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The Interaction between Gut Microbiota and Pathogenic Bacteria: Implications for Human Health

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Annotation: The bacteria in the human gut—known collectively as the gut microbiota—play a vital role in promoting health. The ability of beneficial microorganisms in the gut to reduce the ability of harmful microorganisms to colonize the gut and cause disease is one way that they protect us. Understanding these interactions is critical if we are to be able to develop interventions to manage the composition of the microbiota in patients with infections, and potentially with chronic inflammatory conditions. The relationship between the human host and the bacteria that colonize it has long been perceived simply as the non-sterile host environment contesting the colonizing pathogen. Here, we describe an additional layer of interaction between the beneficial microorganisms that normally colonize the gut and the pathogens that can

cause life-threatening dysbiosis. We illustrate how the beneficial bacteria can coordinate their response to prevent these detrimental disruptions. We are beginning to probe the benefits of these different activities and gain insight on the potential of bolstering beneficial bacterial activity as an alternative strategy for pathogen management.

Over the years, germ theory has led to widespread control of harmful pathogens by chemical means, accompanied by the viewpoint that the majority of bacteria are harmful or of no consequence. However, research into the colonies of microorganisms living in and on humans, namely the human microbiota, has fragmented this view and now we appreciate that the thousands of species of microorganisms residing in our bodies play a crucial role in maintaining our health. When the microbiome becomes unbalanced, and the typical species profile is disrupted, dysbiosis may develop, leading to a potential loss of benefits from the microbiota. Many common pathologies in developed countries, including inflammatory bowel disease, obesity, type 2 diabetes, and atherosclerosis, have been associated with a loss of this microbial balance within the gut. Restoring the balance of the gut microbiota has, in some cases, been shown to ameliorate the resultant disease, but significant challenges remain that will need to be overcome if we are to exploit our beneficial gut bacteria in this way.

1. Introduction

The gut microbiota is a complex ecosystem composed of viruses, fungi, protozoans, and bacteria.

The commensal gut bacteria, specialized to colonize the gastrointestinal human tract, play an important role in human health and diseases, including inflammatory bowel diseases, colorectal cancer, obesity, type 2 diabetes mellitus, and disorders of the central nervous system. Recently, research into the gut microbial community has become one of the most interesting and promising fields in human health care. Moreover, the modulation of gut microbiota in different ways, such as probiotics and prebiotics consumption, also offers fresh hope in the treatment of human maladies. However, the ecosystem of the human body remains complex, and there are certain pathogenic and opportunistic bacteria which, when present, cause disease under specific conditions. Since changes in microbiota flora have broad implications for human health, studying the interrelationship between beneficial and pathogenic bacteria in the human gut may provide some clues to effective interventions.

Despite significant technological advancements in prevention and treatment, some bacteria and viruses are still causing a huge burden on human health around the world. To some extent, understanding the dynamics and factors that drive the interplay between the bacterial members of the gut could have an important role in the prognosis of human health and disease. Moreover, it is quite essential to understand how the changes in the composition and interactions among these multivariate bacterial populations lead to significant gastrointestinal and extra-gastrointestinal health effects. The imbalance between the gut microbiota and the host eventually results in a negative health state for humans, such as inflammation, obesity, and other diseases. It is an intriguing question how this negative result in the host arises based on the relationship between the beneficial and pathogenic bacteria. In addition, any efforts to study the interaction might promise the development of new goals for the treatment of human diseases. In this review, we focus on the interaction between gut microbiota and pathogenic bacteria and consider how this mutual effect influences the health status of humans. [1][2]

