Targeting the Human Microbiome With Antibiotics, Probiotics, and Prebiotics: Gastroenterology Enters the Metagenomics Era

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Studies of metagenomics and the human microbiome will tremendously expand our knowledge of the composition of microbial communities in the human body. As our understanding of microbial variation and corresponding genetic parameters is refined, this information can be applied to rational remodeling or "tailoring" of human-associated microbial communities and their associated functions. Physiologic features such as the development of innate and adaptive immunity, relative susceptibilities to infections, immune tolerance, bioavailability of nutrients, and intestinal barrier function may be modified by changing the composition and functions of the microbial communities. The specialty of gastroenterology will be affected profoundly by the ability to modify the gastrointestinal microbiota through the rational deployment of antibiotics, probiotics, and prebiotics. Antibiotics might be used to remove or suppress undesirable components of the human microbiome. Probiotics can introduce missing microbial components with known beneficial functions for the human host. Prebiotics can enhance the proliferation of beneficial microbes or probiotics, to maximize sustainable changes in the human microbiome. Combinations of these approaches might provide synergistic and effective therapies for specific disorders. The human microbiome could be manipulated by such "smart" strategies to prevent and treat acute gastroenteritis, antibiotic-associated diarrhea and colitis, inflammatory bowel disease, irritable bowel syndrome, necrotizing enterocolitis, and a variety of other disorders.

The Metagenomics Era and Gastroenterology

The science of metagenomics and the international Human Microbiome Project[1,2] has ushered in a new era for the field of gastroenterology. Microbes and their genetic content outnumber their mammalian counterparts by 1–2 orders of magnitude,[3] and the spatial topography of these populations within the gut shows a nonrandom distribution that ultimately benefits both microbe and host.[4] New ribosomal RNA- and whole genome-based technologies have highlighted the potential importance of novel microbial species, with populations that differ between individuals, regions of the gut axis,[5] and different mucosal layers at a single anatomical site.[6] Culture-independent strategies such as high-throughput parallel sequencing and comparative genomics, metabolic profiling and functional genomics, fluorescence in situ hybridization, and phylogenetic microarrays will provide new insights into the composition, architecture, and functional roles of the human microbiota.[7–9] These tools have provided key insights into many aspects of gastrointestinal disease, such as the discovery of reduced bacterial species diversity in patients with Crohn disease.[10,11]

As we begin to appreciate the functional significance of these dynamic communities, including their effect on human physiology and disease,[12] new therapeutic approaches have emerged to provide a fresh perspective in the treatment of both acute and chronic disorders. Evidence suggests that perturbations of the gastrointestinal microbiota underlie many diseases and that therapeutic

Abbreviations used in this paper: AP-1, activator protein-1; APRIL, a proliferation-inducing ligand; cfu, colony-forming units; DSS, dextran sodium sulfate; GALT, gastrointestinal-associated lymphoid tissue; GOS, galacto-oligosaccharides; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; Ig, immunoglobulin; IκB-α, inhibitor of NF-κB α; IL, interleukin; LPS, lipopolysaccharide; NEC, necrotizing enterocolitis; NF-κB, nuclear factor-κB; peroxisome proliferator activated receptor-γ; RCT, randomized controlled trial; TGF-β, transforming growth factor beta; TLR, Toll-like receptor; TNBS, trinitrobenzene sulphonic acid; TNF, tumor necrosis factor.

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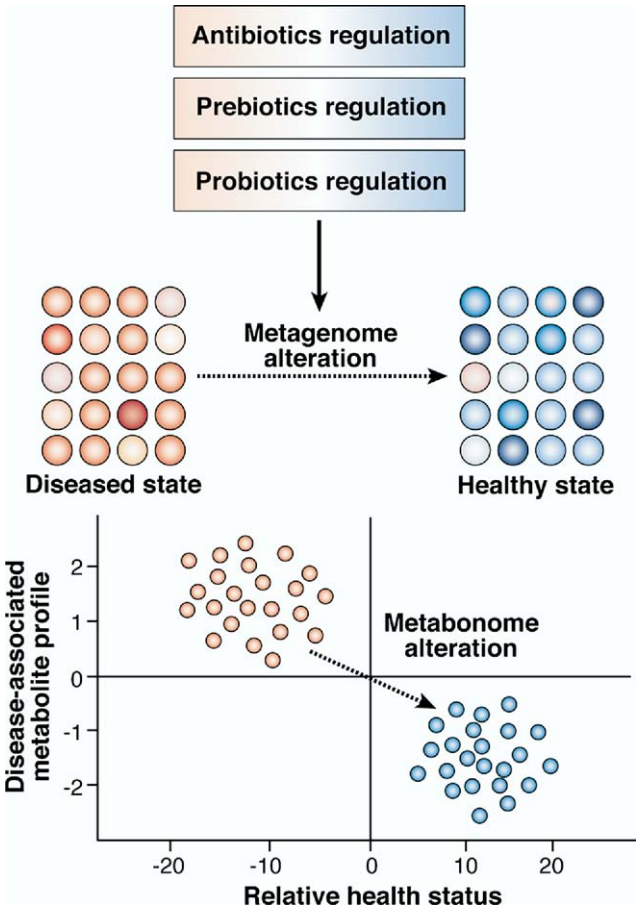

