

The emerging role of the microbiome in precision medicine: An overview

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Abstract

The advent of precision medicine has promoted an influx of research relating to the identification of patient-specific factors, both genetic and acquired, which could be targeted and manipulated in the context of disease. The microbiome is a particularly good example of a potential target of these measures, as it represents a diverse array of unique, modifiable factors, known to play an important role in both normal human physiology and the development of pathology. Given this, the contribution of the microbiome to human disease, as well as the potential utilization of microbial modulation in prevention and treatment, is a burgeoning area of study. In this review, we summarize the recently established correlations between intestinal microbial dysbiosis and disease pathogenesis in the fields of cardiology, oncology, psychiatry, and immunology, highlighting the specific organisms that have been identified as potential therapeutic targets. However, the practicality and potential harms involved in screening for dysbiosis and manipulating the microbiome need to be carefully assessed before these findings can truly be applied to the world of personalized medicine.

Introduction

The role of the microbiome in human health has been one of the most rapidly evolving fields of medical research in the past several decades. With commensal bacteria making up a staggering 57% of our total body cell count by recent estimates, the microbiome is increasingly being recognized as a distinct organ.¹ The impact of commensal flora, ranging from the widely studied intestinal microbiota to the organisms lining the respiratory and genitourinary tracts, has been studied across many fields of medicine. These microorganisms have been found to have an incredible number of interactions with every body system, from neuroendocrine effects on the central nervous system to the stimulation and modulation of our immune systems.² The more we understand about the interaction of the microbiome and its host environment, the clearer it becomes that these microorganisms play an integral role in the development and maintenance of normal physiological functions.

Given our emerging understanding of the importance of these interactions to the healthy functioning of the human body, there inevitably comes the question of the role of the microbiome in disease. Can the interplay between the host and microbiome have an adverse impact on overall health? Where does one draw the line between “healthy” gut flora interactions and pathogenic behaviour? What role does microbial dysbiosis, or the imbalance of microbial composition in favour of more harmful organisms, play in disease pathogenesis?

The remainder of this review will serve as an update on the progress of our understanding of the role of the intestinal microbiome, the most thoroughly researched portion of our commensal flora, in various diseases. While the gut microbiome has been found to play a role in nearly every field of medicine, we will specifically focus on its involvement in the fields of cardiology, immunology, oncology, and psychiatry, as well as the evidence surrounding the correlation between specific bacteria and the initiation and progression of illness. Finally, we will consider the potential for microbial manipulation—whether one day, the knowledge of a patient’s specific microbial balance may play a role in the prevention and treatment of disease.

Role of microbiota in various fields of medicine

Cardiology

The role of the intestinal microbiota in cardiovascular disease has been a point of great interest in recent years. These studies have investigated variances in microbial composition in patients with cardiac risk factors (including obesity, diabetes, hypertension, and dyslipidemia) and have also utilized animal models to determine to what extent the manipulation of flora could modulate the course of their diseases. One study found that the bacterial phyla Bacteroidetes (including Bacteroides and Prevotella) and Firmicutes were disproportionately represented in the flora of obese subjects (both mice and humans), proposing a mechanism by which these specific bacteria were capable of increased energy harvesting from the diet. Even more strikingly, they found that over time, gut-sterilized mice transplanted with a sample of the flora from obese individuals developed significantly more body fat than their lean-transplanted counterparts.³

Similar findings were established in the context of hypertension. Hypertensive patients were found to have significant overgrowth of Prevotella and Klebsiella species; furthermore, transplantation of the hypertension-associated microbiota into germ-free mice was also found to significantly raise blood pressure, demonstrating a more causal role for these microorganisms in the pathophysiology of the disease.⁴ There have been several studies aiming to characterize the precise mechanism by which these specific bacteria impact metabolism, implicating a set of pro-inflammatory metabolic functions that may contribute to atherogenesis. On the other hand, there is also evidence that the fat-metabolizing properties of certain phyla (particularly studied with Lactobacillus-containing probiotics) may actually provide an atheroprotective effect.⁵ Thus, in further understanding the role of different bacteria in the pathogenesis of (and protection from) atherogenesis, we may develop strategies to specifically modulate each patient’s microbiome for both the prevention and treatment of cardiovascular disease.

