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Immune-Microbiota Interactions: Dysbiosis as a Global Health Issue

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Abstract Throughout evolution, microbial genes and metabolites have become integral to virtually all aspects of host physiology, metabolism and even behaviour. New technologies are revealing sophisticated ways in which microbial communities interface with the immune system, and how modern environmental changes may be contributing to the rapid rise of inflammatory noncommunicable diseases (NCDs) through declining biodiversity. The implications of the microbiome extend to virtually every branch of medicine, biopsychosocial and environmental sciences. Similarly, the impact of changes at the immune-microbiota interface are directly relevant to broader discussions concerning rapid urbanization, antibiotics, agricultural practices, environmental pollutants, highly processed foods/beverages and socioeconomic disparities—all implicated in the NCD pandemic. Here, we make the argument that dysbiosis (life in distress) is ongoing at a micro- and macro-scale and that as a central conduit of health and disease, the immune system and its interface with microbiota is a critical target in overcoming the health challenges of the twenty-first century.

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Introduction

Microbes are the most ancient, most abundant and arguably the most successful form of life on Earth, contributing to the evolution and function of all more complex multicellular organisms. It is estimated that *Homo sapiens* DNA makes up only a small percentage of the overall DNA on and within the human body—far greater genetic contributions are derived from bacteria, fungi, viruses, archaea and other microorganisms as part of a vast (and individually distinct) residential community collectively known as the human microbiome [1]. Technological advances are shedding new light on the sophisticated ways in which microbes influence, and are influenced by, human health and disease. In addition to the important maturation signals to the developing immune system (described in detail below), microbial functions include, but are not limited to, protection against pathogens, maintenance of barriers to the external environment (e.g. epidermal/dermal structures and intestinal mucosa), nutrient extraction, production of vitamins, transformation of dietary phytochemicals, lipid metabolism, provision of short-chain fatty acid and a host of other potentially bioactive metabolites, as well as metabolism of xenobiotics [2, 3].

Among the first to view the intestinal microbiota as a distinct human 'organ' that developed in a co-evolutionary manner, renowned microbiologist Rene Dubos and his colleagues were early pioneers of rodent models to delineate the consequences of disturbances in microbial colonization (through antimicrobials, dietary changes and other strategies) on immune function, behaviour and even brain chemistry [4, 5].

As noted some 50 years ago by Dubos, the true value of microbial contributions to health often becomes apparent only when their normal operations are disrupted by various environmental factors [4].

The comorbidity of noncommunicable diseases (NCDs) including cardiometabolic disease, allergic diseases and mental disorders is extraordinarily high [6, 7], with low-grade inflammation now well-recognized as a common underlying pathophysiological mechanism. The factors contributing to sustained immune activation, or lack of appropriate suppression, of the immune system are now a topic of much discussion [8]. The developing immune system is highly dependent on microbial stimulation, and declining biodiversity (or diminished contact with biodiversity via lifestyle changes) is implicated in both the dramatic increase in early-onset inflammatory diseases such as infant allergic diseases, as well as the risk of inflammatory diseases later in life. Thus, it is important to consider the immune system-microbiota interface through a broad lens as a critical challenge for all aspects of health in the twenty-first century [9••, 10].

Importantly, many of the factors that influence the human microbiome are highly modifiable. Thus, recent advances in this field are fueling guarded optimism for translational applications. These may transform personalized clinical medicine, with greater emphasis on prevention [11].

Microbes and the Evolution of the Immune System

The immune system provides a critical 'sensory' interface between the host and its environment—simultaneously affording both protection from threat and recognition of advantageous elements.

