PERSPECTIVES

Time to Recognize Our Fellow Travellers

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It is increasingly apparent that human health is reliant on our fellow travellers, the innumerable microorganisms that inhabit our bodies. This realization has led to the concept of the superorganism, which suggests that shared metabolic and signalling pathways are crucial for optimal existence of both host and commensal microflora. This commentary focuses on implications of this paradigm for personalized medicine and therapeutics. Study of the microbiome, the collection of microorganisms inhabiting the body, may identify disease-associated microbial profiles with pathophysiological and diagnostic value. As with genomics, companies will emerge offering direct to consumer microbiome analysis. Probiotics can potentially modulate the superorganism for therapeutic benefit. However, the probiotics industry will need to undergo a transformation, with increased focus on stringent manufacturing guidelines and high-quality clinical trials. Ultimately, we suggest that healthcare will move beyond its prevailing focus on human physiology, and embrace the superorganism as a paradigm to understand disease.

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In the past, microbes have been regarded primarily as agents of harm. The germ theory of disease, espoused by Pasteur and Koch, proposes that microorganisms cause many human diseases. The immune system has been viewed primarily as a defence mechanism against such microorganisms, signalling an “us against them” relationship between host and microbe. However, it cannot be ignored that we tolerate the microflora inhabiting our bodies, which outstrip our cells by orders of magnitude. In fact, it is becoming increasingly clear that we rely on our fellow travellers for the maintenance of health. For

example, the gut microflora aid host immunity by instructing development of intestinal lymphoid tissues, and acting as a barrier against pathogenic organisms.¹ Likewise, humans have evolved complex mechanisms to ensure that we tolerate our fellow travellers. Alcohol dehydrogenase and alkaline phosphatase have important roles in degradation of ethanol and endotoxin respectively, both which are microbially derived and potentially harmful.²

The realization of this interdependence has led to the concept of the ‘superorganism’, a functional entity encompassing host and its symbiotic microflora, and dependent on both for optimal existence.¹ This commentary focuses on this transformation of thinking, and the implications it has for personalized medicine and therapeutics.

THE SUPERORGANISM: A NEW PARADIGM OF HEALTH AND DISEASE

The superorganism paradigm requires us to redefine our basic understanding of physiology. Just as the cells of an organism engage in signalling and sharing of metabolic pathways, the microbial and host cells of a superorganism also interact in a similar fashion. For instance, the metabolite trimethylamine is made by gut bacteria and degraded to trimethylamine-oxide by a hepatic enzyme, flavin-containing monooxygenase 3. Individuals with mutations in this enzyme excrete instead the malodorous trimethylamine, a condition known as fish odour syndrome.³ The gut bacteria *Bacteroides thetaomicon* induces production of fucosylated glycoconjugates on the small bowel epithelium, which it can hydrolyse to L-fucose and utilize as an energy source.⁴ This organism simultaneously provides benefit to the host by hydrolysing non-digestible plant polysaccharides. This is an important example of how microbial and host pathways are shared in the superorganism.

There are several clinical examples that illustrate the significance of the superorganism. Perhaps the most widely appreciated example is vitamin K deficiency that follows antibiotic use. This results from the suppression of vitamin K-producing bacterial species and has implications for warfarin dosing; the dose must often be decreased to maintain the international normalized ratio (INR) in a

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therapeutic range. More recently, changes in the gut microflora that enhance its ability to harvest energy have been found to accompany obesity.⁵

A recent set of experiments illustrated the role of gut microflora in modulating predisposition to autoimmunity. ‘Non-obese diabetic’ (NOD) mice, which typically develop autoimmune diabetes when raised in a conventional environment, were protected from disease when deficient in a gene involved in microbial recognition (*MYD88*). However, these *MYD88*-deficient mice developed disease when raised in a microbe-free environment, indicating that the microbes played a role in protecting them from diabetes. Furthermore, exposing microbe-free *MYD88*-intact NOD mice to microflora from *MYD88*-deficient mice attenuated autoimmune diabetes.⁶ Taken together, these experiments suggest the importance of gut microflora in modifying predisposition to autoimmunity in a distant organ.

The superorganism is not limited to interactions between gut flora and host. For instance, the skin is a massive reservoir of microorganisms, and host physiology influences its composition. This is evident in the topographical diversity of bacterial species on the skin, and the dependence of this diversity on characteristics at different skin sites.⁷

THE MICROBIOME: THE NEXT FRONTIER OF PERSONALIZED MEDICINE?