Figure 1. The gut microbiome as a therapeutic target: the "drug the extended" genome strategy. Perturbed metagenomic or metabonomic profiles associated with complex disease states can be restored to homeostasis with rationally selected antibiotic, probiotic, prebiotic, or combination treatment strategies. Adapted with permission from Macmillan Publishers Ltd: Nature Reviews Drug Discovery,[23] copyright 2008. http://www.nature.com/nrd/.

manipulation of microbial communities has the potential to ameliorate different gastrointestinal conditions.[13] The composition of the intestinal microbiome may also affect mammalian physiology in extraintestinal compartments. For example, intestinal microbiome composition represented a key epigenetic factor modifying predisposition to type 1 diabetes in the nonobese diabetic mouse model.[14] Changes in gastrointestinal microbial populations also correlated with specific patterns of metabolites excreted in the urine.[15] These studies suggest that directed manipulation of the microbiome within the gastrointestinal tract may yield health benefits at remote sites. Human trials have shown effects of prebiotics and probiotics on systemic immune responses after oral intake, including overall health maintenance and reduction of duration of common infections. Pregnant women consuming oral probiotics conferred protection to their infants by reducing the risk of atopic eczema,[16] and children given oral probiotics (*Lactobacillus rhamnosus* GG) showed a reduced risk of atopic eczema during a 4-year follow-up period.[17] Probiotics may colonize mucosal surfaces outside of the gastrointestinal tract and confer health benefits at sites such as the oral cavity[18] and the genitourinary tract[19] after oral administration. Probiotic therapy also showed promise in the context of neurologic and psychiatric diseases,[20] as well as in overall health maintenance, including reducing the duration of common illnesses such as upper respiratory infections and reducing absences from work or day care.[21] Intentional manipulation of the human microbiome by prebiotics may also modulate systemic immunity.[22] The plasticity of these microbial communities and their aggregate biological functions indicate similar compositional and functional plasticity in human physiology and the human metabonome (Figure 1).[23]

The ideas of a core and variable human microbiome have been proposed and provide a conceptual framework for considering early development and relationships of the human microbiome with multiple physiologic functions (Figure 2).[1] Microbial colonization of the human intestine within the first few days of life is an intricate process[24] that results in a symbiotic relationship with the

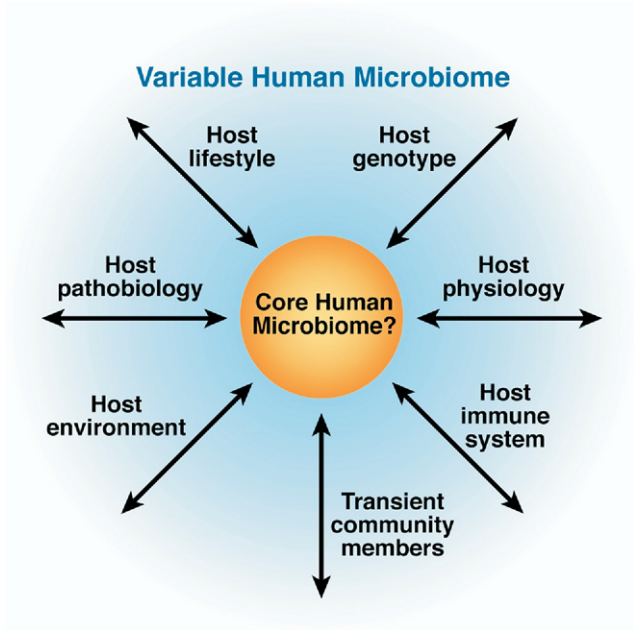

Figure 2. A super-organismal view of the human microbiome. Core and variable components of the human microbiome could have important implications for human health, including nutrient responsiveness, innate and adaptive immunity, and development. As the microbiome affects multiple aspects of human health and disease, host biology influences the composition and function of the commensal microbiota. A subset of microbial genes may be found in most healthy human beings (core microbiome), whereas variable components are present only in specific ethnic groups, age groups, geographic locations, or associated with specific dietary patterns or disease states. Manipulation of either the core or the variable parts of the human microbiome can affect human physiology, overall health status, and disease susceptibilities. Adapted with permission from Macmillan Publishers Ltd: Nature,[1] copyright 2007. http://www.nature.com/nature/.