2. The Human Gut Microbiota

The human gut represents an ecological system hosting a complex community of microorganisms, including bacteria, protozoa, viruses, and fungi. Among these microorganisms, bacteria are the most studied. The large intestine harbors a diverse bacterial community mainly from the phyla Firmicutes, Bacteroidetes, and Actinobacteria, with a smaller proportion derived from the phyla Proteobacteria and Verrucomicrobia. Accordingly, a large variety of bacterial species have been detected in the human intestinal tract. Current literature supports the presence of approximately 1,000 to 1,150 different bacterial species in human feces. The human gut microbiota plays several important physiological roles, such as shaping the immune response, synthesizing essential vitamins, detoxifying prodrugs, providing functions that protect against pathogens, fermenting indigestible dietary components to produce short-chain fatty acids, and providing energy to colonocytes. The human gut microbiota is a dynamic and stable system but is also flexible and can be quickly altered. Each individual's gut microbiota is unique and can be viewed as an individual's "microbial fingerprint," formed according to diet, lifestyle, host genetics, metabolic status, exposure to environmental contaminants and drugs, and the gut abiotic environment, such as intestinal pH and osmotic pressure. All these factors contribute by influencing the presence of the different bacterial teams to form a "healthy microbiome" having an impact on the prevention of many diseases. Indeed, several alterations in the gut microbiome have been associated with human diseases and clinical disorders. While high microbiome biodiversity and richness are considered a hallmark of gut health, reduced gut microbial diversity has been causally linked to several pathological conditions, from diseases of the liver to the central nervous system, and several cancer types. [3][4]

2.1. Composition and Diversity

In the human body, complex communities of microorganisms live in several anatomic sites, particularly in the gut, mouth, skin, and urogenital tract. The most abundant and diverse microbial community is located in the gut, with estimates of over 38 trillion microbial cells. A large body of literature over the last two decades has described the importance of a dynamic and diverse

community of microorganisms in homeostasis as well as in various diseases. The colonization of the human gut starts from birth, and these gut microbial communities develop with time. Shortly after passage through the birth canal, babies have a microbial community similar to that of their mother's vagina. This community develops into a more adult-like community over the first years of life and then stabilizes. In adults, gut microbial communities fluctuate very little and are generally dominated by two bacterial phyla, the Bacteroidetes and the Firmicutes, accounting for 90% of the total microbiota. The relative abundances of these two phyla can vary among individuals, but they are generally at an approximate 70/30 ratio in healthy adults. The overall microbial composition and community structure within individuals is influenced by host genetics and environmental exposures. Metagenomic studies have shown that gut microbiota contributes to a variety of important metabolic and immune functions within the human host. Gut dysbiosis is used to describe changes in microbiota that can increase disease states. An enhanced understanding of the composition and diversity of the resident microbial community is a fundamental step towards understanding how the immune system interacts with other microbial communities, including those that contain pathogenic bacteria. [5][6]

2.2. Functions

1. Introduction—

2.2. Functions

The gut microbiota has numerous beneficial functions, the most important of which are listed above. Together, the gut microbiota contributes to the metabolism of undigestible compounds, such as fibres and proteins through fermentation, and it involves in the control of nutrient absorption and the regulation of lipid metabolism. Furthermore, vitamins such as B7 are synthesized by the gut microbiota, which is also a major source of vitamin K. Meanwhile, increasing numbers of reports indicate that the interaction between microbiota and their hosts involves the biotransformation of different secondary bile acids that influence bile acid pools, lipid metabolism, and the immune response through the modulation of host signalling pathways.

In addition, the gut microbiota maintains a mutually beneficial relationship with the host and serves a key role in immunomodulation through both the innate and adaptive immune systems. For example, the microbiota act to regulate the differentiation and abundance of host immune cells, as well as to produce antimicrobial components, such as IgA, and fight against pathogens to prevent the overproliferation of bacteria. A healthy gut microbiota might produce single-products, such as microbe metabolic substances or cytokines, involved in producing adhesion regions on the epithelium with the same neutralizing phages, which can also trigger signaling pathways in the surrounding tissue to attract pathogenic bacteria, protect against pathogenic bacteria, and regulate immune activity. Furthermore, because they compete for glucose and other needed substances in the gut, the microbiome can protect hosts against pathogenic bacteria. Interestingly, a close association might also be linked to the gut-brain axis using the vagus nerve, and this axis might affect mental health and other vital aspects of the developed world, such as the consumption of a diet, special drugs, and the high alcohol content of a flock. To evaluate the health condition of the population and assist in the diagnosis and treatment of different diseases, the link between the microbiome and diseases has been investigated. The above analysis has proposed that the evaluation of the "species", that is, the growth condition of the local community, has failed to fulfill the function of the gut microbiota. Specimen collection has great impact on the research topics and technical processes of the past study. Conventional state-of-the-art omics technologies result in so larger number of findings that fundamentally suggests people also need some invention of novel approaches to narrowing the search down to the main areas of interest. [7][8][9]

