Post-hunter-gatherer era microbes' role in chronic inflammatory diseases and implications for infectious diseases

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Abstract

This article discusses a variant of the altered microbiota hypothesis, the leading hypothesis to explain the increase in allergic/autoimmune/inflammatory diseases with westernization. Instead of emphasizing the microbes that are missing/reduced due to westernization, this article focuses on those that are relatively novel. Environmental microbes encountered in association with a pre-agricultural lifestyle would presumably be the most coevolved with the human immune system, and thus they would be less likely to promote debilitating chronic disease. Post-hunter-gatherer era microbes (PHM) are microbes that are encountered more frequently and/or at higher levels since humans ceased to live as nomadic hunter-gatherers. Research will be discussed that suggests that some PHM suppress/dysregulate the immune system, potentially causing chronic inflammatory diseases and increased vulnerability to severe infections. PHM colonization or infection, hypersensitivity reactions and associated chronic stress could significantly impact multiple diseases. Exploration of this hypothesis might generate insights into pathogenic mechanisms and improved treatment approaches.

Introduction

This article proposes an extension of the altered microbiota hypothesis[1], which is the dominant hypothesis to explain the increase in many chronic inflammatory diseases in the last 75 years in association with westernization. The altered microbiota hypothesis is an updated version of the hygiene hypothesis. The hygiene hypothesis suggested that the recent increase in allergies is due to reduced exposure to pathogens. Instead, the altered microbiota hypothesis proposes that it is primarily a reduction of commensal and environmental microbes that we coevolved with that is responsible for increased rates of chronic inflammatory diseases.

The absence/reduction of certain coevolved microbes likely plays an important role; however, this article focuses on microbes that are relatively novel. The category of post-hunter-gatherer era microbes (PHM), as discussed here, comprises microbes that are encountered more frequently and/or at higher levels since the advent of agriculture and permanent settlements.

The microbial communities (microbiotas) that humans have been exposed to have changed as human activities have changed. The most intense and rapid changes in these microbiotas likely occurred recently in association with westernization and industrialization. A large proportion of the human genetic makeup evolved during the 200 million years during which humans and their mammalian ancestors lived as hunter-gatherers or gatherers. Microbes commonly encountered in that era would presumably be the most coevolved with the human immune system and would thus tend to cause less disease and/or be beneficial. In contrast, humans are now exposed to many microbes that they did not coevolve with[1]. It is proposed here, in the PHM hypothesis, that some proportion of the less coevolved PHM suppress/dysregulate the immune system, contribute to multiple chronic inflammatory diseases and increase vulnerability to severe outcomes in acute

infections through their colonization or infection and accompanying hypersensitivity reactions and chronic stress.

Microbes could be considered to be PHM due to being novel, such as mutated strains found in association with newer products/substances or novel conditions[1]. Alternatively, microbial species or strains could be PHM due to being increased by changing lifestyles (e.g., intestinal Candida albicans overgrowth due to factors such as high dietary refined carbohydrates and antibiotics).

The PHM hypothesis focuses on the sources of microbes that may contribute to disease and emphasizes microbes' cross-reactions with varied internal and external antigens. In addition, it integrates the environmental chemical (xenobiotic) hypothesis with the PHM hypothesis by noting the likelihood of PHM being associated with chemicals from certain occupations and air pollution from burning fossil fuels[1]. In addition, it is compatible with the cold chain hypothesis that links Crohn's disease with cold-tolerant bacteria (e.g., Yersinia spp and Listeria spp) in refrigerated food[2]. PHM are more likely to be present in certain types of food consumed commonly in westernized societies, including refrigerated and ultra-processed foods/beverages[1]. Microbes associated with food additives are also potential sources of PHM (e.g., halophilic Archaea from salt[1,3]).

The term westernization, as used here, refers to factors associated with a modern lifestyle that may be associated with health effects. It includes a sedentary lifestyle and increased exposure to xenobiotics/pollutants. New exposures from western medicine, like antibiotics, are also included. The westernized diet typically includes increased consumption of animal products, fat (especially saturated animal-derived fat and vegetable oils), sugar, ultra-processed foods/beverages, salt, and food additives.

