# Gut Brain Axis and Its Microbiota Regulation in Mammals and Birds

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**KEYWORDS**

• Microbiota • Microbiome • Bacteria • Gut-brain-axis • Serotonin

**KEY POINTS**

- The intestine harbors a highly complex microbial ecosystem consisting of bacteria, fungi, viruses, and parasites.
- Bacterial culture and fecal cytology does not allow proper assessment of intestinal bacteria, and molecular-based methods are now standard in the assessment of bacterial microbiota.
- The intestinal microbiota is a highly active immunologic and metabolomic system that is crucial to host health.
- Various microbiota-derived metabolites contribute to neuroendocrine pathways that provide signaling to the brain via the gut-brain axis.

## INTESTINAL MICROBIOTA AND ITS FUNCTION

The intestinal microbiota is defined as the collection of all living microbes (bacteria, fungi, protozoa, and viruses) residing in the gastrointestinal (GI) tract. Until a decade ago, bacterial culture was the most commonly used technique to describe bacteria within the mammalian and avian GI tract. The recent advance of molecular tools, especially next-generation sequencing technologies that allow to inexpensively amplify, sequence, and thereby identify which bacterial taxa are present in a sample, has revolutionized understanding and revealed that the GI microbiota of mammals and birds is much more species-rich than previously thought.[1] In mammals, it is estimated that 100 trillion bacterial cells populate the GI tract and the total sum of bacteria is approximately 10 times more than the number of host cells. The collective genome of all these microbes (referred to as microbiome) exists in close relationship with the host and, through its immunologic and metabolic function, this highly complex microbial-host ecosystem has a crucial impact on host health, including the nervous system.

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Resident bacteria provide many beneficial mechanisms, such as fending off transient enteropathogens, aiding in nutrition and harvesting energy from diet, providing metabolites that feed enterocytes, and stimulating the host immune system. Although most data about the functions of the intestinal microbiota are derived from studies in mammals and fewer data are available in avian species, it is likely that many microbiota–host interactions are evolutionary and conserved across various animal species. For example, in mammals, complex fibers obtained through the diet (eg, starch, cellulose, pectin) are fermented by intestinal bacteria. The end products of this bacterial fermentation are short-chain fatty acids (SCFA). These are partially absorbed and serve as an energy source for the host (eg, propionate, acetate), regulate intestinal motility, and are also used as important growth factors for the intestinal epithelial cells. SCFA are also important stimuli for maintaining intestinal barrier function, thereby minimizing bacterial translocation.[2,3] SCFA are also immunomodulatory by activing regulatory T cells in the intestine.[4] Although SCFA are the most studied bacterially derived metabolites, novel metabolomics approaches have revealed various other metabolites that are produced by intestinal microbiota, such as indole, a byproduct of tryptophan degradation, which is anti-inflammatory and enhances intestinal barrier function.[5] Of importance is that bacterial metabolism and immunologic stimulation in the intestine have consequences that reach far beyond the GI tract. It is now well-recognized that a gut-brain connection exists that is modulated by gut microbes. Modulation of gut microbiota is an exciting emerging area of research with the potential for better understanding of pathophysiology and treatment of various intestinal and metabolic, as well as neurologic diseases.

## ASSESSMENT OF INTESTINAL MICROBIOTA

Until a decade ago, most information about the composition of the intestinal microbiota was obtained using traditional culturing techniques. Bacterial culture is a useful tool for determination of an active infection of known pathogens (eg, *Salmonella*, *Campylobacter*) and antibiotic susceptibility testing in clinical specimens. Individual isolates and their virulence factors can be typed for epidemiologic surveys of specific strains. It is now well-recognized that there are several limitations associated with bacterial culture of intestinal samples. Bacterial culture widely underestimates the total bacterial numbers in the intestines. Most gut bacteria cannot be isolated on routinely used laboratory media because not enough information is available about their optimal growth requirements. Most microbes in the gut are strict facultative anaerobes, hindering their successful isolation in vitro. It is estimated that less than 10% of intestinal bacteria can be cultured on routine media and only a small fraction can be correctly classified using classic morphologic and biochemical criteria. Therefore, clinical examination of intestinal samples by culture is currently biased toward the minor cultivable portion of the gut microbiota.

Because of these limitations, the use of molecular tools is now standard. The principle is that DNA is extracted from intestinal samples and 16S ribosomal RNA (rRNA) genes are amplified using universal bacterial primers. This approach allows in theory amplification of DNA from all known and unknown bacterial species present in a sample. To identify the phylotypes present in the sample, the PCR amplicons can be subsequently sequenced by high-throughput sequencing platforms.[6] These platforms allow for analysis of several thousand sequences within a few hours, yielding a deep identification of the intestinal microbiota. If the sequence for a particular phylotype is known, specific PCR assays can be designed for its detection. Real-time polymerase chain reaction (PCR) assays (with universal-specific, group-specific, or