Psychiatry

There has been a great deal of interest surrounding the potential role of the microbiome in the pathogenesis of psychiatric conditions. There have been many studies demonstrating the physiologic

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connection between the microbiome and the mind through the relationship between the enteric and central nervous systems. It has been hypothesized that psychiatric pathology could be fueled by neuroendocrine dysregulation secondary to bacterial production of neurotransmitters. The pioneering studies in this field aimed to characterize the difference in microbial composition between healthy subjects and those with mental illness. These studies illuminated several *Lactobacillus* and *Bifidobacterium* species, often depleted in patients with depression and anxiety, as key players in the body's stress response via the modulation of the hypothalamic–pituitary axis (HPA) through the vagus nerve.⁶ A more direct link demonstrating the effect of microbial dysbiosis on mental illness was demonstrated in a murine model. Transplanting the microbiome from depressed human patients into rats was found to induce significant behavioural changes, including an increase in depressive symptoms (as measured by the sucrose preference test, in which a decreased level of voluntary sucrose ingestion is interpreted as anhedonia) as well as anxiety-like behaviours (measured through validated experimental methods to gauge anxiety in rats, such as the elevated plus maze and the forced swim test).⁷ These results raised the interesting possibility that the altered microbiome itself may be a direct player in the pathogenesis of psychiatric disease, as opposed to simply reflecting a by-product of the disease state itself.

In an attempt to apply these findings to the clinical world, there have been several recent studies demonstrating the positive effect of microbial modulation on mental health. Probiotics containing the key contributory bacteria *Lactobacillus rhamnosus* (often depleted in anxiety and depression) were initially tested in murine models and were found to decrease anxiety/depressive behaviours, likely by inducing changes in GABA receptor expression in the hippocampus and prefrontal cortex.⁸ Follow-up human trials with a probiotic containing a separate *Lactobacillus* strain (*L. casei* strain Shirota) demonstrated a decrease in salivary cortisol as well as the physical manifestations of anxiety in academically stressed medical students, and another study demonstrated that a mixed *Lactobacillus/Bifidobacterium* probiotic cocktail was able to decrease cognitive reactivity (including rumination and aggression) to sad mood in healthy subjects, suggesting a possible role for probiotics in the prevention of depression in its early stages.^{9–10} However, the human trials of probiotics have so far been limited in scope, and there has yet to be a systematic trial definitively demonstrating the role of probiotics in addressing or preventing mental illness. Nonetheless, the data so far have been supportive of a causal relationship between intestinal bacterial composition and mental health. With a greater understanding of the specific organisms responsible for contributing to these diseases, this research may enable microbial modulation (including the probiotic supplementation of protective bacteria) to become an alternative treatment modality in psychiatric illness.

Immunology

Given that the intestinal microbiome is involved in countless interactions with its host's immune system, the presence of a relationship between microbial composition and immunologic disease is unsurprising. The most established correlation has been in the context of inflammatory bowel disease (IBD). Organisms such as *B. fragilis*, segmented filamentous bacteria, and mucosal-adherent *E. coli* have been implicated in disease progression, primarily through toxin-mediated mucosal barrier disruption and pro-inflammatory mucosal invasion.^{11–12} Treatments targeted at favourably shaping the flora

have already been trialled in mouse models; treatment with low-dose penicillin in early life, aimed to specifically target the harmful segmented filamentous bacteria, was found to protect against the development of drug-induced colitis.¹² There has been a selection of other postulated IBD treatments targeted to work by similar mechanisms, including other specific antibiotics (including metronidazole), probiotics, and fecal transplant.¹³ At this point in time, there has been no clear therapeutic advantage elucidated in human trials; however, there is considerable room for advancement in this field. Using a more precise approach and considering the specific factors in each patient's microbial profile may enable us to make more targeted efforts to therapeutically modulate the microbiome. Additionally, more research into the role of these microbial-modulating measures in healthy subjects may help identify those at risk for IBD development and ultimately lead to clinical benefit through prevention.