The role of other hypotheses and mechanistic explanations could be complementary to the role of the PHM or be related to the processes that stem from the effects of the PHM.

The role of microbes in chronic inflammatory diseases

As many of the more obvious effects of microbes in disease have already been elucidated, the more subtle, delayed, and chronic effects are increasingly being studied. Methodological advances have led to the detection of microbial communities in tissues previously thought to be sterile in healthy individuals, e.g., the blood[4], the lungs[5], and possibly even the brain[6]. Despite these recent advances, a problem that has become increasingly recognized is the difficulty of detecting rare species/strains. The situation has been compared to an iceberg, with much of the microbial diversity under the surface still undetected[7].

This limited attention to rare species may seem justified, since abundant species may be considered to be more important. However, the low abundance oral bacteria and likely PHM, Poryphyromonas gingivalis, has been implicated in varied diseases. Also, antifungal therapy has shown benefit in asthma even when fungi have been too low in abundance to be detected[8].

Presumably at least some of these rare microbes come from the environment; however, for various reasons, they do not become abundant in the human body. The less abundant and often unknown microbes that are changing with human cultural practices may play a key role in disease. It is known from ecological studies of diverse environments that there are typically many rare species, often with patchy distributions.

Allergy, hypersensitivity and stress

The traditional view of allergy is that allergenic substances are essentially harmless and allergic reactions are a "mistake" by the immune system. In recent decades, there is growing support for an alternative "toxin hypothesis" in which allergy is seen as an important defense mechanism that protects the host from harmful environmental substances, i.e., venoms, toxins, irritants and substances produced by biting insects[9]. More recent research continues to support this hypothesis, and it has been proposed that this response may also promote avoidance of some microbes[1,10].

Palm et al[9] describes how the high sensitivity of IgE-mediated responses may have evolved to allow anticipation of dangerous exposures and thus cause avoidance of noxious substances. Experiments in mice and

rats sensitized to a specific allergen have shown stress/anxiety effects and avoidance behavior associated with trace amounts of allergen in their cages[1,9]. Stress-related neuropsychiatric disorders have also been associated with allergic reactions in humans[11,12].

The PHM hypothesis proposes that PHM-associated antigens would also produce a stress response. Thus, the observed stress effects (e.g., increased anxiety, sleep disruption, elevated heart rate, and lower heart rate variability) that occur in a wide range of diseases could be at least partly due to frequent elicitation of the stress response by exposures to PHM and other sources of allergens.

Thus, greater levels of physiological stress could be due to a higher level of PHM colonization, leading to a higher level of response to PHM and cross-reacting allergens/antigens inside and outside of the body. Chronic exposure to known or unknown allergens, including some PHM, could lead to elevated cortisol, damaging inflammation, elevated heart rate and hypertension.

In support of this view, there is increasing published evidence for IgE-mediated bacterial and fungal allergy, auto-allergy (IgE against self-tissue), and IgE responses that appear to be protective against pathogens. And these pathogens are not limited to parasites. Studies have suggested that anti-microbial IgE antibodies may help inhibit HIV-1 disease progression and may play a role in anti-Borrelia burgdorferi immunity[13]. These findings are compatible with microbial allergy being an evolved defensive mechanism against infection as well as a potentially important contributor to allergic/hypersensitivity reactions. Cross-reactions between microbial antigens and self-tissue could account for the IgE against self-tissue in auto-allergy. The fact that selective IgE deficiency is associated with increased asthma, chronic sinusitis, otitis media, autoimmune disease and cancer suggests that IgE responses might be protective and may be a response to potentially harmful substances/microbes (for additional references, see[1]).

