Biology of the Microbiome

Interactions with the Host Immune Response

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KEYWORDS

• Microbiome • Innate immune system • Adaptive immune system • SCFA • Histamine

KEY POINTS

- Highly sophisticated cellular and molecular networks need to be constantly coordinated in order to tolerate the presence of many diverse bacteria on mucosal surfaces.
- Different types of bacteria induce different immune responses, and these effects are strain specific.
- Bacterial metabolism of dietary factors generates metabolites, which have significant effects on host immune responses.
- More accurate endotyping of patients with inflammatory disorders may be assisted by determining the composition and metabolic activity of an individual's microbiome.
- Novel therapeutics directly targeting microbiome activities may be considered as complementary to existing drugs for treatment of inflammatory disorders.

INTRODUCTION

The mammalian gastrointestinal tract is a highly evolved system specialized to perform the essential functions of nutrient digestion, absorption, and waste disposal. The intestinal mucosal immune system must maintain intestinal integrity in the presence of a vast quantity of external or foreign antigens, such as food proteins and the microbiome. The

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ability to tolerate a wide range of bacterial antigens is a unique feature of the mucosal system that is not seen with the systemic immune system. Tolerance to food and microbial antigens at mucosal surfaces is not a passive process. Highly sophisticated cellular and molecular networks need to be constantly coordinated in order to tolerate the presence of many diverse bacteria, and protective immune responses to potential pathogens must be maintained and induced on demand. Expression of pattern recognition receptors (PRRs) allows the immune system to discriminate between commensal and harmful microbes. Inappropriate immune responses to bacterial or dietary antigens is a significant component in several intestinal pathologies, including inflammatory bowel disease, irritable bowel syndrome, and food allergies.[1,2]

The balance between immune tolerance and inflammation is regulated in part by the crosstalk between innate and adaptive immune cells and the intestinal microbiota. Disrupted communication between the microbiome and the host due to altered microbiome composition and/or metabolism is thought to negatively influence intestinal immune homeostatic networks.[3] This negative influence can be clearly seen in mice bred under germ-free or sterile conditions, whereby mucosal tolerance mechanisms do not fully develop; these mice display increased allergic sensitization to food antigens.[4] The deliberate modification of microbial species and their metabolism has led to the probiotic and prebiotic concepts.[5] Probiotics can be defined as live microorganisms that, when administered in adequate amounts, confer a health benefit on the host. Notably, the definition of a probiotic does not differentiate between the wide range of potential health benefits; it is clear that not all probiotics will influence the immune system in the same way. Prebiotics can be defined as selectively fermented ingredients that allow specific changes, both in the composition and/or activity in the gastrointestinal microflora, that confer benefits on host well-being and health. As with the probiotic definition, not all prebiotics will have the same effect on immunologic functions. The combination of probiotics and prebiotics is termed synbiotics.

The mucosal immune system is classified as organized or diffuse gut-associated lymphoid tissues (GALTs). The organized GALT includes Peyer patches, mesenteric lymph nodes, and solitary lymphoid follicles in the gut wall where antigen uptake, processing, and presentation occur. In contrast, diffuse GALT is a nonorganized system whereby individual cells, such as intraepithelial lymphocytes, are dispersed throughout the gut. Finally, epithelial cells themselves provide a barrier to antigen translocation and actively participate as sensors of luminal bacterial activity.

INNATE IMMUNE SYSTEM

The innate immune system is composed of many different cell types, and these cells are often the first cells to come into contact with intestinal microbes and their metabolic products.

Dendritic Cells

Intestinal dendritic cells are located within specific intestinal lymphoid tissues, collectively termed GALTs, or diffusely distributed throughout the intestinal lamina propria.[6] Dendritic cells are very important cells that act as sensors of microbial ligands through activation of innate immune receptors (eg, toll-like receptors [TLRs] and c-type lectin receptors). For example, a *Lactobacillus rhamnosus* bacterial strain is recognized by dendritic cell TLR-2 and Dendritic Cell-Specific Intercellular adhesion molecule-3-Grabbing Non-integrin.[7] The signaling pathways triggered by bacterial-derived molecules allow for changes in dendritic cell phenotypes and cytokine secretion, which polarize the subsequent adaptive T-cell immune response into T helper 1 (T_H1), T_H2,