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Perspective

Human holobionts: Metaorganisms hidden in plain sight?

Who are we? What is our place in the scheme of creation? These are profound philosophical questions that have been explored through various schools of thought. Evolutionary biologists place *Homo sapiens* at the pinnacle of the evolutionary tree. With enough evidence to justify pride of place, we have taken our evolutionary success for granted. This brings us to a more introspective question – did we reach this position all by ourselves? It would be conceited of us to think so.

A recent paradigm shift in the way one perceives the interconnectedness of life forms has led to the concept of 'holobionts'[1], wherein the human body and its associated microbiome are not two different entities but one single entity called the holobiont. Our idea of the 'self' has moved beyond the approximate 37 trillion cells derived from one fertilized human egg to include an almost equal number of microbial cells that live in and on the human body. Both groups of cells are thought to have undergone symbiogenesis and committed over a long period of time to becoming one metaorganism, that is, the holobiont[2]. Gene expression patterns of both groups of cells are reciprocally regulated by each other; hence, it is conceptualized that the genes of both jointly comprise a single hologenome[3]. From an evolutionary perspective, natural selection is likely to favour a hologenome due to the fitness and survival benefits accrued through the integrated gene pool[4]. Our evolutionary success, therefore, is not entirely our own.

A mathematical model to elucidate the process of holobiont evolution revealed two variants of the process[5]. In one variant, the entire hologenome (the human host genes and the microbiome) is vertically transmitted to the juvenile holobiont. In the other variant, the microbiome part of the hologenome is assembled from the source pools of parents through horizontal transmission. Either way, holobiont selection appears to be a carefully orchestrated evolutionary force. However, the more charismatic human part of the holobiont has traditionally taken credit for this evolutionary success. This has resulted in presumptuous and short-sighted strategies for the preservation of human health.

A focus on only the human part of the holobiont to the exclusion of the microbial part is a flawed strategy for the prevention or treatment of any disease. Our microbial half has a major role to play in health and disease. Recent work in human gut biology shows the existence of different stable states of the holobiont, each stable state indicating a healthy state, a pre-disease state or different diseased states. Each of these states is characterized by a specific composition of the microbiota and associated variations in host immunity and physiology[6].

In the healthy state, the holobiont draws heavily on its microbial half for facilitating many of the processes exclusively attributed by default to the human half. For example, the gut microbiome enhances the digestive capabilities of the human holobiont and produces molecules that send signals to the cells of the human part of the holobiont, which often signal back. This conversation seems particularly prominent with the nervous system, forming the basis of the gut-brain axis. Neurotransmitters like serotonin, GABA and catecholamines, produced by our microbial half, may play an important role in cognition, perception and action by the human part of the holobiont. Our microbial symbionts are even thought to influence System-1 thinking, which include instantaneous decisions driven by intuition, perception, and associative memory[7]. Studies indicate that microbiota colonising the gut play a role in the programming of social behaviours[8]. Gastrointestinal microbiota communicates invariably through endocrine, neural, and immune pathways influencing the brain function as well as behavior[9,10]. We may, therefore, have to revise the way we think about how we think.

A disease state is a dysbiotic state, where the holobiont ecosystem is disrupted. In such an ecosystem, the microbial and human parts of the

holobiont mutually sustain each other in a condition of dysbiosis. Symptoms manifested by the human part result usually from inflammatory/oxidative stress and/or alterations in epithelial/endothelial permeability. A pre-disease state is a transition state between a symbiotic and dysbiotic milieu. Prevention of disease, therefore, is required to be designed such that the transition from a healthy to a pre-disease state of the holobiont is averted. Nutrition could play a key role in averting such a transition. One way to go about this would be to revert to ancestral style unprocessed foods rich in microbes. To enable transdisciplinary decisions for appropriate nourishment of the human holobiont, recently a systematic risk-benefit analysis (evidence mapping) tool was developed[11]. The evidence maps incorporate clinical data for both infectious as well as non-communicable diseases and demonstrate the impact of agriculture and food management on medical outcomes, underlining the concept of one health.

However, alteration of the epigenetic effects in the microbiome-human interactions by manipulating the microbiomes or by dietary supplements is still poorly researched. In this regard, one opportunity for research is an investigation into cross-kingdom communications between the human host and symbiotic microbiota through small non-coding RNAs, which could lead to epigenetic effects. While such information is lacking in regard to symbiotic microbiota, a study on sickle cell anaemia suggests translocation of enriched microRNAs from sickle cell erythrocytes into *Plasmodium falciparum*, leading to impaired ribosomal loading. Such communication appears to contribute to translational inhibition, resulting in resistance of the human part of the holobiont to falciparum malaria[12].

This brings us to the question of whether a constituent/constituents of the microbiome can run rogue and cause active disease in the human half of the holobiont. However, it is argued that specific components do not constitute the microbiome metaphysically. The bacteria that constitute the microbiome may independently influence the well being of the host, however, the microbiome itself, as a part of the human holobiont, cannot. Koch's postulates cannot be applied seamlessly to the holobiont[13], since these were developed in the context of parasitism as opposed to the mutualism that exists within a holobiont. Be that as it may, how would the holobiont protect itself from such rogue, intrinsically pathogenic elements? A complex interplay between the human epithelium, the local microbiome, and resident immune cells actively fosters homeostasis. Bacterial metabolites serve as important signals that continuously ensure proper functioning of the epithelial barrier as well as the immune cells. This system effectively brokers the deal to prevent any constituent part of the microbiome from running riot. Also, epigenetic plasticity and/or epigenetic inheritance are implicated in the removal or control of effectors associated with pathogenicity. Epigenetic changes in either the human or the microbial half of the holobiont also enhance its tolerance to unfavourable conditions[14]. In addition, microbiome-mediated regulation of the host immune system assists the establishment of mutualistic/commensal microorganisms, which, in turn, hinder the multiplication of pathogens.

Still, a diseased state cannot always be prevented. The prevalent notion in medicine regards the body as a war zone, where any microbial invaders are the enemies and must be exterminated. But in the ecosystem of a holobiont, there are no enemies, just life forms in different roles. In the human holobiont, the human host is like a microbiome habitat to be managed, the health of which depends on mutual symbiosis of all its parts. Further, in addition to being an evolutionary unit, holobionts are anatomical, metabolic, developmental and immunological units as well[15,16].

Since the host immunity as well as the physiology are intimately intertwined with the composition of the microbial half of the holobiont, therapeutic approaches should ideally aim at simultaneous action on both parts of the holobiont. Along with targeted therapy, it would be helpful to correct the microbiome with diet, probiotics and microbial complementation/restoration. In addition, addressing human epithelial permeability, inflammation and the ensuing oxidative stress might be an effective, multipronged approach for a sustained healthy state of the human holobiont. It is also time to explore the relationship between diversity in our microbial half and subjective human experience which would be typically attributable to only cerebral processes. Is human emotion, as we know it, dependent on the constitution of our microbial half? Do alterations in our microbiome affect maternal instinct? Research questions such as these may generate evidence that would fundamentally change the way medicine is practised.

John Donne's solemn 400yr old sermon, in which he stated, 'No man is an island unto himself,' is a truism apt and applicable to our non-individual, holobiont existence. For better or for worse, through sickness and health, we are never alone, till death do us part.

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