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EDITORIAL

Low-Grade Inflammation as Trade-Off Causing Chronic Complex Diseases

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Recently, it has been suggested that low-grade inflammation may underlie chronic complex diseases, such as diabetes, dyslipidemia, atherosclerosis, and metabolic syndrome.[1,2] High-sensitivity C-reactive protein has been adopted as a biomarker.[3–5] However, the site of low-grade inflammation has been of debate; whether it is the adipose tissue[6] or other tissues such as the periodontal tissue.[7]

Evolutionary medicine can give us an ultimate cause (ie, "why") of some disease rather than a proximate cause (ie, "how").[8,9] The key concept of evolutionary medicine is the "mismatch" between the selection pressure and the change of environment.[8–13] Some phenotype, which is advantageous for humans against some conditions, can cause several diseases, as trade-off.[8–13]

Humans have been exposed to infections by helminthes and bacteria, both of which have contributed to develop innate immunity as a defense system.[10,12] A proposed mechanism of an increase in allergy, termed the "hygiene hypothesis", is that the appropriate exposure to helminthes early in life is essential to set up immunoregulatory pathways.

Here I propose another paradigm from the viewpoint of evolutionary medicine why low-grade inflammation may underlie many complex diseases. The intestinal bacterial flora has evolved with humans, and they are now known to be fundamental to the development of the human innate immunity system.

Increasing evidences have indicated that innate immunity may be associated with some disorders. For example, Toll-like receptors (TLRs) have been indicated in the pathogenesis of atherosclerosis. Free fatty acids, which are secreted from the adipose tissue, may act as an agonist of TLR4 and cause a pro-inflammatory response of macrophages,[14] or oxidized LDL may be a ligand for TLR4.[15] TLR5 knock-mouse has shown a change of

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gut microbiota as well as a phenotype of metabolic syndrome.[16] Furthermore, very recently, it has been reported that carbohydrate-active enzymes are detected exclusively in intestinal flora of Japanese, which are derived from marine bacteria,[17] suggesting a racial difference in co-evolution of intestinal flora and humans.

Taken, together, it is possible that trade-offs of the innate immunity, which has evolved with intestinal flora, may underlie chronic complex diseases, such as obesity, atherosclerosis, or diabetes. A recent study has suggested that dark chocolate consumption changes gut microrbiota in humans.[18] Since sweet taste is known to affect the secretion of glucagon-like peptide 1(GLP-1), one of the incretin hormones, it may be of interest to investigate whether incretin analog may change the gut microbiota.[19]

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