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Personalized Medicine and Health Promotion: the Gut Microbiome's Key Function

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Abstract:

It has been known for quite some time that gut microbiota plays an important role in human health and illness. Recent years have seen a surge in interest in the human gut microbiota, and the advent of metagenomic investigations has greatly aided our understanding of the resident species and their potential uses. The human digestive tract is home to billions of bacteria, making up the varied gut microbiota. At birth, the gut microbiome begins to take shape and proliferate, and throughout life, numerous genetic, dietary, and environmental variables will shape and multiply this community. Alterations to the gut microbiota's structure and function may affect digestion, metabolism, and the immune system. Meanwhile, personalized medicine, a new therapeutic approach, has opened a new door in the medical sciences, and the link between the microbiome and personalized medicine is one of the most intriguing areas of study going forward. Since the link between this two axis is new, there are few research on it. Therefore, in this review study, the relationship between the gut microbiome, drug interactions, disease progression, and personalized medicine has been discussed.

INTRODUCTION

Biomedical research has mostly focused on identifying and targeting disease-associated pathways to develop pathway-targeted therapies. In multi-factorial disorders, this approach ignores inter-individual diversity in disease emergence and treatment outcome (1). Individual-specific data and its impact on human physiology have been disclosed by the genetic a uprising allowing personalized or precision medicines. Oncology research over the last decade has enabled human genome screening to reveal a range of germ-line encoded mutations, permitting individual-specific preventative and treatment options. Precision medicine has enabled patient categorization based on therapy response and adverse events, as well as genetic contribution to illness etiology (2). The microbiome has recently gained recognition as a key factor to the wellness of humans, and we highlight why the microbiome is an essential component of the precision medicine project in the present article (3).

The microbiome is a complex network of microorganisms that reside inside and on the human body, including their genes and collective activities. A healthy microbiome has a set of shared traits that distinguishes it from non-healthy people; hence, knowing the microbiome's distinctive qualities may aid in the detection and identification of disease-associated microbiomes (4). The healthy person's microbiome is very varied, with a significant amount of beneficial microbes that can withstand the changes that occur during each period of physiological stress; whereas the disease-associated microbiota is less broad, with a lower number of beneficial bacteria that leads to disease in the presence of infection (5). The key issue that researchers are working on is understanding the possible features of microbiome diversity among people. Traditional techniques, such as culture, have produced very little information in this area, but modern approaches, such as NGS, have introduced an adequate knowledge of this population and their combinations, as well as identified the archaea, bacteria, and viruses in the body (6). Disturbance in microbial ecology has been linked to a variety of disorders, including diabetes and inflammatory bowel disease; the human microbiome may be utilized as a major diagnostic indicator, and researchers are also focusing on its therapeutic significance. Although the microbiome is an interesting target for generating personalized

treatment methods, finding strategies for developing reliable and reproducible microbiome-based detection and treatment solutions remains a challenge (7). The scientific community's significant effort, along with its partnership with fast-rising biotech businesses, provides a positive prognosis for creating microbiome-dependent and microbiome-targeted diagnostics and therapies (7).

Co-metabolism between microbiota and the host in drug metabolism and toxicity

The direct and indirect interactions between gut microbiota and xenobiotics on medication pharmacological and toxic effects may cause drug failure and patient mortality. Thus, precision medicine requires an understanding of how gut microbiota affects medication effectiveness and toxicity (8). We examine how gut microbiota affects therapeutic effectiveness and toxicity and the processes. Humans spend their whole lives surrounded by essential microorganisms, which alter their capacity to detoxify xenobiotics (including medications and food substances) through microbiota-host co-metabolism. Phase I and phase II reactions are part of the host detoxification systems (8). Phase I metabolism, which includes oxidation, reduction, and hydroxylation, is primarily mediated by cytochrome P450 (CYP) enzymes in the liver, stomach, and other tissues to improve xenobiotic excretion in urine by enhancing the polarity of foreign substances. The conjugation process, which includes glucuronidation and sulfonation, is part of phase II metabolism (9). To promote urine excretion, foreign chemicals are conjugated with endogenous molecules via host enzyme transfer mechanisms. Sulfotransferase (SULT), uridine 5'-diphospho-glucuronosyltransferase/UDP-glucuronosyltransferase (UGT), N-acetyltransferase (NAT), and glutathione S-transferase (GST) are among the phase II enzymes. Over 70% of the top 200 medications given are processed in the liver, while approximately 25% are removed in the kidney11, and approximately 50% of pharmaceuticals are metabolized through the P450 enzyme system, underscoring the importance of the P450 enzyme systems in drug metabolism (9). In addition to the host drug metabolism system, the gastrointestinal microbiota plays significant roles in drug metabolism via the release of microbial drug-metabolizing enzymes and microbiota-host co-metabolism (10). While the effects of intestinal microbiota on drug metabolism have been studied for many years, only about 40 drugs and natural products have been thoroughly examined to date. The gut microbiota usually modulates the oral drug bioavailability or half-life by altering the capacity of drug-metabolizing enzymes or expression of genes involved in drug metabolism in host tissues. The oral drug bioavailability or half-life by altering the capacity of drug-metabolizing enzymes or expression of genes involved in drug metabolism in host tissues (11). Furthermore, since many illnesses are connected with gut dysbiosis or vice versa, the individual composition or function of gut microbiota is likely to be impacted by environmental variables such as foods and antibiotics, or the host's physiological condition. Individual differences in response to drug therapy are associated with differences in gut microbiota (11). For example, digoxin, an originally isolated cardiac glycoside from foxglove plants, is a typical example of a substance that can be inactivated by intestinal microbiota. Utilizing digoxin in a clinical setting is challenging due to the drug's narrow therapeutic range. In about 10% of patients, a significant quantity of digoxin is converted into dihydrodigoxin, a cardio-inactive metabolite. The conversion of digoxin by gastrointestinal microbiota in patients can account for the inactivation of more than fifty percent of the administered digoxin, which substantially affects the drug's bioavailability and clinical toxicity (12).

