Mutual understanding: uncovering the mechanistic basis of the host-symbiont relationship in human health

Although rotation of the earth around the sun was first proposed by Copernicus, it took Galileo's telescope and Newton's laws of gravitation to demonstrate that heliocentric theory was irrefutably true. Likewise, although Darwin proposed natural selection as the means by which species originated and demonstrated that the natural world was consistent with this hypothesis, the work of Watson, Crick, and Wilkins elucidated the biochemical foundation of trait inheritance. The same opportunity to understand for the first time the mechanistic basis of an eminently significant natural phenomena now presents itself with regards to the integration of microbial symbionts and their human partners.

Recent developments are redefining the role for microorganisms in human health and disease. All multicellular organisms harbor a vast population of bacteria and other microorganisms and form symbiotic partnerships with at least some of their microbial inhabitants. This symbiosis is the product of an eons long and intimately intertwined evolutionary journey, producing a human host and microbial partners whose integrated function is a mutual necessity (1). A human being is thus better defined in its totality as a "metaorganism" composed of not one but many unique and complementary co-evolved genomes (2). The rules which guide the assembly and integrated function of the multi-organismal human being remain almost entirely unknown.

Mounting evidence suggests that dysfunction of the human-microbial symbiosis is a major driver in the pathogenesis of the most common ailments affecting mankind, including cancer, heart disease, diabetes, and even psychiatric disorders. We now know that germ-free laboratory animals are susceptible to gastrointestinal cancer brought on by exposure environmental carcinogens, suggesting that metabolism of exogenous toxins by the microbial community serves an important protection against the most damaging carcinogens. Microbes residing in the gut exert a systemic influence on carcinogenesis in organs that do not harbor a large number of indigenous microbes, and manipulation of the gut microbiota with antibiotics has been shown to reduce tumorigenesis in the liver, lung and breast in animal studies (3). Outgrowth of specific microbes may be an early indicator of minute changes within a patient. New clinical screening

tools that evaluate the composition of the microbiome have recently been shown to improve identification of colorectal adenoma by more than 50-fold relative to screening based on algorithms incorporating all previously known risk factors (4).

The intestinal microbiota serves as the critical link between obesity, diabetes, and heart disease, all among the greatest heath challenges of the 21st century (5). Obesity and type 2 diabetes, often attributed to a high fat and high carbohydrate diet, result in changes in intestinal microbiome composition and altered production of microbial metabolites. In an outstanding recent report, a single microbial metabolite trimethylamine-N-oxide (TMAO) distributed systemically in the circulatory system was found to be a major predictor of heart attack, stroke, and overall mortality among human patients (6). Evidence that dietary changes associated with protection from cardiovascular disease reduce the generation of TMAO by the human gut microbiota provide tantalizing evidence that metabolic syndrome and cardiovascular disease may be preventable by manipulation of the gut microbiota.

A new appreciation for the role of microbial activity in cognition is reshaping traditional neuroscience. Behavioral conditions, in particular autism and schizophrenia, are associated with altered microbial composition. Direct signaling through the vagus nerve, systemic immune trafficking, or the dissemination of microbial metabolites have all been proposed as mechanistic bases for an apparent gut-brain signaling axis (7). Perhaps the most compelling findings on the neurocognitive influence of our microbial symbionts stems from research on the ubiquitous protozoan Toxoplasma gondii, commonly transferred to human hosts via domesticated cats. Colonization with T. gondii occurs in the central nervous system and is associated with risk taking behavior, depression, and even schizophrenic events (8). This leads naturally to the uncomfortable implication that microbial symbionts influence human behavior and perhaps lends credence to once-antiquated references to "gut feelings". An understanding of the interdependent nature of microbial and eukaryotic life fundamentally challenges the natural view of the individual as a self-directed being.

Given the startling complexity of a human microbial community containing up to 5,000 species and 100 trillion individual organisms, it is perhaps not entirely surprising that the mechanistic

basis of these associations remain poorly defined. We cannot claim to understand the human metaorganism without understanding its microbial inhabitants in all their myriad complexity. The significance of the combined activity of the microbiome has been likened to the discovery of a new organ system. Reflecting upon his first comprehension of the astounding intricacy of the circulatory system, physician William Harvey wrote in his 1628 treatise On the motion of the Heart and Blood:

"...I found the task so truly arduous... that I was almost tempted to think... that the movement of the heart was only to be comprehended by God."

Despite Dr. Harvey's initial misgivings, here we stand in a world in which lifesaving re-routing of the circulation is conducted routinely, in which life can be extended and even improved through the use of artificial hearts, and in which statins can preclude the blockage of circulation, in the words of Carl Sagan, eventually saving "more lives than have been lost in all the wars in history". The same opportunity now presents itself in the form of the emerging science of human-microbial symbiosis. Medicine must and will adapt to this revolution in our understanding of the human patient as the unique result of the integrated function of perhaps thousands of distinct organisms, each with its own physiology, life cycle, and evolutionary history. We may one day find ourselves in a world in which therapies directed at the human microbiome restore health and vitality in millions of patients every year. Yet in the midst of this great promise, advances in technology indisputably place the responsibility to pursue this future upon the present generation of scientists and physicians. Investment in multidisciplinary approaches aimed at elucidating the mechanistic underpinnings of human-microbial symbiosis in health and disease will repay all of mankind abundantly in the decades to come.

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