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Health Disparities and the Microbiome

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An individual's microbiome is likely to be an important contributor to certain health disparity diseases and conditions. We present a framework to study the role of the microbiome and the multiple factors that are likely to influence differences in disease predisposition, onset, and progression at the individual and population level.

The contemporary understanding of disease highlights its complex and multifactorial etiology. Effectively reducing disease burden requires better understanding of its determinants in order to address the relevant social, behavioral, cultural, biological, economic, and institutional factors that work in concert to influence the onset, progression, and severity of disease over an individual's life course. The mutable environment in which we live further complicates efforts to solve the mysteries of human health and disease [1]. One area of intense investigation is the human microbiome and its role in health and disease. Humans are host to a multitude of microorganisms that modulate human health and disease. Much of microbiome research has focused on characterizing not only the healthy microbiome but also the microbiome in common chronic conditions such as diabetes and obesity [2]. These studies have yielded valuable insight into the triggers responsible for shifts in microbial communities across many disease states. Multiple factors, such as the host immune system, environment, host lifestyle and hygienic factors, and genetic variation, have been implicated in the reported shifts observed in the human microbiome.

Health disparities are defined as avoidable health differences in the incidence, prevalence, mortality, and burden of diseases and other adverse health conditions that exist among specific population groups in the United States. There are large racial and ethnic differences in health, and researchers have not fully explored the extent to which variation in the microbiome can possibly contribute to our understanding of racial and ethnic health disparities [1]. Racial and ethnic group membership reflects, in part, differences in socioeconomic status (SES) which are strong predictors of variation in health. However, racial disparities persist at every level of SES, and we need to better understand how health is shaped by differential exposure to risk factors and resources, over the life course, in psychosocial, physical, and chemical environments linked to ethnicity and SES and biological adaptation to these exposures [1]. Thus, factors such as diet, lifestyle, and other health-related behaviors likely influence ethnic differences in health and combine with other exposures to potentially modify the microbiome over time, resulting in poorer health outcomes. Inclusion of individuals from diverse ancestral, cultural, and social backgrounds in microbiome studies is a key step in advancing our understanding of health disparities. This is especially true in cases where investigators are able to link prevalence differences in a specific health condition or disease with identifiable population groups. Uncovering the role of the microbiome in health disparities could enhance our understanding of why some populations have poorer survival rates, greater severity of disease, and overall elevated disease risks compared to others. Furthermore, exploring the microbiome and the differences therein is likely to be important in efforts to reduce and eliminate health disparities while shedding light on how social and environmental exposures interact with biology to affect disease risk and outcome [1]. For example, skin pigmentation and exposure to sunlight and ultraviolet radiation are likely to impact skin microbial communities, yet have not been systematically explored in the context of skin health or disease.

One commentary by Fortenberry challenges the use of race and ethnicity categories in microbiome research [3]. Fortenberry, in our opinion, appropriately cautions the scientific community to be far more critical of the use of racial and ethnic categories as proxies for the true causes of microbial diversity. Microbiome research has the potential to translate its insights into better understanding of health disparities while precluding attribution of causal inference to specific racial and ethnic population groups [4].

Researchers studying the microbiome have captured limited information on socioeconomic, psychosocial, cultural, and behavioral factors as well as diet in ancestrally diverse study populations [4,5]. For example, previous studies have shown that black and Hispanic women in the United States of reproductive age tend to have higher rates of adverse pregnancy outcomes (i.e., pre-term births and miscarriage), sexually transmitted infections (STIs), bacterial vaginosis, and yeast infections. The vaginal microbiome was characterized in a cohort of women of European and African ancestry, revealing ethnic differences in vaginal pH and the microbiome. European women were more likely than the African American women to harbor a *Lactobacillus*-dominated microbiome. *Lactobacillus* and other related organisms appear to help maintain vaginal health [5]. Another study analyzed the gut microbiome in European and rural African children from two distinct geographical locations and cultures [6]. Significant differences were observed in the gut microbiome of two groups and were heavily influenced by geography and diet, one high in fiber, and the other high in fat [4].

Although the above studies reveal interesting features of the microbiome in ethnically diverse populations, limited environmental, social, and behavioral data on study participants continue to be an important limitation. For example, interest is emerging in understanding the role of the early feeding environment and its potential effect on the intestinal microbiome and immune responses. Researchers speculate that early feeding practices can shape weight loss/gain, alter the gut microbiota, and increase risk for developing chronic conditions such as obesity later in life. Moreover, feeding practices correlate with biological and behavioral factors such as maternal weight, eating habits, sleep patterns, socioeconomic status, and other health-related behaviors (e.g., smoking and alcohol use). Basic science researchers who study the role of the immune system and the microbiome in health and disease should incorporate a comprehensive examination of an individual's environmental context, including cultural practices, diet, chemical exposures, stress, and the effects that these may have on the microbiome.