The Role of the gut microbiota in drug-drug interactions

Drug-drug interactions may also be attributed to gut microbiota. Antimicrobial drug resistance has become a severe worldwide health concern, contributing to a rise in infection-related deaths. In the clinic, the use of antibiotic combinations is promoted to treat multidrug-resistant bacterial infections; however, their effects on microbiota are unknown (13). Profiling of roughly 3,000 antibiotic, human-targeted medication, and food additive combinations revealed that 70% of drug-drug interactions are species-specific, 20% are strain-specific, and antagonism is more prevalent than synergism. Aside from antibiotics, the most notable example of medication-drug interactions involving gut microbiota is the co-administration of the antiviral medicine sorivudine with the anticancer drug 5-fluorouracil (5-FU) or 5-FU prodrugs, which has resulted in fatalities and severe adverse effects in Japan. Sorivudine may be converted by gut bacteria into (E)-5-(2-bromovinyl) uracil (BVU). BVU inhibits liver dihydropyrimidine dehydrogenase, a catabolic enzyme responsible for 5-FU detoxification. Thus, combining sorivudine and 5-FU raises circulation 5-FU levels, resulting in 5-FU-associated mortality (14).

The function of microbiome metabolites in disease progression

With the emergence of sophisticated illnesses such as cancer, the relationship between environmental, microbiome, and cancer consequences may become quite complex. Cancer is indicated by changes in cell metabolism and inflammation (15). Even if host-microbiome reactions to cancer are not viewed as a necessary event, the presence of microbial compounds

in certain malignancies, such as colorectal cancer (CRC), can be indirectly significant. Cancer cells communicate with bacterial quorum sensing peptides (QSP) according to in vitro research (16). Bacillus-derived QSPs can induce invasive tumor cells in a process called Epithelial mesenchymal-like (EMT-Like) (involved in CRC metastasis) when the bacteria are under duress. Under these circumstances, QSPs engage in both metastatic and angiogenesis activities. In some kinds of cancer, microbial activity may limit treatment efficiency or influence tumor formation. Lifestyle and food are other important factors in shaping the microbiome (17). Furthermore, the creation of numerous metabolites by gut microbiota is efficient in cancer-promoting and cancer-protective induction; however, distinct drivers remain unknown. Microbiome-derived metabolites have been shown to have the ability to contribute to cancer development (18). Food is a rich source of these metabolites; for example, high-fat and high-protein meals are common in the current Western diet, which is one of the risk factors for cancer incidence. Bile acid (BA), on the other hand, is a signaling molecule related to metabolic balance. Specific enzymes convert BA to SBA, which may be carcinogenic (19). In vitro, investigations have demonstrated that 1 hour of exposure to SBA compounds such as deoxycholic acid (DCA) and lithocholic acid (LCA) causes substantial DNA damage with a dose-dependent behavior. According to studies, the African-American population had a higher incidence and mortality rate from CRC than the Native American population (19). The microbiomes of these two groups (African-American and Native American) were analyzed, and the African-American group was plentiful in Bacteroides species, while the Native American group was abundant in Prevotella species. Furthermore, the encoded genes for SBA and fecal SBA in the first group had higher levels, whereas short-chain fatty acids were higher in Native Americans, and thus studies reported that phenotypic and developmental differences of a specific disease are possible, and these differences are primarily due to different diets and microbiome combinations (20). Saccharolytic fermentation is induced by fiber-rich diets owing to several kinds of gut microorganisms that create short-chain fatty acids, notably acetate, propionate, and butyrate (21). Bacteroidetes, for example, contain high quantities of acetate and propionate, while Firmhicute bacteria have high levels of butyrate. Butyrate is linked to some anti-cancer actions. Butyrate, for example, may promote S-phase ablation in colorectal cancer cells, resulting in growth suppression through apoptosis and the production of cell regulators such as P21 and cyclin B1. Interestingly, the butyrate effects are cell-dependent; in normal cells, butyrate increases proliferation as a source of energy, but in cell lines, butyrate suppresses proliferation and produces death (21).

