Post-hunter-gatherer era microbes' role in allergic, autoimmune and chronic inflammatory diseases

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Abstract

Diverse hypotheses exist to explain allergic and autoimmune diseases. There are 3 factors common to most, if not all, of these diseases: 1. Microbial imbalances, microbial triggers and/or infections, 2. Allergy/hypersensitivity to food and/or environmental substances and 3. Stress. The post-hunter-gatherer era microbe hypersensitivity-enhanced colonization/infection (PHMHEC) hypothesis presented here proposes that these factors are part of a phenomenon that involves an extension of the altered microbiota hypothesis, which is the current leading hypothesis to explain the increase in allergic and autoimmune diseases in the last 75 years in association with westernization. The category of post-hunter-gatherer era microbes (PHM), as defined here, includes many microbes that are encountered much more frequently since humans ceased to live as nomadic hunter-gatherers and began living an agricultural or urban lifestyle. The microbial communities (microbiotas) that humans have been exposed to have changed as human activities have changed. It is postulated that the most intense and rapid changes in these microbiotas have occurred in recent decades in association with westernization. Human genetic makeup evolved largely during the 200 million years during which humans and their mammalian ancestors lived as hunter-gatherers or gatherers. It is proposed here that environmental microbes commonly encountered in association with that lifestyle in a pre-agricultural age would be the most coevolved with the human immune system, and thus the immune system would generally respond to these microbes without leading to debilitating chronic disease. In contrast, according to the PHMHEC hypothesis, at least some of the microbes newly encountered or encountered at higher levels during the post-hunter-gatherer era, the PHM, would be more likely to evade the immune system and/or cause hypersensitivity reactions. A mechanism called hypersensitivity-enhanced colonization/infection (HEC) is postulated to be one means by which low abundance microbes cause disease. Microbes sometimes cause hypersensitivity reactions in a manner that increases their virulence, and these reactions could be enhanced by increased exposure to similar or identical microbes in the environment. Slight differences between antigens of environmental and colonizing microbes could make the colonizing microbes even more difficult for the immune system to effectively target. Multiple secondary opportunistic infections resulting from PHM-induced immune dysregulation/suppression could exacerbate disease processes. Vulnerability to more severe acute infections (e.g., severe COVID-19) could also be increased. The long-term colonization/infection of multiple PHM and accompanying hypersensitivity reactions could contribute to physiological and psychological stress and tax the immune system and other systems of the body and be an underlying factor leading to many allergic, autoimmune and chronic inflammatory diseases. The united holobiont disease hypothesis, which is analogous to the united airway disease hypothesis, is discussed, as well as the view that the concept of sterile inflammation needs revision and perhaps should be replaced with "inflammation without apparent infection" (IWAI) in light of the potential role of low abundance microbes. The relationship between the PHMHEC hypothesis and other hypotheses is discussed for a variety of diseases, ending with a discussion of implications for research and treatment.

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