There is little doubt that microbes have shaped evolution of the immune system, and still do. As vertebrates have evolved, so have more complex immune systems. The early precursors of the adaptive immune system emerged relatively 'suddenly' around 500 million years ago in some species of non-jawed vertebrates, possibly the result of mobile microbial DNA 'infecting' marine creatures. The transposon theory of 'jumping genes' is one explanation for the emergence of new genes, such as the early recombination activating gene (RAG) homologs, that appeared in our marine ancestors to provide the machinery for lymphocyte diversity. It has been proposed that these RAG transposons evolved into the genes for V(D)J that generate our repertoire for B cell and T cell diversity [12]. Throughout evolution, transposable elements (TE) may have provided a rich reservoir of DNA that the host may selectively exploit, and these may account for >25 % nuclear DNA in some species [13, 14]. TE are inherently 'selfish' and potentially deleterious. This can explain why overlapping epigenetic mechanisms have evolved in eukaryotic cells to silence the expression and mobility of transposable elements. Given their ability to recruit the silencing machinery, TE can help with the exploration of epigenetic phenomena from an evolutionary perspective [15].

The adaptive immune system provides vertebrates with finely tuned specific immune responses and confers many advantages to the host. While it may have been originally considered that this advantage was largely around for 'better' defence against pathogens, it now appears equally, if not more likely, that sophisticated immune specificity allowed the host to selectively encourage the growth or 'beneficial' microbes for metabolic and physiological gain. Thus, enhanced capacity for symbiotic mutualism is likely to be a major factor in the evolutionary success of vertebrates—a function that was itself driven by the interplay between microbes and the immune system [16, 17].

Adding further to this story are the new risks posed by the evolution of the adaptive immune system. A new system of more targeted responses created the new risk of inappropriate or misdirected specificity—and the potential for allergy and autoimmunity. This necessitated the development of the complex secondary pathways to regulate this. Microbial exposure is also likely to have been a key element in the evolution of regulatory T cell (Treg) function [18]—and undoubtedly plays a role in the activation and the maintenance of these pathways today.

Microbiota in Early Immune Maturation

Microbial interactions are arguably the most potent factor driving normal maturation of the immune system. In the early postnatal period, this is likely to be a key factor in maturation of both T helper 1 (Th1) [19, 20] and Treg function [21], and in the functional suppression of the normal neonatal propensity for T helper 2 (Th2) responses which are still dominant in the perinatal period [22]. While there were initial assumptions that these host-microbial interactions were largely initiated in the early postnatal period, microbes have now been detected in placental and fetal tissues in normal pregnancies (reviewed in [23]). This suggests direct interactions that might provide an important source of antenatal immunostimulation.

Certainly, variations in maternal environment appear to modulate fetal immune responses, with measurable differences in both effector and regulatory T cell responses in cord blood of newborns whose mothers inhabit more diverse microbial environments compared to those who do not [24]. This has been well illustrated in rural Germany where children in the setting of rich microbial exposure have reduced risk of allergic disease [25], and *antenatal* exposure largely accounts for this protective effect [26].

Notably, these protective effects appear to be conferred by maternal contact with cows, straw and unpasteurized farm milk [27], all measures of high microbial diversity. Already

at birth, these children have enhanced neonatal Treg and Th1 function, and reduced Th2 responses [24], supporting an antenatal effect. Moreover, newborns from farming families also have distinct epigenetic methylation patterns (in both Treg pathways [24] and asthma- and allergy-related genes [28]) suggesting that this microbial exposure may be, at least in part, mediating epigenetic changes. These effects appear to be persistent with more efficient Treg [29] and stronger Th1 [28] responses in children from farming families as they approach school age. This pattern of maturation is likely to be important in suppressing the development of allergy in the critical period after birth and is consistent with a series of observations that lower perinatal microbiota diversity is a risk for allergic disease [30, 31].