The microbiome's involvement in precise diagnosis and personalized therapy

Precision medicine and personalized nutrition are now recognized as potential techniques for improving health outcomes by adapting treatment tactics and dietary regimens to a person's unique genetic, environmental, and lifestyle characteristics (22). These methods seek to shift away from the conventional one-size-fits-all approach to health care and nutrition in favor of offering individualized treatment that is suited to the individual's particular requirements. The function of the microbiome in improving health is a prominent topic of research in this discipline. The process of detecting and describing an individual's unique microbial profile, known as microbiome analysis, may give important insights into an individual's health condition and be utilized to build individualized therapies. Microbiome analysis, for example, has been used to identify particular microorganisms related to various health disorders such as inflammatory bowel disease and type 2 diabetes. This data may be utilized to create targeted therapies based on the individual's unique microbial profile (22).

Various data show that disruption of the microbiota-host interaction is linked to a variety of disorders, including IBD, diabetes, cirrhosis, and colorectal cancer (23). Recently, studies on the interactions between bacteria and cancer treatment drugs have been conducted, and the findings suggest that interactions of the bacteria mediated by the immune system are required for drug efficacy, even though little information is available on the effects of human microbiome combinations and treatment outcomes in cancer patients (24). Many studies have indicated that patients can react to or not respond to immunotherapy based on gut microbiota combinations, which may be taken into account when evaluating medication interactions. Furthermore, the importance of the gut microbiome as a biomarker for illness phenotype, prognosis, and treatment response is extensively established in connection to the modification of microbial population structure in diverse diseases (25). Microbiome analysis sheds light on the intricate relationships that exist between microbial populations and human health, as well as the function of the microbiome in disease genesis and progression. Microbiome analysis, for instance, has been used to discover distinct microbial communities linked to illness states, such as the depletion of certain bacterial species in individuals with inflammatory bowel disease (26). This knowledge may be utilized to create novel diagnostic tools and medicines that target the microbiome, eventually enhancing disease control and patient outcomes. A

better knowledge of the components that contribute to illness genesis and progression may be gained by microbiome study. Microbiome analysis drives the development of novel diagnostic tools and therapies that target the microbiome by finding distinct microbial populations that are related to disease states. For example, fecal microbiota transplantation (FMT) is a microbiome-based treatment that is beneficial in treating recurrent Clostridium difficile infection, a disease that is often resistant to standard antibiotic regimens (27). FMT includes the transfer of fecal matter from a healthy donor into the patient's gastrointestinal tract to restore a healthy microbiome composition and function. FMT has been found in studies to be very successful in treating recurrent Clostridium difficile infection, with cure rates as high as 90%9-11. Microbiome analysis, in addition to FMT, informs the development of additional microbiome-based medicines (27). Probiotics, prebiotics, and synbiotics are all examples of treatments that try to change the makeup and function of the microbiome. Microbiome analysis can be utilized to determine specific microbial communities associated with disease states and to select probiotic strains that can restore a healthy microbiome composition and function. Similarly, prebiotics and synbiotics can be utilized for boosting the growth of beneficial microbial communities and recover a healthy microbiome structure and function (27).

Other intriguing findings revealed that Akkermansia, Faecalibacterium, and Bifidobacterium strains are connected with anti-inflammatory reactions, which is an immune system arm that inhibits over-response activation and leads to the development and maintenance of homeostasis. For example, the relative fall of A. muciniphila in the gut has been linked to a variety of disorders, including IBD, type II diabetes, and others. Similarly, F. prausnitzii reduces intestinal inflammation caused by the generation of particular metabolites generated from host cells or bacteria in the intestines and peripheral circulation (28). All of these researches indicate that precision medicine, including the gut microbiome, has therapeutic promise.