Air pollution

One possible source of PHM is the fine particulate matter component of air pollution from burning fossil fuels. In many studies, microbes are only identified to the genus level. Interestingly, studies of crude oil reveal diverse microbiotas, including at least some genera that are the same as those found in humans, such as Pseudomonas and Mycobacteria. It seems possible that some studies might fail to detect microbes originating from fossil fuels.

A recent study found the proportion of pathogenic species increased with air pollution levels associated with urbanization[14]. A study also found that there were changes in the pharyngeal microbiota following a severe air pollution event, including detection of 142 new genera in the pharynx[15]. Some of the microbes found in cigarette smoke also might be considered to be PHM and might play a role in tobacco-associated diseases.

A number of studies have linked fine particulate matter exposure to increased rates of allergic diseases[1]4, respiratory infections[16] and overall mortality[17]. Air pollution has been associated with evidence of stress effects as measured by blood pressure, heart rate, and heart rate variability.

Built Environment Microbiology

Groundbreaking research on the microbes in built environments is compatible with the PHM hypothesis[1,18,19]. Over 150 fungal and dozens of bacterial allergens have been found[18]. A study of 15 persons using wearable sampling devices found that over 2500 species of microbes were encountered, and 43.7% of the DNA information could not be classified[20].

Horve et al[18] pointed out how harsh conditions, including exposure to cleaning solutions, could lead to mutant forms. Gilbert et al[19] discussed new materials, which are treated with diverse chemicals, thus providing unique selective pressures that could shape microbial evolution. The new species/strains that could result would fit the category of novel PHM.

Cross-reactions

Cross-reactions play an important role in the PHM hypothesis. Trost et al[21] found that “no human

protein is exempt from bacterial motifs." This extensive cross-reactivity may be quite significant. It might be that plant microbiomes have a similar level of cross-reactivity with plant proteins. This might mean that food hypersensitivity of multiple types might be at least partly due to microbial antigens found in plants cross-reacting with food allergens. Plant microbes that increase after harvest and thus reach elevated levels in stored food (both from plants and potentially the animals that consume them) might be a source of cross-reacting PHM. These cross-reactions could magnify the effect of low-level microbial colonization.

The level of colonization by a PHM could explain why one person reacts to a particular substance and another does not. The location that the microbe has colonized could potentially determine the type and location of the reaction. For instance, colonization of the skin might lead to atopic dermatitis, colonization of the intestines might lead to diarrhea, and colonization of blood vessels might lead to cardiovascular signs and symptoms.

Cross-reactions might be a significant part of the processes that lead to chronic inflammatory disease, as suggested by two recent examples. Bacher et al[22] provided evidence that a cross-reaction between intestinal C. albicans and lung Aspergillus fumigatus could, under certain circumstances, lead to the inflammatory lung disease, allergic bronchopulmonary aspergillosis. These two fungal species could be considered to be PHM. High A. fumigatus exposures can occur with certain farming exposures or due to water-damaged buildings. C. albicans overgrowth might arise from a westernized diet and antibiotics, as mentioned above.

The second example is a recent study[23] that found that Pseudomonas fluorescens, an environmental bacteria, cross-reacts with gliadin and might possibly be linked to celiac disease. P. fluorescens is cold-tolerant and can survive in refrigerated food, and is found in moldy buildings and on walls and shower fixtures[24]. Thus, it is potentially a PHM.

Many chronic inflammatory diseases share features compatible with the PHM hypothesis

Features of diverse chronic inflammatory diseases suggest compatibility with the PHM hypothesis[1]. Briefly, allergy/hypersensitivity to foods and inhalants is increasingly being found in autoimmune and other inflammatory diseases. Stress has been found to be associated with the initiation and exacerbation of many inflammatory diseases. Markers of chronic stress, such as elevated heart rate and low heart rate variability, have been associated with numerous diseases and all-cause mortality. Opportunistic pathogen presence and/or dysbiosis has been documented in many diseases. Autoantibodies are increasingly being found in diverse inflammation-related and allergic diseases. More traditional diets that reduce consumption of ultra-processed foods/beverages (e.g., Mediterranean diet) are showing benefit.