Experimental animal models also demonstrate that maternal exposure to bacterial endotoxin [32] or commensal bacteria such as *Lactobacillus rhamnosus* [33] during pregnancy can attenuate allergic sensitisation and inflammation in the offspring. Interestingly, similar allergy-protective effects are also achieved by administering non-pathogenic bacteria isolated from German barns (*Acinetobacter lwoffii*) to pregnant animals [34]. This was found to induce activation of maternal innate immune pathways, namely toll-like receptor (TLR) signalling with associated epigenetic effects in immune genes (interferon-gamma) in the newborn offspring [35]. These observations are also consistent with human evidence that maternal probiotics in late pregnancy significantly modulate the expression of TLR-related genes both in the placenta and the fetal gut [36].

In addition to direct stimulation by microbial antigens, the metabolic products produced by bacteria may also have direct systemic effects on the fetus during pregnancy. In particular, there is now considerable focus on the effect of short-chain fatty acid (SCFA) metabolites, produced by the bacterial digestion of dietary fibre and starch. Animal models clearly demonstrate that modulation of the maternal microbiota with a high-fibre diet increases SCFA production and prevents the development of allergic disease in the offspring [37••]. This effect can be reproduced by giving the SCFA (acetate) directly; these metabolites cross into the fetal circulation to promote Treg differentiation and tissue-specific effects that protect against allergic airway disease in offspring. Specifically, the experimental model results demonstrated reduced airway eosinophils, reduced Th2 responses (IL-5, IL-13), reduced serum IgE, and airway responsiveness [37••]. In humans, there are preliminary reports that the level of dietary fibre intake in pregnancy is associated with higher serum SCFA (acetate) and that infants whose mothers had SCFA levels below the median were more likely to develop recurrent wheezing in the first 12 months [37••].

These observations further support the contention that host-microbial interactions are well-established before birth. Indeed, they may have a persistent effect on phenotype and subsequent disease risk over the life course. Furthermore, experimental studies demonstrate that early-life gut microbiota are responsible for select DNA methylation, underscoring a potential epigenetic relationship between human-associated microbes and facilitation of postnatal epigenetic processes [38••].

Shaping the Microbiome

The developmental origins of health and disease (DOHaD) paradigm provides a construct for understanding far-reaching, later-life consequences of early-life stresses, dietary choices and microbial exposures, often through epigenetic changes in the patterns of human gene expression [39]. Just as the human epigenome is developmentally programmed by the early environment, so too is the human microbiome shaped by a range of early factors—also beginning in utero. Even in the absence of infection or inflammation, bacterial exposure across the placental barrier is possible, if not normal [40••]. Moreover, meconium is also rich in a variety of microbes [41]. At this point, it is unclear *how* microbes might be gaining access to the fetus, although gut epithelium translocation and/or oral to bloodstream are leading candidates [40••, 42]. Antenatal factors including stress may also have residual effects on the postnatal microbiota. A recent study showed that measures of maternal prenatal stress (including salivary cortisol) was a significant determinant of microbial profiles of vaginally delivered infants in the first 110 days of life (e.g. higher proteobacteria and lower lactic acid bacteria) [43].

In the postnatal period, gestational age, antibiotic exposure, delivery mode, breastfeeding, formula milks, timing and types of solid foods and genetic factors can influence microbial colonization. Both the stability and diversity of intestinal microbiota increase significantly through the first 1000 days of postnatal life [40••]. While microbial communities begin to take on an adult-like structure by 5 years of age, the healthy pre-adolescent gut microbiome still harbours compositional and functional qualities that indicate ongoing development [44••].

Although each individual harbours a unique microbial profile, a core bacterial composition includes members of four primary phyla—*Actinobacteria*, *Proteobacteria*, *Firmicutes* and *Bacteroidetes*—and several hundred species [45]. *Firmicutes* and *Bacteroidetes* dominate, and relative expansion of the *Proteobacteria* is emerging as a marker of a number of NCDs [46••]. Alterations of gut microbiota noted in wide-ranging NCDs, of course this does not prove causation. However, the idea that an altered microbiota may be a 'transducer' organ responsible for signalling low-grade inflammation and metabolic dysregulation is well supported in animal models [9••, 47]. Among specific genera, researchers are particularly interested in *Bacteroides* and *Prevotella* groups as possible indicators of healthy lifestyle and reduced NCD risk [46••, 48]. At this point, the results are equivocal.