Improving health by targeting the microbiome

The microbiome's appealing feature is its flexibility and ability to change portions of the microbiome, in addition to acting as detecting and therapeutic biomarkers and influencing therapeutic responses to drugs (29). Antibiotics have typically been employed to target microbial populations, that are necessary as well as efficient for managing systemic diseases induced by invasions of pathogens. However, the negative impacts on microbial community structure alongside human side consequences make targeting the microbiome as precision medicine less appealing. In addition, there is still a need to develop pathogen-targeted medicines by identifying specific targets that limit the antibiotic's reach. A novel technique includes mining the microbiota for potential therapies through recognizing specific behaviors that influence the host, allowing us to modify the microbial community's functioning without harming the microbial population itself. One example is the role of tri-methyl amine oxidase (TMAO) in atherosclerosis, as well as the inhibition of microbe TMA lyases by 3, 3-dimethyl-1-butanol (DMB), which lowers bacterium TMA production in an excessive choline diet-fed mice animal. Even though precise route focusing on, DMB generated microbiome modifications, demonstrating the complexities of microbial relationships within these natural environments. Probiotics, prebiotics, and nutritional therapy are among more ways to address the microbiome (31, 32).

Early probiotics (living microorganisms that provide health advantages to the human body when eaten in proper amounts) were dominated by organisms of the genera Lactobacillus and Bifidobacteria, but they lacked precision in terms of addressing a purpose in biology (33). In comparison to a placebo, a recent comprehensive review of medium to superior controlled research using probiotics indicated no major impact on gut flora. The clinical effectiveness of present-day probiotics is hard to evaluate because of small sample sizes hindering power, variation in bacteria strains used, endpoints, treatment duration, and molecular methods for studying the gut microbiota, storing of initial parameters like eating habits, and the absence of robust preliminary mechanistic information (33).

Because diet is the major source of nutrition for organisms, it has a considerable impact on the microbiome. Dietary interventions may be divided into three groups. Using microbiome markers to improve dietary interventions, customizing the diet depending on the microbiome, and changing the microbiota via nutrition are all examples of how to use microbiome indicators to optimize dietary interventions. Dietary therapy that lower fermentable oligo-, di-, monosaccharides, and polyols (FODMAP) have been shown to aid persons with IBS (34). Continuous use of such a measure, on the other hand, may diminish microbial short-chain fatty acid production, which might be harmful to individuals.

New research revealed microbial indicators that indicate a good response to FODMAP72, which has the potential to enable therapeutic optimization and the reduction of unwanted side effects in patients who are less likely to react. Considering the importance of the microbiome in dietary metabolism of nutrients, one critical function of the intestinal microbiome is its influence on host reactions to food components (35). In an excellent investigation of 800 participants, Zeevi et al. discovered considerable interpersonal

variability in post-prandial glycemic reactions to dietary components. They observed that incorporating microbiome-derived characteristics significantly improved the accuracy of the prediction of glycemic reactions in the forecast engine used to create these forecasts. It is worth mentioning that modifications in the intestinal microbiota in response to a comparable dietary change may vary based on a person's microbiome (35). Considered together, it is obvious that, while the relationship between food and the gut microbiota is multifaceted, it is critical in defining host responses to diet and anticipating alterations in the microbiome in the face of diets.

CONCLUSION

In this work, we underline the importance of integrating the gut microbiome as a part of customized or precision medicine to improve detection, reduce illness danger, and increase early identification and treatment. Microbial fingerprints have the potential to be precise, non-invasive, accessible, and cost-effective tools for phenotyping, degree of severity, and prediction in disease diagnosis. Because the microbiome is involved in the metabolism of several chemical compounds, it is a key component in affecting medicine accessibility, efficacy, and toxic effects, making it necessary for devising personalized therapy regimens.

Last but not least, the ability to alter the microbiome makes it attractive for developing personalized therapeutic approaches through precise microbiome targeting. Treatments for multi-factorial diseases including inflammatory bowel disease, obesity, and type 2 diabetes may be developed using strategies that target specific microbial pathways appropriate to a person's microbiome. The next frontier in the field of customized healthcare will be the development of precision probiotics through genetic engineering, next-generation prebiotics as a result of a greater understanding of metabolism interactions among members of the microbial environment, and personalized diets tailored to a the individual's microbiota. The future is generally quite positive, but there are also considerable challenges. We must create standardized collecting, sequencing, and analysis protocols that improve the repeatability of data across centers and reduce biases in their interpretation if we are to apply microbiome-based diagnostics and therapies. The bulk of present research is focused on illness association; however, in order to generate more precise biomarkers, we need to better understand the processes by which the microbiota affects many aspects of human disease. The function of other microorganisms like fungi, bacteriophages, and parasites is also still poorly understood, as is the communication between different kingdoms of microbes and the host. We will develop more thorough techniques to counter the effects of the microbiome on the host as we elucidate different facets of these complex relationships. Despite these challenges, a key element of the future age of patient care will be the integration of microbiome-based detection and therapies with other aspects of customized healthcare, such as Pharmaceutical Genomics and epigenomics. The proper patient will receive the right therapy thanks to this integration, which will also help to cut down on negative side effects and medical expenses.

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