Relationship of PHM hypothesis to infectious diseases

Diseases that have been associated with inflammation, air pollution, and a westernized diet (cardiovascular disease, diabetes, obesity, and chronic lung disease) are some of the comorbidities associated with severe COVID-19. It has been proposed that the severe inflammatory component of COVID-19 could be related to an intensified immune reaction to components of the microbiota present in various tissues[25]. These microbes might be PHM or opportunistic pathogens that take advantage of PHM-induced immune dysregulation and thus could underlie these comorbid conditions. Up until the severe viral infection, the immune system may have been reacting to these resident microbes with low-grade inflammation. When the upregulated immune response occurs due to the acute infection, this low grade inflammatory response to the PHM might develop into an excessive inflammatory response. A similar intensified reaction to PHM might also occur in other conditions where excessive inflammatory responses occur, such as influenza and sepsis, and might play a significant role in disease progression.

PHM-induced dysregulation/suppression of the immune response might also increase susceptibility to a variety of other infectious agents. Del Poeta et al[26] notes that our ability to determine immunodeficiency is limited. Thus, relatively subtle immune defects caused by PHM might be an issue to consider.

The PHM hypothesis proposes that disease might develop in genetically susceptible individuals in the following way. PHM from the environment colonize particular areas of the body, often after a higher-than-usual

environmental exposure. Acute infections or chronic stress might serve as triggering factors, which might be followed by a vicious cycle of increasing hypersensitivity reactions, increased physiological stress, barrier breakdowns, further PHM colonization, secondary infections and tissue damage.

Immunosuppression and disease persistence

The ability of many of these inflammatory diseases to benefit from immunosuppressive therapies, such as corticosteroids, might be considered contradictory to the PHM hypothesis. However, the apparent benefit of immunosuppressive therapies in some chronic inflammatory diseases may result from the suppression of an essentially ineffective immune response against relatively low virulence microbes. High virulence for their animal hosts is considered to be of questionable value to many microbes[27], and thus low virulence may be quite common.

According to the PHM hypothesis, the ineffectiveness of the immune response against the PHM in chronic inflammatory disease is shown by the persistence of the disease. This ineffectiveness could be due to varied factors, including the microbes' antigenic changes, heterologous infection effects related to immunodominance, microbe-induced Th1/Th2/Th17 imbalances, and microbes that produce substances that have toxic effects on the immune system[1]. Chronic exposure or repeated reinfection could also play a role.

Conclusions

PHM colonization and cross-reacting antigen exposures leading to increased susceptibility to acute and/or chronic secondary infections may be a plausible explanation for the heterogeneity common in many chronic inflammatory disorders, the frequent comorbidities, the dietary effects, the relationship with xenobiotic/pollution exposures, the periodic exacerbations, and the varied target organs/tissues.

Disease could result from effects of PHM colonization/infection and/or the immune system's defensive reactions against PHM antigens that cross-react with environmental and self-antigens. Allergy/hypersensitivity reactions would enhance intestinal permeability and microbial translocation. Rare microbes could have significant effects since their effects could be magnified via hypersensitivity, cross-reactions, and the synergistic effects of multiple PHM. Treatments might aid the elimination/reduction of PHM (e.g., dietary changes, anti-microbials, microbiota manipulation, allergen avoidance, stress reduction methods, and immunotherapy). Treatments might also enhance PHM toleration.

Given the ubiquity and adaptability of microbes, the changes in sources of microbial exposures accompanying westernization, the frequent cross-reactions, and the ability of some environmental microbes to infect thru "dual use" virulence, it seems reasonable to consider the PHM hypothesis. If this hypothesis is valid, it might lead to reduced morbidity through adequate knowledge of PHM and associated neurological, immunological and hormonal effects.

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Competing interests

JCW has plans to file one or more patents that are related to this hypothesis and plans to donate all proceeds from her share of any profits from them to charity, including charities that fund medical research. JCW may possibly receive a salary from a company or nonprofit related to these plans.

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