BIOLOGY OF THE HUMAN GUT MICROBIOME

Semester Project Report (BI3313)

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1. Introduction

The human gut is home to trillions of microorganisms, making up a complex gut microbiome consisting of Archaea, Bacteria, Eukarya and Viruses. The microbiome plays a vital role in human health and development – it contributes significantly to the digestion of complex dietary polysaccharides that are indigestible to the host, synthesis of essential amino acids and vitamins, modulating efficacy and toxicity of xenobiotics, maturation of immune system, lymphocyte homeostasis, tissue and organ development, and protection against pathogens (Das and Nair 2019).

Through this semester project, I have tried to capture the essential features of the human gut microbiome that would be useful in constructing a model based on biologically relevant insights. I have done this by reading research articles and reviews on the topic and summarizing them in topic-specific documents, which can be found here. The following sections of the report encapsulate the main points.

2. Diversity and Distribution

The adult gut microbiome is mainly comprised of bacteria from *Bacteroidetes* and *Firmicutes* phyla. The small intestine is dominated by *Lactobacilli* and *Enterobacteria*, whereas the large intestine is colonized by obligate anaerobic bacteria such as *Bacteroides* sp and *Provatella* sp. Bacterial density in SI is controlled by low gastric pH, faster peristalsis, bile acids and antimicrobials released by Paneth cells. The bacterial density in LI is 10^6 times greater than in SI. They are kept in check by a thick inner mucus layer (which prevents them from coming into contact with the epithelium) and microbial interactions. (Donaldson et al., 2016).

Bacterial diversity among individuals converges in functionality rather than taxonomy. Vieira-Silva et al., 2016 characterized the species-function relationship of bacteria in the gut microbiome. They found that half of the species are generalists about overall substrate preference. The core metabolic repertoire is conserved over distant taxa, which contributes to the resilience of the microbiome because of functional redundancy. (Vieira-Silva et al., 2016)

3. Factors that influence microbiome composition

Age – The microbiome reaches a stable composition around three years of age. The diversity of the microbiome increases with age, whereas interpersonal variation among individuals decreases with age. (Yatsunenko et al., 2012).

Diet – It is a major exogenous factor that shapes the composition and diversity of the microbiome. Microbiome resulting from protein-rich and carbohydrate-rich diets show a clear distinction. Short term changes in the diet don't affect the microbiome; it returns to its previous stable state. Dietary choices have significant impacts on colonic health. Diet is in turn affected by geography, age and the recent human evolution. (Yatsunenko et al., 2012, O'Keefe 2016).

Mode of delivery – Initial composition of an infant's microbiome is modulated by the mode of delivery (cesarean or vaginal) and by the subsequent mode of diet. The initial state may have long-term effects on the adult microbiome. (Dogra et al., 2015)

Immune adaptations – The immune system tightly regulates microbial biomass by minimizing direct contact, killing penetrant bacteria and through the mucosal immune firewall (Hooper and Macpherson 2010). The gut microbiome (through its composition and the compounds it secretes), in turn, influences the immune responses in the body. *Bifidobacterium* is a major component of the infant gut microbiome, where it digests milk oligosaccharides and stimulates the production of IgA from B cells.

Other factors – lifestyle (exercise and stress), host genome, infection, and so on also shape the microbiome.

4. Immune interactions

Microbiota nourishing immunity (Miller and Baumler 2021) is a set of habitat filters that regulate the shape, size and distribution of the microbiome. It is fundamentally different from sterilizing immunity. Low pH, fast peristalsis, production of antimicrobials and IgA regulate the microbiome in the small intestine, and the same is maintained by a thick mucus layer, physiological hypoxia and release of hydrogen peroxide in the large intestine.

Aside from immune adaptations that maintain homeostasis in the gut, and habitat filters that shape the diversity and distribution of bacteria, there are other interactions between the gut microbiome and the immune system. For these diverse microbes to colonize the gut, they have to be tolerated by the host's immune system. Rather than the immune system learning to distinguish between commensals and pathogens, there is an alternate view that commensal bacteria have adapted by promoting their immunological tolerance (Donaldson et al., 2016). Immunomodulation by gut bacteria is an essential aspect of the host-microbiome interaction.

5. Metabolism and Cross-feeding

The human genome primarily encodes enzymes that degrade starch. Gut bacteria produce hundreds of individual enzymes to digest plant-based dietary polysaccharides and endogenous glycans of the host mucus layer. Bacteria that feed on host glycans have an advantage during times of nutrient scarcity, and it may help stabilize the gut community and promote mucin secretion and barrier function (Porter and Martens 2017, Cockburn and Koropatkin 2016).

Most of the gut bacteria process mono-, di- and oligosaccharides, but carbohydrate reaches the large intestine mainly as polysaccharides. This paradox is explained by cross-feeding interactions – bacteria in the gut exist in a series of cross-feeding networks where metabolites are exchanged, with keystone species acting as critical nodes. Cross-feeding can occur due to competition for the released sugars, differential utilization of constituents of a polysaccharide or further processing of fermentation products, all of which is spurred on by the lower energy yield from carbohydrate utilization in an anoxic environment. (Cockburn and Koropatkin 2016).

Short-chain fatty acids (SCFAs) are the fermentation products of plant polysaccharides. The concentration of SCFAs is an indicator of gut health status. Butyrate has a variety of positive effects on gut health. Butyrate obtained from natural dietary fibre can help maintain gut homeostasis and reduce the idiopathies of various diseases that develop due to dysbiosis. (Anand et al., 2016)

6. Dysbiosis

Dysbiosis is considered as an alteration in microbiota community structure and/or function, capable of causing/driving a detrimental distortion of microbe-host homeostasis that specifically initiates or propagates disease (Butto and Haller 2016). Dysbiosis can be caused by endogenous factors such as genetic susceptibility, and exogenous factors such as infection, inflammation, antibiotics, diet and selection of pathobionts. Dysbiosis of the gut microbiome is associated with a wide variety of pathologies, but it is hard to establish whether this is a cause or consequence of the disease. Dysbiosis is closely linked with the pathogenesis of inflammatory bowel disease, irritable bowel syndrome, *C. difficile* infection and other such diseases of the GI tract. Prebiotics, probiotics and faecal microbiome transplant have been shown to alleviate these diseases with varying success.

7. Prospects and Conclusion

The gut microbiome is a very complex entity that is associated with the host throughout life and affects its development, health and function. While all humans share more than 99% of their genome, the variation in their microbiome is enormous. Each person has a unique and stable (yet dynamic) microbiome which makes it challenging to make generalizations and design ubiquitous treatments. Other important aspects of the microbiome are – mapping its stability and resilience, characterizing the nature and strength of cross-feeding interactions among bacteria, the role of bacteriophages and gene transfer in the microbiome, and constructing the paradigm of heritability of the microbiome.

The complexity of the microbiome and the intricacy of its interactions are what makes it very fascinating. There are several papers describing various models of the human microbiome. I hope the information compiled through the course of this project aids in creating a model of the microbiome based on biological insights.

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