The compendium of microorganisms inhabiting the human body is termed the human microbiome. Our ability to catalogue this ecosystem was once reliant on culture of microorganisms to identify and study them. Technological improvements now permit sequencing of either 16s ribosomal genes to catalogue bacteria species in a culture-independent fashion, or of entire genomes to define the functional capacity of the microbiome. The human gut microbiome contains at least 3.3 million non-redundant genes.⁸

The human genome project raised hopes that fundamental biological research would transform healthcare into the era of personalized medicine. Up to the present, however, ‘omics’ research has delivered only a handful of clinical innovations.⁹ One reason for the slow progress may be a lack of appreciation of the superorganism’s importance in health and disease. Systems biology research to date has largely focused on traditional biochemical pathways, investigating genomics, transcriptomics, and proteomics.

However, there is increasing interest in exploring the microbiome’s diversity across individuals in health and disease states; as with genome-wide association studies, a case-control design can be used to explore associations between the microbiome’s composition and disease. The Human Microbiome Project, a counterpart of the Human Genome Project, is underway among other global efforts,

funded as a five-year \$157 million NIH initiative beginning in 2008.

Just as genomics data has subsequently been commercialized with emergence of companies offering direct to consumer genetic testing, comparable initiatives focusing on microbiome data are sure to develop. These initiatives will likewise suffer from issues of clinical applicability, given the complexity of interpreting multiple modest effect sizes.

IMPLICATIONS OF THE SUPERORGANISM FOR THERAPEUTICS

The superorganism concept will affect therapeutics in two major ways. First, the gut microflora have the potential to influence drug metabolism, especially because most drugs are orally administered. Characterization of the microbiome may become important in predicting drug response and toxicity. Secondly, therapies such as antibiotics and probiotics, which have the potential to change the microbiome’s composition, are likely to be harnessed in new ways to shape the superorganism.

The term ‘probiotics’ refers to live microorganisms delivered to the host for a beneficial effect. In the past, probiotics have typically been the bastion of health foods and alternative medicine, with claims of benefit based on anecdote. Defining the size of this industry is difficult, given probiotics’ incorporation into other products such as dairy foodstuffs. Industry regulation has been slow to keep up with rapid changes in the industry. In the United States regulation has fallen under the control of the Center for Food Safety and Applied Nutrition at the Food and Drug Administration (FDA), which considers probiotics in the category of food and dietary supplements.¹⁰

There are currently no probiotics approved by the FDA for treatment of human disease. However, a number of small clinical trials evaluating probiotics have been undertaken for treatment of gastrointestinal disease such as inflammatory bowel disease, irritable bowel syndrome, and diarrheal illnesses. Unfortunately, results have been lackluster,¹¹ with key exceptions such as a recent meta-analysis confirming that probiotic treatment of preterm neonates reduces all-cause mortality and rates of necrotizing enterocolitis.¹² Although there is proof of concept for the use of probiotics in this clinical setting, clinical applicability has been hindered by the absence of an approved product. There are numerous challenges to pass FDA approval for a biological drug product,¹⁰ especially undertaking high quality clinical trials. Important logistical issues exist surrounding the production, storage, and effective delivery of live microbial therapies. These are major hurdles for the probiotics industry.

Furthermore, a change in nomenclature is overdue. The term probiotic (which roughly translates to ‘for life’) naturally carries the connotation that such microbes are

inherently beneficial; however the relation between probiotic and pathogen is not a dichotomy, but in fact a continuum. Probiotic prophylaxis in severe pancreatitis resulted in increased mortality, highlighting the potential harm of these agents.¹³ Given that there was an increase in mesenteric ischaemia in the group receiving probiotics, the authors speculated that probiotics may cause harm by increasing oxygen demand or inducing mucosal inflammation.

CONCLUSION

The recognition of the superorganism represents a shift in our understanding of health and disease, requiring us to redefine the notion of self to include our fellow travellers. Increasingly, there is evidence that our fellow travellers are important in the development of diverse diseases, such as obesity and type 1 diabetes. Study of the microbiome promises to identify microbial profiles with diagnostic and therapeutic potential, and thus contribute to future personalized medicine initiatives. Probiotics have potential to modify the superorganism for therapeutic benefit, but for this to occur the probiotics industry will need to undergo a transformation, with increased focus on stringent manufacturing guidelines and high-quality clinical trials. In the future, the healthcare industry as a whole is likely to move beyond its prevailing focus on human physiology, instead embracing the superorganism as a paradigm to understand disease and guide development of new therapies.

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