Recently, tantalizing clues concerning early-life-associated microbes that may afford protection against asthma have emerged from a Canadian study involving over 300 infants. The relative abundance of the bacterial genera *Lachnospira*, *Veillonella*, *Faecalibacterium* and *Rothia* during the first 3 months of life was significantly decreased in children who developed subsequent wheeze and asthma [49••]. Remarkably, the administration of a cocktail of these microbes in a germ-free animal model reduced airway inflammation in adult offspring. This opens a door of possibility that certain microbial taxa may emerge as both diagnostic and therapeutic. Notably, the microbiome differences related to subsequent asthma risk (clearly observable at 3 months) had mostly disappeared in the faecal samples taken at 1 year of age, suggesting that timing of testing (and perhaps therapeutics) is critical [49••].

Modern Dysbiotic Drift: the Effects of Lifestyle Transition

Populations living very traditional lifestyles, including those who have been largely isolated from western influences, are generally differentiated by far greater alpha-diversity of faecal microbiota relative to westernized groups [50]. This raises several questions including whether they are 'dysbiotic' in relation to still-traditional-living human relatives and ancestors who have gone before. Dysbiosis is a widely used term to describe perturbations to the structure of complex commensal microbial communities; a term that was originally defined broadly as 'difficult living' or 'life in distress' [51]. Primarily, these changes can threaten symbiosis and involve the loss of beneficial microorganisms, the expansion of potentially harmful microbes and/or the loss of overall microbial diversity [52].

The hygiene hypothesis and its variants are grounded in what is missing—i.e. an *absence* of traditional early-life microbial exposures that favour optimal immune-microbiota relations and long-lasting epigenetic influences. However, the adoption of westernization also includes, to varying degrees, the *presence* of active detrimental exposures that further contribute to a 'dysbiotic drift' [53], such as environmental contaminants, unhealthy diets, food additives, advanced glycation endproducts and circadian disruptions as a result of westernized lifestyle. Both aspects of this adverse continuum contribute to dysbiosis, and it is likely their sum is greater than their individual NCD-provoking parts. It is critical to consider dysbiosis in this wider context.

Dysbiosis and Dietary Patterns

The higher diversity of faecal microbiota in traditional versus westernized communities is explained in large part by dietary practices. Although there are dietary differences between traditional-living populations in geographically distinct locations, these are generally united by higher intake of fibre and phytochemical-rich foods and the relative absence of sodium-rich, refined sugar and added fats common to ultra-processed foods—dietary patterns clearly linked to NCDs including mental disorders [54].

There are also many examples of traditional, healthy dietary patterns within developed countries (e.g. Nordic, Japanese and Mediterranean diets) often exemplified by higher intake of fruits, vegetables, fish, monounsaturated fats, as well as minimally processed protein sources [55]. The well-known metabolic benefits of the 'Mediterranean pattern' also extend to decreased risk of depression and allergic disease in addition to cardioprotective effects [56–58]. At least part of these effects are likely to be mediated through beneficial influence on intestinal microbiota producing higher levels of anti-inflammatory SCFA [59••].

Although there is still a paucity of interventional studies, the available evidence indicates that diet-induced shifts in microbiota composition are possible. Certainly, short-term dietary changes can influence genus- and species-level microbes with functional effects, even though the major phyla composition may not alter greatly [60••, 61, 62••]. Importantly, increased consumption of dietary fibre markedly increases bacterial gene richness [63], which has been associated with reduced risk of NCDs and adverse biomarkers such as insulin resistance and lipidaemia [64].

