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Microbial exposure and human health

Anukriti Sharma[1,2] and Jack A Gilbert[1,2]

The human body comprises of micro-ecosystem made up of trillions of microbes (i.e. bacteria, archaea, fungi, protists and viruses). The total microbial gene content, which is referred to as the human microbiome, is fundamental to human physiology and immunity. There exists an intricate relationship between the surrounding microbial world (i.e. the environment) and the endogenous human microbiome, mediated by the immune system. Disrupting this relationship can a profound effect on human health and disease. Understanding how microbial exposure influences immune response and the feedback on endogenous microbial metabolic activity could have profound implications for the development of novel microbial therapeutics. The term 'microbial exposure' is used generally to refer to exogenous environmental microbial interaction, while 'exposome' accounts for both the environmental exposures and the impact of lifestyle-associated microbial impacts, such as diet influences on endogenous microbial metabolism. In this review, we focus on how environment and lifestyle-associated microbial exposures shape the human immune system and microbiome, and how the resulting changes can shape human health, especially during critical developmental windows, that is prenatal, postnatal and adult. We conclude this review by proposing approaches to characterize the microbial exposome so as to accelerate the development of a precision microbial therapeutics for both practical and clinical intervention.

Addresses
[1] Department of Surgery, University of Chicago, Chicago, IL 60637, United States
[2] BioSciences, Argonne National Laboratory, Lemont, IL 60439, United States

Corresponding author: Sharma, Anukriti (anukriti.sharma8@gmail.com)

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Introduction

The classical view of the human body has been restricted to the host somatic cells which are encoded by the human genome [1]. However, technological advances in nucleic acid sequencing and chemical characterization have allowed us to study the human body as a superorganism, harboring trillions of microbes living both inside and outside. Collectively this is known as the human microbiome [1,2]. The human body is continually interacting with the external microbial environment through our surroundings (both natural and built) and lifestyle preferences, which cumulatively we describe as the microbial exposome [3]. In the past, our understanding of the role of microbial exposure in human health was restricted to elucidating the hazards of virulent and infectious microbes [4,5]. However, the majority of microbial exposures are benign and in fact could be essential in human development [3]. During the phase of human development in which the majority of people lived a hunter–gatherer lifestyle, diet and environmental interaction characteristics are likely to have had a significant impact on our ancestors microbial exposure, which will have shaped the selection of relevant immune traits [6,7]. According to the 'old friends' hypothesis, slow but consistent changes in the environment over time led to the loss of beneficial microbes (i.e. 'old friends'), which played a substantial role in the selection of host traits and disease phenotypes within our ancestral populations [3,8–10]. This loss of microbial diversity has been connected to many diseases such as allergies, inflammatory bowel disease (IBD), cancer, type 2 diabetes, depression, and vascular disorders [3].

Microbial encounters start *in utero* (i.e. prenatal life) and carry on through postnatal microbial colonization with the environment (both natural and built), urbanization, lifestyle, and diet having profound influences on the microbes we are exposed to and our susceptibility to that exposure [11–15]. This exposure stimulates immune responses which in turn influence the composition and function of the endogenous microbiome; disruption of endogenous microbial function and composition may play a significant role in host physiology and disease susceptibility. The role of the microbial exposome in human health and wellness will require much greater investigation and interpretation if we are to optimize microbiome exposure therapeutics [16]. Important questions include, which microbes are important? Which cell-surface antigens are responsible for immune activation? What microbial metabolites play a role in influencing host health? What is the appropriate dose for microbial exposure to have a health benefit? How long should someone be exposed? Is there a critical window in human development for exposure to be beneficial?

