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Gut Microbiota: The Conductor in the Orchestra of Immune–Neuroendocrine Communication

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ABSTRACT

Purpose: It is well established that mammals are so-called super-organisms that coexist with a complex microbiota. Growing evidence points to the delicacy of this host–microbe interplay and how disruptive interventions could have lifelong consequences. The goal of this article was to provide insights into the potential role of the gut microbiota in coordinating the immune–neuroendocrine cross-talk.

Methods: Literature from a range of sources, including PubMed, Google Scholar, and MEDLINE, was searched to identify recent reports regarding the impact of the gut microbiota on the host immune and neuroendocrine systems in health and disease.

Findings: The immune system and nervous system are in continuous communication to maintain a state of homeostasis. Significant gaps in knowledge remain regarding the effect of the gut microbiota in coordinating the immune–nervous systems dialogue. Recent evidence from experimental animal models found that stimulation of subsets of immune cells by the gut microbiota, and the subsequent cross-talk between the immune cells and enteric neurons, may have a major impact on the host in health and disease.

Implications: Data from rodent models, as well as from a few human studies, suggest that the gut microbiota may have a major role in coordinating the communication between the immune and neuroendocrine systems to develop and maintain homeostasis. However, the underlying mechanisms remain unclear. The challenge now is to fully decipher the molecular mechanisms that link the gut microbiota, the immune system, and the neuroendocrine system in a network of communication to eventually translate these findings to the human situation, both in health and disease. (*Clin Ther*. 2015;▮:▮▮▮–▮▮▮) © 2015 Elsevier HS Journals, Inc. All rights reserved.

Key words: brain, enteric nervous system, gut microbiota, immune system.

INTRODUCTION

Our knowledge of the host–microbe interrelationship is accelerating because of the availability of rapidly expanding molecular techniques, especially in combination with the use of reductionist in vivo host models. A growing body of research continues to show that the normal mammalian structure and function are significantly dependent on their constant engagement in complex interactions with microbes.[1] For example, the intestinal microbiota with its components and metabolites affects the host physiology in various ways to control energy homeostasis, gut barrier function, mucosal inflammation, and behavior.[2–4] Subsequently, the host modifies many of the microbial activities, which suggests a feedback mechanism that could influence the microbiota and drive a further cycle of biological changes to host physiology.[5] This multidirectional interactive dialogue seems to strongly influence an expanding repertoire of human disorders, including obesity, depression, and irritable bowel syndrome; the goal is to decipher the tête-à-tête between the host and its commensal organisms.[6,7]

The present review highlights emerging evidence, which provides a framework for appreciating the

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impact of the host–microbiota interplay on health that is undoubtedly much broader than previously thought. This review outlines the impact of the gut microbiota on the immune system as well as the neuroendocrine system, both of which point to a potential role of the microbiota as crucial coordinators in the cross-talk between these systems.

MATERIALS AND METHODS

Literature from a range of sources, including PubMed, Google Scholar, and MEDLINE, was searched to identify recent reports on the impact of the gut microbiota on the host immune and neuroendocrine systems in health and disease. All data were gathered for the latest available years.

RESULTS

The Host–Microbiota Dialogue

Over the past decade, remarkable advances toward a better understanding of how the host–microbe interactome is linked with most pathways that affect health, disease, and aging were made possible with novel technologies; these include high-throughput DNA sequencing, bioinformatics, and gnotobiotic animal models.[1] The intimate interactions between the host and its microbes that outnumber the host's cells by 10 to 1 are required to stimulate the complete maturation of an efficient intestinal barrier that can promote niche colonization by commensals and opposes colonization by pathogens.[4,8] Only microbial populations that are capable of establishing a mutualistic relation with the host can be maintained in the gut ecosystem,[3] creating a habitat that exerts restrictive selection on its microbial inhabitants. This restrictive selection of specific microbial groups is illustrated by the relatively low phylum-level diversity observed in the microbiota of the gastrointestinal (GI) tract of many mammalian organisms, including mice and humans; this is dominated by the phyla of the *Bacteroidetes* and the *Firmicutes*, with *Proteobacteria*, *Actinobacteria*, *Fusobacteria*, and *Verrucomicrobia* phyla present in relatively low abundance.[9] In contrast, the diversity at the genus and species levels is enormous. Advances in metagenomic approaches helped to illustrate that despite the variation in species composition, the microbial communities encompass a relatively similar set of metabolic functions in healthy individuals, which are referred to as the "core microbiome."[10] Furthermore, diet and its nutritional value are partly shaped by (and they in turn can shape) the gut microbial community, supporting the notion that "we are what we eat," a process that starts early in life.[11,12] Indeed, this scenario is now being exploited for medical innovations along the diet–host interface in line with Hippocrates' dictum that "Let food be thy medicine and medicine be thy food."

The primary individual microbiota colonize at birth. However, there is growing evidence that the in utero environment may not be sterile, as originally thought: bacteria such as *Enterococcus faecalis, Staphylococcus epidermidis,* and *Escherichia coli* have been isolated from the meconium of healthy neonates.[13] The infant gut microbiota is more variable in its composition and less stable over time. In the first year of life, the infant intestinal tract progresses from sterility to extremely dense colonization, ending with a mixture of microbes that is relatively stable and largely similar to that found in the adult intestine.[14,15] The composition of the gut microbiota is shaped by a variety of factors, including prenatal and postnatal variables as well as birth factors.[16] Altering the intestinal microbiota, particularly during early life, has been shown to have lasting consequences on the host.[17] For example, the variation in early-life environmental exposure that includes the method and place of delivery and a nourishing neonate regimen influences the microbiota of infants.[18,19] The microbiota of infants delivered vaginally is dominated by microbial groups that colonize the vagina, whereas infants born by cesarean delivery have microbiota that more closely resembles those of the maternal skin community.[16,20] However, the duration of the influence of these factors on the host remains obscure, with contradicting findings available to date. As a final age-related microbial shift, the elderly have a core microbiome different from that of younger adults, and the composition is directly correlated with health outcomes and the decline in the immune system.[21]

The gut is home to a diverse array of trillions of microbes that influence almost all aspects of human biology through their interactions with their host.[1] Although the host provides the microbiota with the ecological niche and nutrients required of its survival, the indigenous microbiota, in turn, provides the host with full maturation of the innate and adaptive arms of the immune system, modulation of the nervous system function, nutrient absorption and fat distribution, contribution to digestion (eg, the ability