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Gut Microbiome

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Synonyms

Gut microbiota

Definition

The human gut microbiome is a community of roughly 40 trillion bacteria, fungi, archaea, and protozoa which reside within the human gastrointestinal tract. Variations in gut microbiome composition have been implicated in a variety of psychological, physiological, and behavioral traits.

Introduction

A variety of environments, including many human organs, contain within them communities of microorganisms, including bacteria, fungi, archaea, protozoa and viruses. This community is collectively referred to as the microbiome or microbiota. Traditionally, the term microbiota was used to refer to the community of organisms, and microbiome to refer to the collective genomes of organisms within those communities. While the term microbiome can still refer to a set of collective genetic material, these two terms are also now used synonymously to refer to the community of organisms within a given environment (Ursell et al. 2012). The human gastrointestinal tract contains roughly 40 trillion microorganisms which collectively form the gut microbiome (Sender et al. 2016). Of these organisms, bacterial species are the best understood, of which there are approximately 1000 species, belonging to 4 dominant bacterial phyla: *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, and *Proteobactiria* (Guarner and Malagelada 2003).

Human gut microbiomes are established at birth, when an infant is seeded with microbes from the mother's vaginal canal, skin, and feces. Infants born via caesarean section present with different compositions of gut microbes, which resemble microbes found on their mother's skin, compared to those born vaginally whose gut microbiomes more closely resemble the mother's vaginal canal (Dominguez-Bello et al. 2010). These caesarean-associated early gut microbiomes have been implicated in the risk of later diseases such as celiac disease, type 2 diabetes, and asthma (Mueller et al. 2015). The gut microbiome is further colonized during breastfeeding and continues to change throughout development in response to the environment. By 3 years of age, the infant gut microbiome is structurally similar to those found in adults (Palmer et al. 2007).

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There is a lot of individual variation in gut microbiome composition, though those differences remain relatively stable over one's lifespan (Costello et al. 2009). However, this stability can be altered by diet, disease, and the use of medications like antibiotics (Becattini et al. 2016; Power et al. 2014; Turnbaugh et al. 2009).

Microbiome diversity is understood using metagenomics, which uses bioinformatic techniques to identify multiple species from environmental samples of large amounts of DNA. In 2012, a reference database for the human gut microbiome was completed, as part of the first phase of the Human Microbiome Project (Human Microbiome Project Consortium 2012).

Symbiosis and Evolution

Gut microbes exist in a symbiotic relationship to their human hosts. Many are thought to be commensal, imparting no direct harm or benefit to their human host. Other relationships are mutualistic. For example, some gut microorganisms help to metabolize compounds so that human hosts can access otherwise inaccessible nutrients. Others digest carbohydrates, ferment dietary fiber, and synthesize vitamins, fulfilling important digestive roles (Turnbaugh et al. 2007; Liang et al. 2018). Parasitic relationships also exist where microorganisms in the gut harm their human hosts, causing disease and, in extreme cases, death.

Mutualistic relationships suggest a persisting evolutionary history between microbiomes and their hosts, as each relies upon one another for vital functions, and thus are thought to have coevolved. This type of coevolution is sometimes understood as a holobiont – an entity which includes both the host (macroorganism) and its symbiotically related microorganisms (microbiomes). A related concept is the hologenome – which in this case is the complex of genomes of microbiomes and their hosts (Rosenberg 2013).

There is emerging evidence that gut microorganisms can influence human behavior. This has led some researchers to consider whether the evolution of some human behaviors can be explained in light of the benefits to their associated microorganisms (Turnbaugh et al. 2007). For example, Alcock et al. (2014) have theorized that food cravings and eating behaviors with negative human health impacts have originated as a mechanism by which some microbes acquire nutrients and defeat competitor microbes in the gut, in order to maintain their own existence.

Human Physiological and Disease Associations

Differences in the composition of the gut microbiome have been implicated for various human diseases. Microbiomes associated with disease states are termed "dysbiotic" and often display reduced diversity, along with under- and overrepresentations of certain bacterial phyla. Inflammatory bowel disease, which includes Crohn's disease and ulcerative colitis, has been associated with decreased overall microbial diversity, as well as compositional differences when compared to healthy individuals. It is thought that these diseases develop from an interaction of gut microbes with the mucosal immune system (Kostic et al. 2014).

Asthma and many allergies are also associated with compositional differences in the gut microbiome. Mechanisms of gut microbiome alteration in these cases may be due to diet or because of lack of early life infections which alter the T-cell response in immune system (the hygiene hypothesis) (Shen and Wong 2016).

The gut microbiome has also been implicated in cancer, with both *Bacteroidetes* and *Clostridium* associated with increased tumor growth rate and fewer tumors observed in germ-free (thus microbiome free) rats and mice. Specific bacteria, such as *Helicobacter pylori* (associated with gastric ulcers), are thought to contribute to cancer with epithelial injury and inflammation. Other kinds of bacteria are thought to prevent tumor formation, such as *Bifidobacteria* and *Lactobacillus* (Schwabe and Jobin 2013).

Individuals with a higher relative abundance of *Firmicutes* rather than *Bacteroidetes* are more likely to be overweight, and humans who have lost weight through dieting reduced their increased abundance of *Firmicutes* (Ley et al. 2006). However, it is not known in this instance whether microbiome composition is a cause of obesity or obesity is a cause of microbiome composition. In order to investigate this further, experimental manipulations in animal models have extensively addressed the obesity question (discussed below).

