

Host Microbiome Interactions and Implications for Human Health

The macroscopic life we experience daily is made possible by the processes of the cells that are omnipresent and invisible to the unaided eye. Billions of years of evolution has shaped the cells responsible for life today. The Prokaryotes are not only the predecessors of the Eukaryotes, but have also been incorporated inside cells, and now function as semi-autonomous organelles. The symbiotic relationship goes far beyond the primary and secondary endosymbiosis that drives much of energy capture and release on this planet. The presence of bacteria since the beginning undoubtedly has shaped life. Whether enemies or friends, these tiny, single-celled organisms harness the power to kill or enable life. All animals are colonized by enormous numbers of microbes. This host microbiome interaction has been fervently studied and has yielded fascinating results. As Dr. Charles Bevins stated in his presentation during the first Phenotyping Metabolic Health conference at UC Davis in June 2012, “We must understand the host microbiome interaction and its role in human health.” He presented several articles including one discussing the role of species associated microbial communities in hydra, [1] and another that described experiments conducted on mice and zebrafish raised in a germ-free environment then colonized with the microbes of the other species. [2] An important take home message was that “the host influences the microbiota, just as the microbiota influences the host”. The microbiota interacts with human health in many aspects. One example is the inflammation of the gastrointestinal tract. Dr. Bevins also explained how Inflammatory Bowel Disease (IBD) is interrelated with gut physiology and the ensuing microbial community. [3] First, a study on hydra.

It turns out, no metazoan has escaped this evolutionary pressure bacteria have imposed. Even the hydra, a basal organism, maintain very specific microbial communities on their surface.

[1] In this study, researchers analyzed epithelial microbial communities in two closely related hydra species *H. vulgaris* and *H. oligactis*, both in laboratory cultures that have been maintained for over 30 years, and in the wild. The microbial community is important to the hydra's ability to fight pathogens and germ-free organisms are susceptible to infection. Sterile hydra are also unable to reproduce asexually by budding, but resume doing so when reinoculated with their "friendly" bacteria. This indicates that the microbial community is essential to life in more than one way. Only the *H. oligactis* species was found to have an endosymbiotic relationship with a bacterium living inside their epithelial cells, both in laboratory culture and in the wild. The *H. vulgaris* was found to have a more diverse microfauna. When comparing the long kept laboratory culture with the original species from location in the wild where the organism was first harvested, each respective lab species was found to have remarkably similar surface bacterial colonies to their wild counterpart. All animals have species specific bacteria that live in and/or on the organism. In exchange for their protective abilities, these microbes have a safe place to live. This mutualistic relationship has proven to be vitally important. Not only has host microbe interaction been studied in hydra, but it has also been explored in mice and zebrafish.

One method of studying the ever complex interaction between hosts and their resident microbiota is to raise a test animal under germ-free conditions, and later introduce specific microbes or collections of microbes and document the outcomes. Microbes from the zebrafish gut were put into the germ free gut of a mouse. [2] A reciprocal cross was done by putting mouse microbes into the zebrafish gut. The proportions of microbes shifted to resemble that of the host they were implanted into, rather than that of the host they came from. This shows that there is an inherent link between the host and their internal microbiota. The host clearly influences the microbial composition.

It is evidently important to study how the host influences the microbiota and how the

microbiota influences the host. [3] Bacteria play a major role in our lives by teaching our immune systems and helping the gut develop. Along with his colleagues, Dr. Bevins researched the effect of the microbial community on intestinal diseases and inflammation. Experimental evidence from other studies was drawn upon by the researchers in order to give a broad overview of the topic at hand. One must first understand the general functions of the gut inhabiting obligate anaerobes including growth, development, protection, immunity, and digestion. Gut bacteria and all their functions are often referred to as the gut microbiome. This “extra organ” is essential to extracting otherwise unavailable nutrients and synthesizing important vitamins. Without these important bacteria, mice were found to have infections, and need an increased caloric intake to maintain normal weight. Also, mice models have shown that certain bacteria have been linked to obesity, as they extract an overabundance of energy from food. Other bacteria have been linked to insulin resistance and type two diabetes.

It was previously thought that IBD was linked to the presence of intestinal gut microbiota. [3] Mice models treated with broad spectrum antibiotics proved otherwise. Those with reduced numbers of colonizing microflora were much more susceptible to DDS (Dextran Sodium Sulfate) induced colonic inflammation. The gut associated lymphoid tissue does not develop in germ free mice. They also have decreased number of helper T immune system cells. Human gut microbiome is also intimately related with other forms of inflammation such as allergic reactions.

It is important to understand that the delicate internal ecosystem is carefully mediated, and that in response to the ever-present bacteria, organisms have evolved to express antimicrobial proteins that researchers have termed defensins. [3] The alpha defensins that are relevant to this topic work by compromising the structural integrity of gram positive and gram negative bacterial membranes. They are a link between the innate and adaptive immune system

as they not only target invaders, but also communicate with immune system cells. They function as part of the innate immunities because they are expressed constitutively; regardless if bacteria are present. However, other antimicrobial agents are expressed only when bacteria are present. The level of defensin increases as the organism develops. Alpha-defensins are expressed by the Paneth cells in the entire length small intestines. These Paneth cells also secrete other antimicrobial agents, but the alpha defensins are the most plentiful. Researchers have discovered the gene responsible for the expression of this antimicrobial agent and have found that it is closely linked with the differentiation of intestinal epithelial cells into the specialized Paneth cell. A pool of research suggests “IBD may result from negative or pathological interactions between the commensal microbiota and its host.” Pathogenic bacteria can be responsible for IBD. There is a genetic component to this affliction as well. Those with a mutation which affects the alpha defensin expression in the Paneth cells are more likely to be develop this disease.

This research has also lent itself to insights not only about IBD, but also about the horrible and potentially deadly disease that affects preterm babies: necrotizing enterocolitis. Preterm babies have GI tracts that are not as fully developed and lack some of the basic structural functions such as tight gap junctions found in term babies. [3] Premature infants have a less developed immune system, and their intestinal microflora is different as well. Two approaches to solving this still-poorly understood affliction include helping the intestinal mucosa mature using hormone supplementation. Another approach is using pre- and probiotics to help the preterm babies internal intestinal ecosystem resemble that of term babies.

The host microbiome interaction is not one to be overlooked when considering the overall health and disease outcomes. The microbiome influences the host in many ways. These invisible yet integral aspects of our biology are proving to be more important than anyone could have ever imagined. They play a key role in our health and development. They influence our

gastrointestinal immunity, and facilitate nutrient absorption, and may even influence metabolic health. Researchers have discovered the host influence the makeup of the microbiome as was shown by the hydra experiment and the zebrafish/mouse study. [1,2,3] It is apparent that the host influences the microbial make-up as well.

Without proper microflora, many maladies like infections can ensue. One important avenue of research is that into the field of inflammatory bowel diseases. Researchers like Dr. Charles Bevins and his colleagues have shown that a lack of antimicrobial agent producing Paneth cells in the small intestines may lead to a debilitating imbalance in the internal ecosystem. [3] This research has proven the importance of gaining a deep understanding of the bacteria which reside within us. Understanding the species which live in the microbiome and their implications for current and future health could be major insight into medicine and wellness. It seems to be a promising approach into phenotyping health as well. Once genome sequencing is available to all, practitioners should seriously consider sequencing bacterial genomes, since it has been shown that there is a link between the composition of the microbial community and some of the nation's most costly chronic diseases like diabetes and obesity. It is true that "bacterially mediated" health and sickness is not only complex and diverse in its inner working, but there's so much more than meets the eye.

Works Cited

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