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Review

The role of diet in triggering human inflammatory disorders in the modern age

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Abstract

Previously uncommon human inflammatory disorders are emerging with alarming frequency, possibly triggered by environmental factors introduced through Westernization. This review highlights how Western diets heighten the inflammatory state promoting development of disease. Evidence that this can occur directly or indirectly through perturbations of host–microbe interactions are reviewed.

Keywords: Gut microbiota; Western diet; High-fat; Inflammatory disease; Systemic inflammation; Immunity

1. Emerging diseases of Western cultures

The emergence of "New age" disorders, including rheumatoid arthritis (RA), inflammatory bowel diseases (IBD), and metabolic syndrome over the last half-century has become a worldwide phenomenon [1–4]. Nearly all of these diseases are characterized by a systemic, chronic pro-inflammatory milieu, setting the stage for the development of various inflammatory and metabolic complications [5,6]. While genetic predisposition is clearly involved in the etiology and pathology of these diseases, genetic drift alone cannot account for the rising trend in incidence, suggesting that environmental factors must play a role, in-turn triggering aberrant host inflammatory responses. Previously published work provides strong evidence that dietary intake, particularly a shift to a Westernized high-fat high-carbohydrate diet, contributes to disease development and progression. While it is clear that these types of diets can have direct adverse effects on human physiology, they may also promote heightened states of inflammation through alterations of gut microbiota and host–microbe interactions, resulting in chronic immune and inflammatory imbalances [7,8]. While the etiology of these complex immune disorders appears to be a combination of both genetics and environment, genetic components that contribute to systemic inflammatory diseases have been extensively reviewed [9–12]. Therefore, we will instead focus specifically on dietary factors that impact inflammation and the development of inflammatory disorders, and discuss evidence suggesting the gut microbiota may play a mediating role.

2. Shifts to Westernized diets set the stage for inflammation via direct and indirect effects on the host

While the exact mechanisms underlying the development of "New age" disorders have yet to be elucidated, cultural shift to a Western lifestyle is believed to be a significant contributor to the increasing trend of these diseases. Modern conveniences, larger choices of low-cost, calorie-dense foods, and sedentary lifestyle in industrialized countries have led to a culture of overindulgence and excess. Before the development of agriculture and animal husbandry, dietary choices were limited to minimally-processed, wild plant and animal foods. With domestication of plants and animals, dietary nutrient content

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subtly but progressively shifted toward more processed foods for which the human genome had little evolutionary experience. Refined grains, sugars, vegetable oils, alcohol, salt, and fatty domesticated meats that were not present in the pre-agricultural diet now make up the primary constituents of the post-agricultural, typical Western diet that are consumed both out of balance and in caloric excess. In addition to high dietary fat intake, a key element of the Westernized diet is the substitution of sucrose with cheaper corn-derived fructose sweeteners, most notably high-fructose corn syrup (HFCS). Overconsumption of HFCS has been implicated as a key contributor to the obesity epidemic [13] alongside both metabolic dysfunction and inflammatory-mediated diseases [14]. Thus, relatively rapid changes in Western lifestyle and diet have subjected the human condition to new stresses that challenge evolutionarily-determined relationships between host and environment. In this regard, we have begun to accept the notion that Westernization has, in-turn, significantly impacted our "second genome", that of our gut microbiota, in ways that contribute to states of immune imbalance, heightened inflammatory states, and development of emerging diseases that were previously rare or uncommon.

2.1. The gut microbiota as an essential organ of the host

Countless years of co-evolution have allowed for the establishment of a mostly mutualistic relationship between intestinal microbes and the host. By virtue of its ability to confer an extensive set of structural, protective, and functional properties to the host, gut bacteria can be considered a microbial "organ" dynamically interacting with the host. Over time, commensal gut microbes have evolved in such a way as to possess a genetic and functional repertoire to which the human host is now intimately tied, affecting various aspects of host physiology including nutrient digestion/absorption, behavior, stress responses, and numerous other factors [15]. Consequently, maintaining proper health and functionality of this "organ" is of significant importance. The host is protected from the immunogenic properties of the microbiota through both physical (the gut mucosal barrier) and chemical (antimicrobial peptides) means. However, there remains a delicate balance between gut microbiota and the host mucosal immune system including both innate and adaptive portions. Disruption of this homeostatic equilibrium, whether through external (e.g. environmental) or internal (e.g. genetic) factors, has long been speculated to play a causal role in the pathogenesis of inflammatory diseases [16].

While the human body is comprised of roughly 10^{13} cells, the gastrointestinal (GI) tract houses ten times as many bacteria, representing a microbial genome that far outnumbers that of the host [17]. Since nearly 95% of bacteria remain unculturable, determining precise mechanistic interactions between host and microbes has been limited. However, research in this area has recently blossomed as a result of advances in development of powerful, non-culture based microbial analytical technologies. Low-cost, high-throughput DNA sequencing technologies now provide rapid and deep analyses (based on 16S rRNA gene profiles) of complex gut microbial communities. Unfortunately, the ability to assess microbial function has lagged behind and remains a challenge. Metagenomic and metatranscriptomic analyses to gain insight into microbial community function are limited by incomplete inventories of functional genes and inadequate bioinformatic approaches for analyzing and integrating large data sets. Moreover, most of these data remain unverified because of the limited number of experimental tools currently available that directly assess microbial function.

The employment of gnotobiotic technologies has been extremely valuable in gaining functional and mechanistic insights into host–microbe interactions. Germ-free (GF) mice, for instance, are birthed and raised in a completely sterile environment and are thus devoid of bacterial colonization. Removing the impact of the microbiota in a given treatment, such as dietary manipulation, theoretically allows investigators to understand whether or not gut microbes are required for a particular phenotype. This also provides the opportunity to re-introduce select bacterial species or bacterial communities to observe their impact on the host. Studies involving GF mice have led to many important discoveries involving the gut microbiota, such as their role in energy metabolism and intestinal immune system development. For example, GF mice possess a dramatically immature immune system which can be restored upon exposure to fecal bacteria, termed "conventionalization" [18]. To demonstrate the adaptability of the gut, researchers have created a model of the human gut environment by conventionalizing GF mice with adult human fecal microbiota and reproducing a large majority of the donor's bacterial diversity [19]. While this "humanized" mouse model has been utilized as a proxy for modeling the human host–microbe dynamic and holds great promise, recent studies have suggested that this approach has several significant limitations [20]. Even with these limitations, studies using these animal models have demonstrated that axial gradients and local heterogeneity of microbial distribution exist, resulting in mucosa-associated bacteria establishing "micro-niches" [21]. This coincides with observations that there are distinct functional profiles associated with communities of microbes along the length of the intestine [22]. However, the host–microbe interactions along these sections have not been well-characterized, particularly in host immune system development and how it relates to systemic inflammation, especially in the context of Western dietary intake. Researchers have just begun to delve further into studies examining both environmental and host factors that determine the assemblage of gut microbiota. Moreover, mechanisms dictating the homeostatic balance between commensalism and pathogenicity are of significant interest, particularly when under selective pressure such as a shift in environmental conditions.

2.2. Rheumatoid arthritis

Even though epidemiological evidence supports the notion that the Western diet is one of both high fat and high