A model developed to examine infectious disease, the epidemiologic triad, highlights the influence of the agent, environment, and host in disease onset [7]. The goal of such studies is to prevent disease by modifying one or more of the factors in the triad. The biopsychosocial model, which complements the epidemiologic triad, maintains that biological, psychological, and social processes must be considered in health and disease [7]. We present the immune system as an exemplar biological process for understanding the interaction between the microbiome and the social and physical environment in disease outcomes (Figure 1).

Exposures from the environment are numerous, ubiquitous, hard to measure, and temporally dynamic over our lifetime. Environmental exposures such as chemicals, tobacco use, residential pets, pests, and mold can alter health status. Social

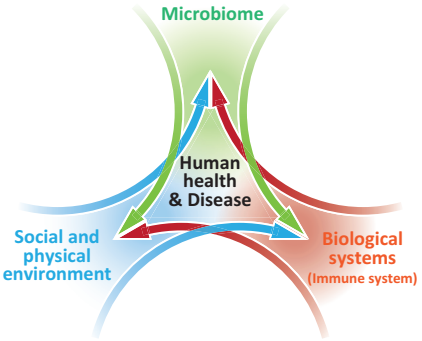

Figure 1. Framework for Human Health and Disease. This conceptual framework explores three overlapping but distinct and complex areas of health research – the microbiome, biological processes (e.g., immune system), and the social and physical environment. This framework provides an integrative approach to redefine our current understanding of how these areas shape human health and disease.

factors such as segregation, violence, poverty, poor education, health practices, and limited access to healthy food options and medical care can contribute to poor environmental health, all of which are likely major contributors to the patterns of health disparities and health inequities. More thorough and in-depth studies, combining the microbiome with detailed and comprehensive delineation of environmental exposures, are required to fully capitalize on the ways in which the microbiome can inform our understanding of the causes and consequences of disease risks and enhance our ability to effectively combat disease.

Stress is an important psychosocial factor that can increase disease risk. Stress impairs multiple physiological systems, including the immune system, and increases the likelihood of risky health behaviors that can adversely affect health outcomes [8]. Physiologic responses to stress include an increase in cortisol levels and reduction in glucocorticoid sensitivity. We speculate that a number of factors which include but are not limited to discrimination, stigma, depression, and poor environmental health conditions likely play a major role in this framework through an interaction with the immune system.

The host immune system is extremely sensitive to changes in the environment and the microbiome. Consequently, perturbations of any kind may result in an aberrant immune response and increased susceptibility to chronic disease. We speculate that a bidirectional interaction exists between the microbiome and psychosocial indicators, and both change in response to the health status of the individual. We recognize that the microbiome may possibly change in response to the immune system, and conversely, the immune system may respond to changes in the microbiome. Furthermore, the same bidirectional relationship observed between the microbiome and psychosocial indicators exists between overall health status and psychosocial indicators. A detailed examination of the impact of participant-reported stress, stigma, discrimination, and anxiety on one's health is essential in unraveling the contribution of each factor in disease onset and progression.

This framework investigates three distinct but overlapping areas of health research – the microbiome, biological processes, and social and physical environmental factors – to offer an integrative theory to our current understanding of human health and disease (Figure 1). It is important to note that this model is not limited to the information presented here but may include other chronic disorders (e.g., metabolic or mental health) that influence changes in immune status over time. Variation in disease phenotype is multifactorial, including differences in access to health care, immunity, environment, and the host microbiome. Researchers have begun exploring the role of the microbiome in certain health conditions for which there are disparities, including asthma, diabetes, sickle-cell disease, colon cancer, pre-term birth, and bacterial vaginosis which we reference in Table 1. Other examples, not discussed here, include obesity, and periodontal and cardiovascular disease. We contend that this model will have broad utility in the investigation of prevention strategies, interventions, and improved

Table 1. The Role of the Microbiome in Examples of Health Conditions with a Health Disparity

Health condition	Contributing factors	Disparity in incidence	Relevant studies	Refs
Asthma	Genomics, lifestyle, health behaviors, pollutants, and environment	Black, Hispanic	Early-life microbial (and allergen) exposures may offer protection against asthma: • Housing characteristics affect indoor microbial communities; asthma severity in children associated with microbial exposures in the home • Asthma severity in atopic (eczema) children is associated with fungal community composition in the home environment	[10]
Diabetes	Genomics, diet, lifestyle, health behaviors, environment, and physical inactivity	American Indian, Alaska Native, Black, Hispanic	Gut microbiota characterized: • In Mexican-American cohort with high risk for type 2 diabetes	[11]
Sickle-cell disease	Single gene mutation influenced by genomic variation and environment	Black, Hispanic, Southern European, Middle Eastern, and Indian	Neutrophil ageing and microbiome in sickle-cell disease: • Neutrophil ageing is regulated by microbiota in mouse models with sickle-cell disease	[12]
Colorectal cancer	Genomics, diet, health status, lifestyle, health behaviors, and environment	Black	Gut microbiota characterized: • Dietary habits in Blacks linked to modifications in the gut microbiota • Increase in heterocyclic amines and decrease in dietary intake of vitamins such as vitamin D likely responsible	[13]
Pre-term birth	Genomics, health status, lifestyle, health behaviors	Black, Hispanic, and others	Vaginal microbiome characterization during pregnancy: • Vaginal microbiome in pregnancy correlates with race/ethnicity • Uncultured vaginal bacteria play an important role in pre-term birth and race/ethnicity	[14]
Bacterial vaginosis	Genomics, diet, health status, lifestyle, health behaviors, and environment	Black, Hispanic	Vaginal microbiome characterized in four ethnic groups: • Vaginal bacterial community composition likely an estimation of disease risks • Ethnic differences in vaginal pH differences	[15]

and/or novel research methods for understanding health disparities.