3. Pathogenic Bacteria in the Gut

Pathogenic bacteria are bacteria that reach the human host from the external environment and cause illness, which can result from either external sources or from the overgrowth of species that are

already contained within the human body. Pathogenic bacteria can be present in every part of the gut, including the stomach; however, the most extensive number of pathogens inhabit the gastrointestinal tract, especially the large intestine. These pathogenic bacteria reside within the lumen of the intestines and they often function in such a way as to resist removal methods of peristalsis and food absorption, to help ensure their continued transmission to new hosts. Most pathogenic bacteria have one or more of the following capabilities: adhesion to host cells; invasion of host cells; spread within host tissues; production of a toxin causing loss of water from the bowel, which helps the pathogen to escape from a host. [10][11][12]

The mass action of pathogenic bacteria reproducing in the intestinal lumen can lead to considerable inflammation reflected by fever and increased levels of inflammatory acute phase proteins in the blood during acute infection. In the long term, pathogens in the lumen can elicit a persistent immune response that elevates the levels of anti-inflammatory proteins. Pathogenic bacteria can also have systemic effects by spreading to tissues beyond the gut by breaking the barrier of the gut lining. Acute infection is generally cleared rapidly by the immune system, but in persons with low immunity or severe malnourishment, pathogen infection can lead to a variety of conditions. Despite the systemic control of these acute diseases by treatments such as antimicrobials or dehydration relief, infections with pathogenic flora can have long-term negative impacts on gut health. Gut conditions range from loss of balance in the overall microflora of the gut to reduced absorption of water and sugars by the loss of gut integrity caused by infection. In cases where the pathogen has destroyed a significant proportion of microvilli on the surface of the cells, there may even be an increased risk of being infected by another microorganism. An example of this is cholera patients having an increased risk of contracting another infection. [1][13][14]

4. Interactions Between Gut Microbiota and Pathogenic Bacteria

Gastrointestinal colonization is a major characteristic of gut microbiota, which contains a large number of bacteria, viruses, and fungi. As the biggest microbial reservoir of a human being, gut microbiota inevitably interacts with ingested pathogenic microbes in the gastrointestinal tract. The interactions can be generally divided into three categories: (1) competition for nutrients between gut microbiota and pathogens, (2) competition for ecological niches, and (3) the regulatory effects of gut microbiota on the intestinal microenvironment. Ensuring nutritional availability is the most direct way to establish a "cordon sanitaire" for the successful settlement of beneficial indigenous bacteria in the gastrointestinal tract by preventing colonization by pathogens. Once pathogenic bacteria successfully colonize the gastrointestinal tract and infect the host, they must navigate through gut microbiota to cause diseases. Thus, the next important question is: do the pathogenic bacteria compete with the beneficial microorganisms to gain a better-adapted position in the gut ecosystem or interact with these gut microbes during the pathogenic infection process?

Bacteria from the guts of conventional laboratory rodents and humans can significantly inhibit the growth of Salmonella Typhimurium. The beneficial bacteria employ several mechanisms to compete with the pathogenic bacteria either passively or actively, as shown in vitro and in vivo. First, many beneficial strains are associated with a reduced availability of nutrients essential for the growth and survival of pathogens. They may also directly inhibit pathogens by releasing bactericidal and bacteriostatic metabolites or fending off the pathogens from the mucosal surfaces by competing with pathogens for binding to epithelial cells and mucus components. Additionally, the flora can also produce antimicrobial proteins to limit the growth and colonization of Salmonella enterica. The colonization of O157 by the indigenous microbiota is also limited by competition for metabolic substrates and stimulation of the host response. Furthermore, the microbiota directly inhibits EPEC growth with the Type 6 Secretion System, which is important for the fitness of EHEC in the gut and can efficiently colonize the murine GI tract. Immune responses triggered by the gut microbiota to a certain extent determine the density and metabolic activities of the pathogens and may inhibit or limit the growth of pathogens to a concentration that can be controlled by the host. For example, some beneficial gut microbiota can improve the immune defense mechanisms of the host. Lastly, the growth advantage in the gut niche can influence the competition between commensals of the gut