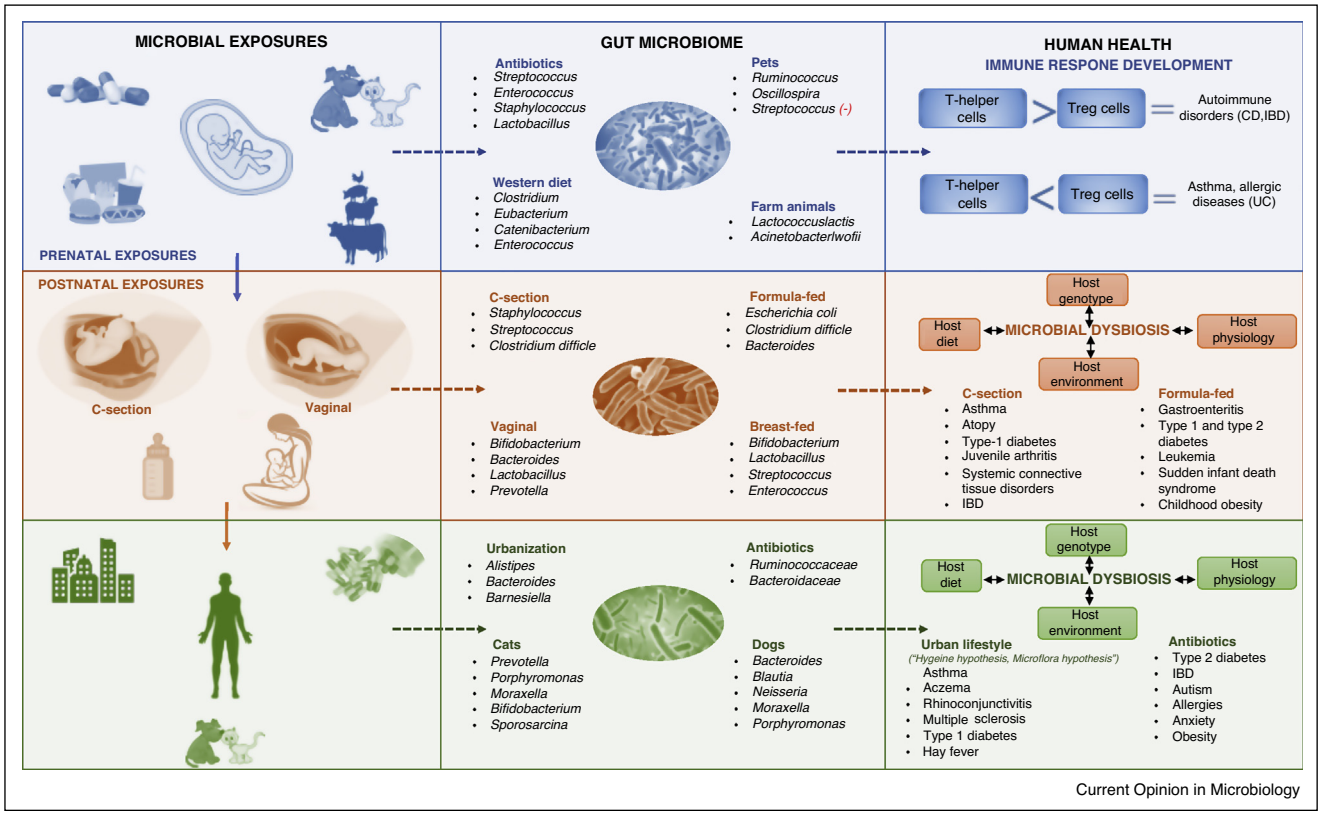
Efforts to remodel host immune and microbial phenotypes through constrained microbial exposures (e.g.

deliberate exposure to highly diverse environmental microbiota prenatally or specific diet/lifestyle traits that promote positive microbial exposure), will require a much more in-depth investigation of the effective dose and time frame of the exposure to be truly clinically relevant. The timing of exposure is also important, with prenatal and postnatal exposures relevant for critical host-developmental windows, while exposures during adulthood may have other effects on health status (Figure 1). Clinical and preclinical reports do support the use of microbiome manipulation (i.e. coordinated microbial exposures) to alter disease susceptibility which we review below. However, while microbiome undoubtedly offers a substantial prospect in disease prevention, there remains a dichotomy around what are 'protective' and 'detrimental' microbial exposures. Therefore, at the end of this review we briefly outline a framework for integrated meta-analyses using multi'omics data, which can be employed to prioritize microbiome-based targets for diagnostics and therapeutics with greater precision, especially by accounting for host-specific epidemiology (Figure 2).

Impacts of prenatal and postnatal microbial exposure on human health

Recent microbiome surveys have highlighted the role of prenatal microbial exposures in immune responses and future disease disposition [30–33]. For instance, the maternal microbial exposure plays a significant role in infant immune function and the development of allergies and asthma [34] (Figure 1). Ege and colleagues demonstrated that the maternal exposure to an horse-stable environment during early pregnancy associated a reduction in atopic sensitization and an increased expression of immune response genes (i.e. TLR2, TLR4, and CD14) [35]. Bacterial species such as *Acinetobacter lwoffii* and

Figure 1



The role of microbial exposome in human health. Microbial exposure in early life (i.e. prenatal and postnatal) play a significant role in disease susceptibility by stimulating immune responses, which feedback on the endogenous microbiome. Endogenous microbial communities and even fetal immune responses and development are also affected by maternal antibiotic use, diet and exposure to animals. Infants undergo microbial colonization at birth (i.e. vaginal or C-section) and during nursing (i.e. breast-fed or formula-fed), which can influence disease onset or progression later in life. Other factors affecting the human health during the later stages of life include diet, occupation, cohabitation with pets, prescription and recreational drug use, etc. 'Gut microbiome' includes microbial taxa that have been shown to increase in abundance under specific exposure events, and those that have been shown to have reduced abundance (–) under specific conditions [17,18,9,19–29]. The text in the third vertical column that is 'Human health' shows the disease conditions that arise from microbial exposure events. However, the associations between disease and microbial dysbiosis is complex and depends on other factors such as host-genetics, host-environment, host-diet and host physiology.