

Evolving Host-microbiome Relationships and Therapeutical Implementation Methodologies

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Abstract

Host-microbiome relationship broadly explains the host's interaction with its associated microorganism population. Such interactions can either be beneficial, harmful or have no effect on the host. Microorganisms can associate physically with other organisms in various ways, including mutualism, cooperation, parasitism, commensalism, predation, amensalism, and competition. Host naturally responds to such association in favor of its survival, as seen when an infective agent disrupts the host's machinery, it tries to protect its system from the invasion by adopting defensive and offensive approaches and keeps evolving for better survival. Consequently, they are also studies presenting enhanced pathogenicity in microorganisms, owing to their simpler organization and ability to mutate much faster. In the present work, we will focus on human-microbiome relationships and their effect on the health of an individual.

Keywords: Microorganism; Flagella; Host-microbiome

Host-microorganism interaction

Microorganism communicates with the host through physical structures; like flagella, and receptors on the surface; as seen in HIV infection, or through chemotaxis; wherein secretion of certain chemicals attracts a specific microbial community. Furthermore, there are several ways a microbe can associate with the host and take part in its microbiome, or consortium. The predominantly researched ones are listed below [1]:

- Mutualism- both the host and microorganism benefit from each other. Ex: Ecosystem of ruminants harboring methanogens.
- Amensalism- a unidirectional interaction describing the adverse effect that one organism has on another organism. Ex: production of antibiotics that can inhibit or kill a susceptible microorganism

- Parasitism- this is a relationship between two organisms in which one benefits from the other, and the host is usually harmed. Ex: infection of fishes by ciliates.
- Commensalism- one symbiont, the commensal, benefits while the other (sometimes called the host) is neither harmed nor helped, ex: colonization of some microbes on the human body surface, which derive organic compounds from skin orifices but do not harm us.

Factors affecting host-microbiome relationships

It is noteworthy that variation in microbial consortiums greatly depends on factors like environment, diet, consumption of drugs, antibiotic treatment, personal health, and hygiene maintenance [2]. Any changes observed in the host's lifestyle influence the microbiota since alteration of host metabolism may affect its phenotypes or the expression of genes, similarly, any variation in phenotype or genotype of a microbe affects the

response of the host. Consequently, the host keeps on modifying its internal environment in terms of metabolic activity, for instance, metabolite concentration in the liver or expression of certain enzymes [3]. Microorganisms interacting with the said host either fail to do so because it no longer identifies the host as its 'ideal' host, or alter themselves to adapt to the changes (surface receptor modification, altered structure of cell and metabolic pathways) occurring in the host and continue their association.

Interaction of humans, as hosts, with their microbiome

Humans have evolved alongside their microbiome, developing a diverse set of innate immunodefenses against infection while still retaining a microbial presence. The past decade has seen many studies done in understanding the dynamic relationship of humans with their microbiome, from gut to respiratory tract microbiota. These relationships range from commensalism, as observed in all opportunistic organisms in the body, to intestinal symbiosis [4]. Given below are three occasions of human interaction with the body's microbiota:

- Human gut microbiota - The gut microbiota influences various host functions such as nutrient metabolism, immune system regulation, etc. [5]. Based on factors mentioned before, any modification in the host's metabolism can lead to similar adaptation by the microbe, or may invite pathogenic traits in otherwise harmless bacteria.
- Human skin microbiome - the skin microbiome is in constant and intimate contact with the epithelium, unlike the gut microbiome, which is separated from it by a physical layer of mucous [6], modulating both innate and adaptive immune cell functions. For instance, keratinocytes, predominant in the epidermis, directly participate in the body's immunity. They trigger antimicrobial peptides and cytokines when exposed to pathogens and induce inflammation [6]. Under normal conditions, they do not secrete such chemicals and maintain an unperturbed microbiome.
- Human urinary tract microbiota - the investigation of the role of the microbial community in urogenital health, such as the *Lactobacillus* genus, is required to understand urinary tract infection (UTI). These are generally treated by antimicrobial therapy, topical estrogen, and surgical intervention; however, they do not guarantee the restoration of healthy microbiota of UT [7]. Osmolarity, adhesion sites, and pH significantly affect the growth of UT microbiota.

Challenge to synthesize therapeutics for control and treatment of microbial diseases

Current trends in the treatment of hosts, specifically humans, of any detrimental effect caused by microbial associations mostly include the maintenance of homeostasis and administration of drugs. Prevention of dysbiosis, which involves pathobiont expansion, reduced diversity, and loss of beneficial microbes, is typically carried out through pre- and probiotics and antimicrobial agents, depending on the type of dysbiosis [3]. Probiotics, containing healthy microbes, often aid in restoring normal gut microbiota to derive beneficial outcomes from them [1], in contrast to prebiotics, which consist of substrates required for the survival of microbes conferring health benefits [4].

Another therapeutic approach is the use of drugs and monoclonal antibodies. Immunization through antibodies prevents the attachment of microbes to the host surface that cause infection. For instance, *in vitro* studies on mice with chronic colitis showed disease improvement on the administration of interleukin-33, proving to be a key cytokine in the regulation of host/microbiota interaction at mucosal surfaces. Furthermore, to avoid microbiota encroachment on said mucosal surfaces, anti-flagellin protein has been found to reduce bacterial motility by disrupting the microbes' flagellar movement which assists them in attaching to the host [8].

Identification of detrimental interactions and distinguishing them from beneficial ones becomes crucial in synthesizing optimum treatments. This could be understood from an *in vitro* study, where *Fusobacterium nucleatum*, detected in higher abundance in colorectal cancer patients, has been shown to increase cell proliferation of these cancer cell lines. Conversely, *Bifidobacterium adolescentis* displayed colon cancer cell line inhibition through the production of butanol [9].

This has become one of the main focuses for *in vitro* studies, mimicking human diseases in model organisms or organoids, which reveal the characteristics of host-microbiome interactions, thereby providing a lead to develop the corresponding drug that disrupts harmful associations. It can further be extended to cataloging beneficial microbes and synthesizing probiotics accordingly. This goes hand-in-hand with the development of diagnostic techniques and delivery methods, usually of drugs. One such method is the use of biodegradable nanoparticles or silica microcapsules as carriers

of drugs to the targeted microbial niche [10]. Emerging sequencing techniques like 16S rRNA amplicon sequencing and organoid generation paved the way to analyze the relationship between the microbiome and host gene expression efficiently [7,11].

The continuous dynamic nature of host-microbiome interactions demands equally advanced therapeutic approaches, to combat harmful effects on the host. Research continues to provide comprehensive evidence of factors associated with evolving host-microbiome interaction and thereby construct treatment accordingly.

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