the host immune system, and recognize how alterations in the gut microbiome can be associated with human disease.

Gut Microbiome and Its Advantages
Humans are colonized by numerous commensal organisms that outnumber the cells in the body by approximately 10 to 1. Microbes are found both on the skin and in the gut; however, the gut harbors a much greater proportion of the microbes. The gut microbiome is made up of more than 100 trillion microbes and functions as an ecosystem, which includes bacteria, archaea, protozoans, and viruses. Most of the gut microbiome is acquired from the environment through diet and intake. During the neonatal period, the gut microbiome is shaped by intake of breast milk. The gut lining closely interacts with the microbes and, in turn, the microbes help the host with numerous functions, including digestion, protection from pathogens, production of nutrients, detoxification, and regulation of the immune system. The microbes perform a variety of useful functions for the host, including helping with digestion of dietary fiber, nutrient and mineral absorption, synthesis and production of amino acids, and formation of vitamins, including vitamin K and B7 enzymes, and short-chain fatty acids. The microbiome consists of many coexisting species, but the majority of the commensal organisms in the human gut are composed of 4 main phyla: Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria. The byproducts of the
metabolism of microbes such as acetate, propionate, and butyrate, serve an energy source for epithelial cells and help to maintain integrity of the epithelial barrier. The gut immune system makes up a significant portion of the human immune system. Microbes in the gut play a large role in the induction, formation, and function of innate and adaptive immune responses. The molecules derived from the microbes provide immunomodulation and protection against pathogens. The gut microbiome has been found to regulate host immunity, including the local and systemic immune system. Certain bacterial species stimulate the immune system to release cytokines that have an anti-inflammatory response, whereas certain bacterial species stimulate production of cytokines that cause inflammation. Molecules derived from commensal organisms absorbed or diffusing from the gut into the bloodstream help to maintain immune functions, such as the microbicidal activity of neutrophils, hematopoiesis, and the release of macrophages from the bone marrow into circulation. For example, the killing activity of bone marrow–derived neutrophils is stimulated by recognition of peptidoglycan from gut microbes. The immune response–enhancing effect of microbial translocation is exploited in bone marrow transplant settings and some immunotherapies by use of total body radiation to cause microbial translocation, which, in turn, enhances the immune response.

Gut Microbiome–Immune System Interactions and Beneficial Effects

The intestinal immune system coevolves with the gut flora. The early interaction of microbes with the neonatal immune system and colonization of the neonatal gut by commensal bacteria occurs without much inflammation because the neonatal immune system is still developing. The neonatal immune system integrates recognition of conserved microbe-associated molecular patterns or molecular signatures of microbes, which serve as signals for interaction between the host and microbiome. This type of interaction stimulates immune regulation, which helps the bacteria coexist peacefully with the host. Some of this regulation involves antigen-presenting cells; dendritic cells develop tolerance, whereas macrophages develop inflammation anergy. This interaction maintains healthy microbial colonization.

Microbes in the gut flora are contained by broad and nonspecific modes and are selectively contained in ecological niches as well. The interface between the gut epithelium and microbes has numerous protective mechanisms. One such mechanism is mucus secretion by goblet cells. The second mechanism is production by the epithelium of proteins with antimicrobial functions, also called antimicrobial peptides, one of which is the Reg3 gamma peptide. The third mechanism is stimulation of secretion of IgA antibodies by gut flora; the gut flora stimulate the intestinal epithelial cells to secrete NK-kB, which causes release of signaling molecules for secretion of IgA antibodies. The secretion of IgA antibodies contributes to compartmentalization and diversification of intestinal bacteria and eliminates bacteria that cause inflammation. The intestinal dendritic cells sample commensal bacteria and communicate with T and B cells in the mucosal lymphoid tissue and mesenteric lymph nodes to secrete IgA antibodies that prevent adhesion of bacteria. In other mechanisms, translocation of microbes is prevented by macrophages in the lamina propria that engulf any microbes crossing from the lumen,
through the epithelium, and by uptake by dendritic cells. Additional protective mechanisms include the mucosa-associated lymphoid tissue in the gastrointestinal tract, which plays a protective role against pathogens.

Commensal bacteria are recognized by the immune system constitutively and play a role in maintaining homeostasis. A disturbance in the microbiome and gut homeostasis can lead to pathologic states. Signals derived from the microbes in the gut contribute to the establishment of tolerance to ingested antigens. FoxP3 regulatory T cells play an important role in immune regulation and homeostasis. Gut microbes play a significant role in the induction of macrophages and regulatory T cells. Probiotics are postulated to function by inducing regulatory T cells. CD4 T cells play a major role in the adaptive immune system and are of helper (Th) Th1, Th2, Th17, or regulatory T-cell subtypes. The Th17-lineage T cells play a role in production of cytokines that act on epithelial cells to maintain homeostasis. Gut microbes influence the sampling of orally ingested antigens by mucosal dendritic cells. Innate lymphoid cells in the gut respond to signals derived from microbes and produce the cytokine interleukin 22 (IL-22), which helps to contain the microbes. Metabolites from the microbes exert systemic effects on the immune system, for example, via production by monocytes of mediators such as PGE2, which in turn inhibit activation of neutrophils and reduce tissue damage.