From Dysbiosis to Inflammation

The last decade has witnessed tremendous insight into the mechanisms that link microbial shifts with chronic, low-grade inflammation. Chief among these pathways is increased intestinal permeability (IP). Disruption of the normal intestinal barrier enhances access of Gram-negative cell wall parts such as lipopolysaccharide (LPS) endotoxin and even whole microbes into systemic circulation, triggering inflammatory cytokine release from innate immune cells through toll-like receptor activation. Even small elevations in blood LPS levels (0.5–1.0 ng/kg) can provoke an inflammatory immune response in humans [65] with far-reaching systemic consequences. For example, low levels of systemic endotoxin in otherwise healthy humans can interfere with cognition and provoke emotional symptoms and 'sickness behaviours' through elevations in inflammatory cytokine release [66]. Indeed, it is now possible through positron emission tomography (PET) imaging to witness the activation of immune cells (microglia) within the brain in concert with low-level LPS administration [67••]. This highlights the far-reaching influences of LPS-induced immune activation—indeed IP and low-grade endotoxaemia is implicated in many other NCDs including cardiovascular disease, type II diabetes, obesity,

allergic diseases and even mental ill health [68, 69]. In the brain, microglial dysfunction has been linked to depression and other brain-related NCDs [70]. Notably, in animal models, loss of intestinal microbial complexity compromises microglial function, while oral SCFA derived from dietary substrates may largely restore microglial impairments [71••].

Westernized dietary patterns have been associated with increased IP. Experimental and emerging human studies show that such diets lead to changes in microbial communities that might otherwise play important roles in mucus thickness and gut barrier function [72]. On the other hand, the administration of non-digestible carbohydrates, omega-3 fatty acids and dietary phytochemicals can attenuate western diet-induced microbial changes, IP and low-grade inflammation [73–75]. Thus, there is clinical optimism that improvement of dietary patterns may provide benefits in NCD prevention and treatment via IP, LPS and microbial pathways [76].

Immune Dysregulation in Relation to Wider Loss of Biodiversity

The variety of life, including species, their genes, and the ecosystems they form, have clearly demonstrated benefits for human health and well-being [77]. Although many species are still not catalogued, available evidence indicates that marked reductions in biodiversity are now commonplace [78]. With already well-recognized implications for the risk of infectious disease, there are now also emerging relationships between biodiversity and NCDs [79]. Some of these benefits may be rooted in evolutionary 'needs' for natural environments (so-called green and blue space) and may be mediated by visual aesthetics and opportunities for physical activity and social capital [79]. However, microbial biodiversity encountered by contact with natural environments (e.g. airborne bacteria, soil and/or plant associated microbes) may have critical additional health benefits especially early in life. This biodiversity hypothesis was published as a Consensus Statement in the World Allergy Organization Journal: "*Biodiversity loss leads to reduced interaction between environmental and human microbiotas. This in turn may lead to immune dysfunction and impaired tolerance mechanisms in humans*" [80]. The hypothesis is not exclusively directed at allergic diseases and is projected to fit with other NCDs [81].

The biodiversity hypothesis is supported by a number of studies, including those (mentioned above) that found perinatal and childhood proximity to a farm diminishes the risk of allergic disease [82] in conjunction with epigenetic changes in specific asthma- and allergy-related genes [28]. Additional support comes from populations who experience more traditional environments in early life and have diminished reduced risk of chronic low-grade inflammation in late life (e.g. reduced baseline C-reactive protein) compared to their counterparts in Western nations [83].

Clearly, environmental differences are multi-factorial and include diet and differential incidental exposure to various environmental microbes [84]. However, it is becoming increasingly evident that diverse bacterial signals early in life can have long-lasting influences. Researchers from Finland have brought a degree of specificity to the discussions of biodiversity loss (both at the macro- and micro-level) and allergic disorders. Specifically, the level of green space and biodiversity of vegetation surrounding the primary residence is a key driver of diversity of commensal skin bacteria and lower odds of an allergic response [85, 86].