Human Behavioral Associations

Interestingly, the human gut microbiome has also been implicated in many behaviors and mental capacities. The proposed mechanism of influence is the gut-brain axis, which encompasses a bidirectional pathway between the central nervous system and the digestive system. This axis includes the vagus nerve, hormone secretions, inflammatory molecules, and signalling molecules (Carabotti et al. 2015).

The gut microbiome is thought to influence mood via its effects on serotonin and tryptophan – hormones which regulate stress responses and influence cognition. There is some evidence that people with depression have altered microbial compositions in their gut, though no differences in species richness have been observed (Dash et al. 2015). There is also some evidence that probiotic usage can decrease the likelihood of depressive and anxiety-related symptoms in humans (Foster and Neufeld 2013).

A large number of children with autism also present with gastrointestinal problems, and an increase in the relative abundance of *Clostridium* has been observed in autistic children. However, interventions on the microbiome via diet and probiotic use have so far proved unsuccessful for the treatment of children with autism (Chen et al. 2013).

A major issue with associative studies is identifying the causal structure of each association. Microbiomes may be causing human differences in behavior, psychology, and disease, or it may be that human behaviors and human diseases causally impact upon microbiomes. It is also possible that a third factor is a common cause of both microbiome compositional differences and the trait of interest. For instance, autistic children are often picky eaters, and so differences in diet may account for differences in microbiome composition. Relatedly, obese individuals often have markedly different diets and lifestyles compared to nonobese individuals.

For this reason, researchers have used animal models in an attempt to uncover the causal processes underlying gut microbiome associations. Animal models provide the advantage in that microbiomes may be manipulated and other confounding variables minimized.

Evidence for Behavioral Influences in Animal Models

Animal models, particularly using rodents, have been used to make inferences about the causal role of human gut microbiota. Germ-free (GF) mice are most often used, which have been birthed surgically and raised in sterile environments, meaning that they have no gut (or other) microbiomes. GF mice are then artificially colonized by the microbiome of interest. Fecal matter (representing the donor gut microbiome) is transplanted surgically into the host GF mouse via gavage in a process termed fecal microbiota transplant (FMT). The fecal transplant is sourced either from another mouse with a particular phenotype of interest (mouse-mouse FMT) or from a stool provided by a human donor with a phenotype of interest (human-mouse FMT). Transfer of phenotype from both donor mice and humans has been demonstrated most compellingly for obesity. Recipient mice which receive FMTs from obese mice, or from obese humans, become obese themselves, suggesting strongly that the gut microbiome is a causal factor in the development of obesity (Turnbaugh et al. 2009).

The success of transfer of phenotype studies for obesity has spurred experimental research investigating other microbiome associated traits in humans – including human psychological attributes. These include developmental disorders, such as autism, and mood disorders like

anxiety and depression. To date, there has only been one successful transfer of behavioral phenotype study using human donor FMTs. FMTs from depressed humans into antibiotic-depleted rats induced depression and anxiety-like behavior (Kelly et al. 2016). Mouse-mouse FMTs have also been shown to decrease anxiety-like behaviors (Bercik et al. 2011). Other evidence for the microbiomes influence on behavior comes from indirect interventions on the gut microbiome. Autism-like behaviors were observed in mice which had in utero disruption, altering the microbial composition of their guts (De Theije et al. 2014). Probiotic administration has been shown to decrease anxiety and the severity of stress response in mice, thought to act indirectly via changes in microbiome composition (Sudo et al. 2004; Diaz Heijtz et al. 2011).

One problem with the animal model approach is that complex psychological traits are measured using behavioral proxies in mice and rats. For instance, tests of depression are made using the forced-swim test, where animals are placed into a water-filled cylinder and their attempts at escape are timed. Individuals who stop swimming or "give up" after a shorter period of time are deemed depressed, compared to those which continue to try and escape for longer. Anxiety tests include recording the amount of time an animal likes to spend in an exposed environment (prominent examples are the light-dark box test and the elevated plus maze). The least amount of time spent in a very light or exposed environment, the more anxious the animal is thought to be. Autistic-like mice are characterized by reduced socialization, increased anxiety, fewer vocalization, and obsessive behaviors like grooming and marble burying. Given these limitations, some (Hooks et al. 2019, Lynch et al. 2019) have questioned some of the scientific conclusions made about microbiome causality, suggesting that claims about the influence of the human gut microbiome on behavior have been overblown or at the least are premature.

Concluding Remarks

The human gut microbiome is the most well-studied and complex microbial community on the human body. Without these microbes, humans would be unable to perform many vital metabolic functions, and so many microbes persist with their human hosts in a mutualistic symbiotic relationship. Differences in the relative abundance of microbes, or microbiome composition, along with increases or decreases in overall diversity, are implicated in a number of health in disease states, such as inflammatory bowel disease, cancer, obesity, allergies, asthma, autism, and mental health. The gut microbiome is thought to influence human behavior via the gut-brain axis, and some human behaviors are hypothesized to be due to the evolutionary interests of gut microbes.

Associative evidence for physiology and behavior are potentially confounded, and so manipulative experiments colonizing germ-free rodents with microbes provide the majority of evidence for microbiome causality. These experiments have successfully demonstrated manipulations on the microbiome resulting in disease states, obesity, anxiety, depression, and autism-like behaviors. However, critics of these studies point out that murine behavioral analogues are not sufficient to demonstrate the causal role of microbiomes in human health, disease, and behaviors.

Cross-References

- ▶ Anxiety Disorders
- ▶ Autism
- ▶ Depression
- ▶ Mental Health
- ▶ Obesity
- ▶ Symbiosis and Mutualism

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