microbiota and pathogens. Good metabolic performance can open an alternative metabolic niche in the gastrointestinal tract that cannot be fully utilized by the intestinal microbiota and can be occupied by pathogens. As a result, some opportunistic pathogens, such as Escherichia coli, often colonize the hosts. Thus, the regulatory effects of gut microbiota on the intestinal microenvironment can depend on complex cooperative and antagonistic interaction networks established between gut microbiota and pathogens. [15][16][17]

4.1. Competition for Nutrients

Gut microbiota and pathogenic bacteria exist in a competitive environment in the gut, and the acquisition of nutrients that are available only in limited amounts is an important target for competition between gut symbiotic bacteria. Competitive metabolic interactions can occur through the acquisition of a given nutrient modality by certain intestinal species, which in turn alters the availability and assimilation of this nutrient class. Competitive clearances act on the established gut microflora to establish resilient bacterial communities and compete with other later colonizing microbial strains. The competitive exclusion principle assumes that beneficial commensals suppress the growth of pathogens by consuming nutrients and/or secreting compounds that block pathogenic uptake. Additionally, diversity in the microbial community can guard against those pathogens, because a healthy, diverse population would be difficult to displace.

Several pathogens rely on exogenous sources of essential nutrients for their growth, and they must compete with the microbiota for those nutrients in the human gut. Intracellular selenium utilization is essential for transmission of the intracellular pathogen Salmonella enterica serovar Typhimurium within the gut, and other trace elements are essential for S. Typhimurium systemic infection. This means that the presence of selenium and trace elements in the diet increases the risk of Salmonella colonization in the gut. Several studies also revealed the effects of dietary nutrients on infection with other pathogens. Dietary fiber and amino acids in food influence the environment and immune responses in the gut, and the metabolites derived from fiber perform anti-microbiota effects. Nutrient availability during infection can also influence the pathogen burden and pathogen clearance. These studies indicate the cross-regulation of microbiota and colonization by pathogenic bacteria in the gut through nutrient competition. [18][19][20]

4.2. Immune Responses

The immune system plays a key role in shaping the outcome of infections with pathogenic bacteria. Gut microbiota have been shown to help the host fight infections through different mechanisms. Interactions between gut microbiota and the immune system allow for several protective functions. Indeed, the immune system can help to maintain microbiota homeostasis by restricting the invasion and penetration of invading bacteria and enhancing antibacterial defenses. Conversely, the microbiome plays a pivotal role in influencing immune development during the neonatal phase and also in conferring immune protection against infections. For early infection protection, gut microbial diversity is crucial for the proper development and function of the mucosal and systemic immune system. Gut microbiota are thought to enhance the neutralization of dangerous bacteria through specific and non-specific mechanisms. Germ-free mice succumb earlier to infections with common pathogens, showing a blunted response and an inability to rapidly recover as compared to conventional mice. Moreover, differentiated immune cells are impaired in their abilities to be recruited to infected tissues in germ-free mice due to altered production of cytokines and chemokines. In humans, microbiota can affect inflammation and susceptibility of hosts to enteric pathogens.

Conversely, the loss of diversity or presence of dysbiotic microbiota results in susceptibility to infections. Indeed, to prevent excessive inflammatory and pro-inflammatory responses and establish controls for commensal microbiota, the mucosal immune system has evolved immune tolerance, facilitating the colonization of commensal bacteria in the gut. Superinfections by enteric pathogens occur preferentially in patients who take a broad spectrum of antibiotics or proton pump inhibitors, thus arguably having lost their beneficial microbiota and their colonization resistance properties.