Oncology

The role of the intestinal microbiota in the pathogenesis of cancer is less well characterized and is still in the early stages of correlational studies. However, there have been several studies which have demonstrated the potential of the microbiome to promote a pro-inflammatory state, which in turn is known to be a predisposing factor for carcinogenesis. One notable example is hepatocellular carcinoma (HCC), which has been long known to have a significant association with chronic hepatic inflammatory changes and fibrosis. Given that the hepatic circulation receives the majority of its blood supply from the intestinal venous system, the liver is exposed to a high concentration of gut microbial by-products, including pro-inflammatory bacterial antigens and toxins.¹⁴ An animal study conducted in mice with chronic hepatic injury demonstrated that exposure to common bacterial ligands (including lipopolysaccharide) suppressed apoptosis and promoted further proliferation in HCC tumours.¹⁵ Furthermore, intestinal sterilization during hepatocarcinogenesis reduced overall tumour size by up to 70%, demonstrating the potential role of microbiological modulation in suppressing HCC development. Additionally, there have been many studies linking intestinal microbial architecture with colorectal cancer (CRC), implicating organisms such as *S. bovis*, *B. fragilis*, *E. faecalis*, and *E. coli* as being disproportionately represented in these patients' microbiomes.^{16–17} Moreover, these populations have also been directly implicated in carcinogenesis; certain *E. coli* populations harbouring a DNA-damage-associated pks mutation, enriched in patients with CRC, have been found to promote colon adenocarcinoma proliferation.^{18–19} Similar correlational studies have been done for pancreatic, lung, and squamous cell carcinomas. While there is still much more to be discovered before these study findings can be applied for therapeutic intent, this research is certainly laying the grounds for the exploration of targeted, microbe-specific approaches that may contribute to the prevention (or even treatment) of multiple forms of cancer.

Discussion

The balance of the microbiome has been shown to play a critical role in both the maintenance of health and the progression of disease across many fields of medicine. The key question that remains is whether this knowledge can be applied towards the prevention and management of these diseases. Analyzing each patient's microbial profile in order to identify contributory dysbiosis could offer new targets for therapy, as well as an opportunity to identify those at risk for developing disease. Microbial modulation may represent an entirely new frontier in the

expanding world of precision medicine, providing a new lens with which to guide individualized patient care.

However, much more research needs to be done before this approach could become a reality in the clinical world. To begin with, we need a more complete understanding of the specific microbial imbalances that may have a causal (or protective) role in disease before we can develop targeted treatments to address these factors. As previously discussed, the microbiome plays a critical role in normal physiology and disease prevention, so any intervention aimed at re-shaping the microbial balance could run the risk of disrupting its normal functions. Antibiotic treatments will need to be carefully considered, as the potential risk of impairing normal floral function (or more significantly, of enabling the notorious *C. difficile* infection) could outweigh the potential benefits of intervention. Furthermore, there is the issue of identifying patients whose microbial composition puts them at risk for various diseases. It is unclear which factors would prompt a physician to assess a patient for intestinal dysbiosis, and moreover, as of now, the tools with which this could be done (including genetic sequencing analysis from fecal samples) are unfamiliar, expensive and of questionable accuracy.²⁰ We would need to develop robust guidelines for identifying patients who would benefit from screening, as well as to standardize the analysis of microbial risk factors, whether this involves holistic sequencing of the entire microbial architecture or screening for biomarkers of pathogenic bacteria. Ultimately, this entire process would need to be subjected to the rigorous scrutiny of cost-effectiveness, as with every screening tool.

Conclusion

In short, as attractive as the microbiome is as a novel therapeutic target, there is still a significant amount of research that needs to be done before translating our basic understanding of its role in pathogenesis into clinical practice, both in identifying actionable microbial targets as well as in making these measures a practical reality. Nonetheless, given the strong evidence which has been gathered so far, we may well be looking at a future where a combination of antibiotics, probiotics, and specific microbial-targeted therapies could form its own unique branch of personalized medicine.

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