We now know that the skin is merely a filter to microbial access to deeper dermal stroma and systemic influences—rather than a 'firm barrier' against microbes as previously assumed [87]. This allows for speculation that cutaneous microbes that reflect environmental diversity may influence aspects of the systemic immune system and many associated organ functions. For example, the allergy-protective effects of *Acinetobacter* (isolated from farm settings) may be just one among many relevant indicators concerning biodiversity loss.

Where to Next?

Although the promise of targeted, personalized medicine with the microbiome as a therapeutic targeting is now on the horizon, we may do well to heed the words of Gustav Wislicenus, physician and microbiologist who wrote in 1933 "*For dysbiosis cannot be cut out of the structure of life for independent treatment, nor can (eu)biosis be treated intelligently except in its totality, its all-embracing oneness…*" [88]. Here, Wislicensus was referring to dysbiosis broadly as a distressed or diseased state and eubiosis as full vitality, and not simply in the absence of disease. This cautionary statement applies equally well to the challenge of addressing NCD-related dysbiosis with effective microbial solutions that should also encompass the factors driving dysbiosis in the first place. This required a far more comprehensive understanding of the multi-factorial environmental influences that shape risk. This includes consideration of the broad, real-world environmental forces (marketing and otherwise) that influence dietary choices that facilitate human dysbiosis, especially in periods of psychological stress.

Many factors that contribute to dysbiotic drift are not captured by animal studies, such as how fast-food logo recognition in developing nations increases with wealth accumulation [89]. This does not bode well for the global burden of disease nor leave much room for optimism that a 'probiotic' can undo these complex, biopsychosocially mediated disorders, which will only be effectively addressed by systemic change. It points to the critical importance of improving the food environment and

habitual dietary practices through clinical and public health strategies including policy change [90]. A related part of this dialogue concerning the built environment includes equitable access to green spaces and diverse vegetation.

Conclusion

Disruptions of the evolutionary rooted, finely tuned relationship between microbiota and immune system are clearly implicated in the rising rates of dysbiosis-associated diseases. While there has been intense focus on the nature of these interactions at local cutaneous and mucosal surfaces, there is growing awareness of the systemic effects on health and homeostasis. Collectively, all of these observations provide validation to the notion that we are not really functionally 'separate' from our microbiota. The unfolding research also helps to explain, at least in part, the human vulnerability to environmental change.

At present, there are more questions than answers concerning the immune-microbiota interface and its place in the context of chronic NCDs, including what precisely defines a healthy non-dysbiotic state. For now, these questions remain unanswered. However, the changing relationship between environmental microbial exposures, especially early in life, appears to be intimately connected to the growing burden of allergy, autoimmunity and many other NCDs. In particular, the application of the so-called missing microbes—commensal bacterial genera contributing to NCDs by their relative absence in very early life—may hold some promise when applied as a preventive early intervention [91]. Moreover, since maternal over and/or undernutrition can influence the microbiota of offspring [92, 93]—a dysbiotic effect that may have long-term consequences—ensuring optimal maternal microbiota composition via dietary improvement currently offers important opportunities for preventing poor health outcomes in children.

Today, it can be argued that climate change, environmental degradation and biodiversity loss are a measure of planetary dysbiosis—'life in distress'. Furthermore, changes in human behaviour and lifestyle, including diminished contact with natural environments and biodiversity in general, may also be causing 'distress in life' and shifts in human-associated microbial ecosystems. This provides a much-needed perspective in the contemporary microbiome *zeitgeist*. Attempts at targeting the human microbiome with purely biotechnical solutions may provide important breakthroughs. However, these are unlikely to meet their true potential if the underlying environmental and lifestyle forces that are driving this need are not addressed.

Compliance with Ethical Standards

Conflict of Interest Dr. Prescott declares that she is in the Scientific Advisory Boards of Danone and the Nestle Nutrition Institute. Dr. Logan declares consulting fees from Genuine Health. Dr. Jacka reports no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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