This integrated health disparities science research approach will require the collaboration of investigators from multiple disciplines, including basic and computational scientists, clinicians, social and behavioral scientists, and epidemiologists. Each discipline plays a vital role in delineating the relevant factors that accumulate over the life course to influence disease risk and differences in health outcomes. One challenge to this approach is the need to modify or generate novel analytic tools to integrate social and biological data to investigate disparities in health outcomes. The ability to understand and translate the findings from these studies to a broader audience will be an audacious challenge, but one the scientific field should prepare to tackle. Thus, the future of health disparities research science should include integration of multiple disciplines focusing on the whole person – including the microbiome – to uncover unknown disease etiology and better understand human health and disease [9].

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Spotlight

Biomimetic *Salmonella*: A Next-Generation Therapeutic Vector?

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Designing bacterial vectors for cancer therapy represents a major challenge. Recent studies have explored novel strategies to balance benefit and safety. A study by Mercado-Lubo *et al.* has developed a next-generation concept combining bacterial properties with nanoparticles, demonstrating efficacy in combination with chemotherapeutics.

In modern industrialized societies cancer is a major health problem and economic burden. Despite intensive research and optimized classical treatments, no general cure is yet available. Improved therapeutic options are urgently needed, and novel strategies for intervention, especially targeted immune therapies, represent a promising solution.

Salmonella-mediated tumor therapy (SMTT) represents such a targeted immune therapy. Remarkably, the intentional use of bacteria as antitumor agents dates back to the 19th century and was revolutionized by William Coley [1]. While initial attention was given to obligate anaerobic bacteria such as *Clostridium*, focus has shifted to the facultative anaerobe *Salmonella* which appeared more recently in preclinical and clinical trials [2]. Although trials with spontaneous tumors in dogs had shown great promise, *Salmonella* did not exhibit the same potency in human patients. In the aftermath, over-attenuation was the likely explanation for the inefficiency in these clinical trials.

This illustrates the major obstacle in SMTT. An adequate balance between safety and therapeutic benefit is required for clinical success. To accommodate this balance, two encouraging alternative strategies have recently been described.

The original approach relied on the intrinsic antitumor properties of *Salmonella*. Via optimization of specific pathogen-associated molecular patterns, such as lipopolysaccharide (LPS) or flagella, *Salmonella* was either adapted to the cancer environment by passaging or its immunogenicity improved by genetic modification (Figure 1). These studies resulted in safe *Salmonella* strains that were able to target a broad range of murine tumors [1,3,4].

However, resilient tumors could not be resolved by the intrinsic therapeutic properties of *Salmonella* alone. Therefore, a second strategy was developed that utilized *Salmonella* as a vector system for therapeutic drug delivery [5]. This concept was developed in an interesting way by Din *et al.* in a study recently published in *Nature* [6]. They designed a self-limiting *Salmonella* strain on wild-type background (SL1344) by implementing a lytic system (ωX174 gene E). The expression of this system depends on bacterial density. When producing therapeutic compounds such as cytotoxins or immunomodulators, the system allowed repetitive cargo release during lytic cycles. This study nicely illustrates the potential of *Salmonella* as a targeted delivery system (Figure 1). However, it omitted to describe the bacterial burden on the mice. Even though *Salmonella* was applied intratumorally, it does not exclude the possibility of a chronic infection without apparent clinical symptoms. Therefore, a safety concern remains.

Building on this safety concern, a third promising strategy, introduced by Mercado-Lubo *et al.*, was published recently in *Nature Communications* [7]. To ensure safety, bacteria were replaced by gold nanoparticles (AuNPs) and combined with *Salmonella* proteins to generate a biomimetic. This concept can be considered a next step in the design of therapeutic vectors.

In a previous study, the same research group revealed that the effector protein SipA of *Salmonella* SPI1 (*Salmonella* pathogenicity island 1) locally interacts with the transporter P-glycoprotein (P-gp) which confers multidrug resistance to many tumors [8]. In their most recent study, they unraveled the mechanism by which SipA interferes with the P-gp activity. SipA binds to a PERP (p53 effector related to PMP-22)-associated SipA transmembrane receptor that activates caspase-3. This protease is ultimately responsible for cleaving P-gp and thereby inhibiting its function. Thus, SipA needs only to be available in the extracellular space and hence does not need to reach the cytoplasm of cancer cells.

In order to deliver SipA to cancer cells, and to circumvent the safety concern of using an infectious agent such as *Salmonella*, Mercado-Lubo *et al.* exploited AuNPs conjugated with SipA (Figure 1). *In vivo*,