Indeed, immune tolerance can promote superinfections because it can prevent microbial infection-driven inflammation. In turn, inflammation is triggered by host pattern recognition receptors that recognize the products of pathogenic bacteria. Although mostly not definitive, results from co-housing and direct modulation of gut microbiota highlighted that, in most cases, the protective properties of microbiota are very much dependent on enhanced resilience and immune responses. Extrapolating from preclinical results to human therapy, the neutralizing abilities can stimulate the host's defense network. By understanding how commensal microbiota interferes with the infective capabilities of unwanted bacteria, more fine-tuned and efficacious strategies aimed at promoting microbiota can be designed. [21][22][23]

5. Implications for Human Health

Imbalances in the gut microbiome composition and function have been linked with a range of diseases, including local diseases such as gastrointestinal disorders and systemic diseases such as metabolic disorders and cardiovascular diseases. The gut microbiome is also known to have an impact on drug interactions with the host. This review has highlighted some of the ways in which commensal bacteria may help underpin a healthy and disease-protective environment in the gut. It is increasingly recognized that fecal transplant of live commensals can enable correct gastrointestinal tract development and protection, which has potential implications in prevention and treatment for gastroenteritis, both caused by the increased protection from viral pathogens and reducing the shedding of foodborne bacterial pathogens. Given the diversity of pathogenic bacteria that inhabit the gastrointestinal tract, supporting a healthy pathogen-defense microbiome using naturally occurring commensal bacteria or a personalized treatment is a true personalized medicine approach, as opposed to the use of broad-spectrum antibacterial agents, commonly prescribed for infectious gastrointestinal disease.

Gut lifestyle, including culture and diet, has a profound effect on the composition of the microbiota and metabotypes of an individual, who can influence the development of obesity, type 2 diabetes, autism, and graft versus host security, and likely many other clinical disorders. The use of microbiota-based therapeutics to manage chronic human diseases is high on the research agenda of many scientists. Preliminary data in the field of probiotics and prebiotics suggest a diet that contains probiotics that can not only limit exposure to gastrointestinal tract pathogens via competitive exclusion commensals but further lower pathogenesis due to the downregulation of specific virulence factors of a pathogen by these gut generic commensals, which are different from the usually considered competitive gastrointestinal tract exclusion mode of action of a classic gastrointestinal tract commensal. The next advent of intervening with gut health via dietary means, probiotics, and microbial metabolic products has exciting hope for personalized medicine, thus providing a guide of how to protect and alter, via diet, the composition of the gut environment enabling health benefits. For example, signature microbiota could be correlated with low risk of developing type 2 diabetes and a virus, and we may gain new insights into the role of specific obligate gastrointestinal tract residents that convey significant benefits to an individual. These will no doubt be impacted by genes, lifestyle, infection history, specific healthy gut environment, and the resultant gut metabolic products all regulated by the gut generic microbiota-microbe interactions within the gut environment. [24][25][26]

6. Conclusion

In conclusion, we have summarized the research on the interaction between gut microbiota and pathogenic bacteria. The gastrointestinal tract is a complex ecosystem that contains more than 10^13-10^14 commensal microorganisms, which form a "dynamic equilibrium" with the human body and are crucial for maintaining health. This delicate balance is an essential component of optimal health, and perturbation leads to diseases. Healthy gut microbiota contribute to resistance to enteric pathogens. Research shows that the introduction of a resident of human microbiota can inhibit the initial or transient colonization of some varieties of pathogens. Pathogens can benefit from a resilient gut microbiota and use beneficial microbes as a vector for colonization and

transmission. The efforts of beneficial microbes to inhibit invading pathogens are also considered a part of colonization resistance and serve as important factors that prevent host infection.

We are intrigued by the gut microbiota's supportive role in minimal pathogen attachment, growth, and colonization under normal conditions that work as a barrier. This area of interplay between commensal and pathogenic bacteria may open new therapeutic avenues. In recent years, FMT has grown rapidly as a new measure for the gut microbiota. Further studies are needed before FMT and probiotics can be confirmed as effective tools for good health. In the meantime, a healthy diet and lifestyle will help maintain a prosperous intestinal flora. It is of great importance to complement knowledge of various disciplines and develop comprehensive strategies by joining our forces to achieve ideal gut health. Clearly, the future of this field is extremely promising. Awareness also needs to be raised in the public to draw attention to the impact of a healthy lifestyle on their lifestyle-related health.

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