Pathogens interface with the human body via the skin, gut, and respiratory system. All these systems contain commensal microbes, with which pathogens must interact, in addition to the immune system. The result of this interaction determines the fate of pathogens and possible resulting infection. The presence of numerous microbes in the gut protects the host from disease-causing bacterial organisms. Commensal bacteria protect the host from pathogens by colonization of sites of pathogen interaction, a mechanism called colonization resistance. Competition between pathogens and commensal bacteria for the same sources of metabolites and sites of localization contributes to this resistance. In addition, the growth rate and virulence of pathogens are influenced by nutrient availability and metabolites produced by commensal bacteria. Commensal metabolism can produce a microenvironment that is not conducive to pathogens, and some peptides produced by commensal bacteria can be antimicrobial. These combined mechanisms help protect the host from pathogenic infections.

**Alterations in the Gut Microbiome and Disease**

Food intake and food-derived metabolites regulate the gut microbiome as well as the immune system. Differences in diet in different geographic areas and variations with traditions and culture affect the gut microbiome and possibly contribute to variation in disease prevalence. Increasingly germ-free environments, use of antibiotics, elimination of nematodes, and changes in diet are contributing to a changing microbiome in the human gut. This changed ecosystem may not be sufficiently resilient to maintain a balanced immune response or protect the host from pathogens. Alteration in diversity and
EDUCATIONAL COMMENTARY: IMMUNITY OF THE GUT MICROBIOME (cont.)

number of commensals in the gut bacteria is termed *dysbiosis*. Allergies, autoimmunity, and inflammatory bowel disease arise from immune responses that are directed against the self or are debilitating to self. Often, these immune responses are triggered after exposure to antigens derived from microbes or the environment. However, inflammatory and autoimmune diseases have an underlying genetic predisposition, and environmental factors, including shift in gut flora with acquisition of certain microbes, play a role in disease onset.

Disrupted homeostasis of the gut microbiome with the host immune system can lead to inflammation in the bowel. Abnormal immune responses to bacteria are postulated to cause inflammatory bowel disease. In healthy states, CD4 T-cell clones reactive to indigenous gut flora are present in some amount; however, they can aberrantly accumulate to cause inflammation and inflammatory bowel disease. Inflammatory bowel diseases, such as Crohn disease and ulcerative colitis, have complex causation that includes shift in gut flora, acquisition of certain infections, immune system alterations, and genetic predisposition. In both Crohn disease and ulcerative colitis, the complexity of gut flora is reduced. Indigenous microbes are outgrown by microbes that are borderline between commensal and pathogenic and incite inflammatory responses in the gut. Inflammation in the gut also develops owing to the reduction in commensal microbial flora that induce the activation of regulatory T cells and the inhibition of macrophages and neutrophils.

It is postulated that carcinogenesis in the bowel could be related to a shift in the gut microbiome. Certain organisms, such as *Helicobacter pylori*, are involved in causation of gastric ulcers and gastric cancers. Inflammation, induced by microbes, has been hypothesized to play a role in colon cancers.

Changes in the microbial flora of the gut have been associated with the development of allergies and autoimmune disorders. Alterations of microbes in mothers and neonates have been associated with diseases such as asthma. Studies have found gut microbial flora playing a role in susceptibility to immune-mediated diseases such as rheumatoid arthritis, multiple sclerosis, and type 1 diabetes.

Use of broad-spectrum antibiotics alters the gut flora, allowing drug-resistant microbes to dominate, replacing indigenous flora. This can cause infections by the drug-resistant organisms such as *Clostridium difficile*. Replacement of indigenous flora can be used as a therapeutic option in some of these infections. Reduction of gut microbial flora by antibiotic treatment blunts the immune response to infections, even in organs other than the gut, mainly in the case of viral infections (e.g. in nasal infections with influenza).
Change in microbial flora has been observed in metabolic diseases such as type 2 diabetes, obesity, and metabolic syndrome. Alterations in the gut microbiome are associated with a variety of human diseases including autoimmune, metabolic, neoplasia, and infections.

Summary

The gut microbiome consists of a large population of commensal bacteria that play a role in immunity and interact with the immune system. The microbiome provides numerous beneficial functions to the host, including digestion of fiber, production of vitamins, and protection from pathogens. Alterations in the microbiome are associated with several disease states, including autoimmune diseases, neoplasia, and susceptibility to infections.

References


26. Frank DN, St Amand AL, Feldman RA, Boedeker EC, Harpaz N, Pace NR. Molecular-
phylogenetic characterization of microbial community imbalances in human inflammatory bowel


31. Vijay-Kumar M, Aitken JD, Carvalho FA, et al. Metabolic syndrome and altered gut microbiota in

© ASCP 2019