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Nutritional regulation of immunosenescence for heart health

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Abstract

Immunosenescence via increased inflammatory cytokines may play key regulatory roles in facilitating cardiac infections and heart failure. Based upon recent evidence, we hypothesize that cytokine polarization due to aging directly dysregulates fibroblasts, leading to altered cardiac structure and dysfunction. Some dietary fatty acids should ameliorate heightened inflammatory cytokines thereby retarding cardiac pathology, loss of structural collagen and premature death from heart failure. For example, T-helper (Th) 2 cells' cytokine levels are very high in seniors who have increased heart disease due to suppressed resistance to cardiotrophic pathogens. In addition, such inflammatory cytokines deregulate fibroblasts, thus reducing collagen synthesis, weakening muscle structure and heart pump function for heart failure and hypertension. Therefore, supplementation with n-3 polyunsaturated fatty (PUFA) or conjugated linoleic acids, by reducing Th2 and increasing Th1 cytokines, may provide a sensible and widely available means to treat and even prevent excessive inflammatory cytokines and their cardiotoxic effects. On the other hand, dietary n-6 PUFA may promote cytokine polarization in seniors, exacerbating age-related heart dysfunction.

Keywords: Nutritional regulation; Immunosenescence; Heart health; Heart failure, collagen synthesis

1. Introduction

An emerging issue in nutritional immunology is dietary modulation of regulatory cytokines — especially during immunodeficiency. All four major immune cells (stem cells, macrophages, B cells and especially T cells) show age-related changes [1]. T-helper (Th) 1 cell cytokines that promote cellular immune defenses and activity are suppressed in the aged. Concomitantly, Th2-cell cytokine levels and production increase, suppressing Th1 cells and many immune defenses. As typified by immunocompetent young adults, a balance is needed in Th1- and Th2-cell activities for optimal anticancer and antipathogen defenses. We found that T-cell receptor peptides injected into old mice reduced aberrant cytokine polarization, maintaining resistance to cardiotrophic pathogens and prolonging life [2] while regulating fibroblast function to prevent loss of cardiac collagen and structure. Such pharmaceutical treatments take decades to develop and to deliver to the general public. However, supplementation with n-3 polyunsaturated fatty acids (PUFA) and conjugated linoleic acid (CLA) stimulates Th1 and suppresses Th2 cytokine production in old mice, promoting cytokine regulation. Would such immunoregulatory dietary fatty acids stimulate beneficial Th1 or suppress Th2 cytokine production for cardiac health in the aged?

Mice consuming CLA enhanced IL-2 production and decreased IL-4 production, partially restoring the Th1/Th2 cytokine ratio [3]. In old mice, n-3 PUFA from fish oil blunted immunosenescence by lowering their excessive Th-2 (IL-5, IL-10) cytokine production [4] while increasing IL-2 secretion [5]. Fish oil supplementation also increased interferon-gamma production and lymphocyte proliferation in healthy humans [6]. White n-3 PUFA protect against cardiovascular diseases such as myocardial infarction, arrhythmia, atherosclerosis and hypertension, the preventive mechanism is poorly defined. Conjugated linoleic acid isomers also appear to protect against atherosclerosis. Immune homeostasis (anti-Th2/pro-Th1) could help directly benefit patients with allergies and asthma (likely Th2-based diseases) as well as cancer, heart disease in seniors, HIV infection, immunosenescence and various acquired immunodeficiencies by improving cellular and humoral resistance

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to intracellular pathogens (viruses, bacteria, fungi). Several other nutrients and nutriceuticals modify Th1/Th2 balance in aged humans or mice including plant sterols/sterolins, probiotics, dehydroepiandrosterone, selenium and zinc. These elements therefore are potential dietary regulators of cytokine polarization and related heart disease.

However, could nutrition exacerbate cytokine polarization in the aged to promote heart disease? For example, in many people, the consumption of n-6 PUFA greatly exceeds that of n-3, producing inflammatory mediators (prostaglandins and leukotrienes). These arachidonic acid metabolites stimulate the production of Th2-cell cytokines such as IL-6, affecting balance within the immune system. As predicted, fish oil has been shown to lower inflammatory Th2 cytokines in mice with autoimmune diseases, whereas corn oil (rich in n-6 PUFA) did not. Linoleic acid gives rise to the eicosanoid inflammatory mediators including the two series of prostaglandins, leukotrienes and related metabolites. Prostaglandin E_2 increased the production of IL-6 in mice consuming safflower oil [7] with arachidonic acid — a long-chain, n-6 derivative of linoleic acid being associated with acute myocardial infarction. Saturated fatty acids increase NF-κB and thus IL-6, whereas dietary cholesterol can lower them. In addition, COX-dependent conversion of n-3 PUFA resulted in lower levels of inflammatory cytokine production in vitro compared to COX-dependent conversion of n-6 PUFA. Finally, replacement of n-6 with n-3 PUFA in cell membranes can result in a decreased response to inflammatory stimuli. Such mechanisms could explain why the Jewish population of Israel, whose diet is rich in n-6 PUFA, has a high incidence of ischemic heart disease.

In addition to demonstrating altered disease resistance, we have quite recently shown that cytokines regulate the structure and function of the heart even though it is a nonlymphoid organ [8]. Interestingly, our research reveals that Th2 cytokines, elevated in aged as well as retrovirus-infected mice, dysregulate cardiac fibroblasts. This dysregulation results in adverse structural and functional changes typically associated with the aging process. For example, healthy mature C57 BL/6 mice fed a diet high in salt and/or fat develop cytokine polarization with increased Th2 cytokines. The results are changes in collagen levels and hence arterial structure due to fibroblast dysregulation, yielding hypertension as we recently observed [8].

The composition of the cardiac interstitium reflects the balance between collagen synthesis and heart-health degradation. Cardiac fibroblasts produce most of the fibrillar collagen in the heart as well as most of the collagen-degrading enzymes, degraded by matrix metalloproteinases (MMP) — whose enzymatic activity is decreased by tissue inhibitors (TIMP) [9]. The abnormal matrix regulation of collagen synthesis and MMP/TIMP activity in the myocardium and more specifically in cardiac fibroblasts has been associated with heart failure. Inflammatory cytokines may be involved in the dysregulation of myocardial extracellular matrix, as IL-1β, TNF-α and IL-6 are elevated in the myocardium of heart-failure patients [10]. We have shown that a diet of high-fat and high-simple carbohydrates induces a dilated cardiomyopathy that results in a ventricular diastolic volume 135% greater than control. Ventricular stiffness is reduced by 40% with the same diet, a parameter that directly correlates with cardiac collagen content [8]. Moreover, hypertension induced with an 8% NaCl diet increases ventricular stiffness by 33% [8]. These studies underscore the effect of diet on the collagen-synthesis and degradation processes resulting in abnormal cardiac function (and potentially mediated through the immune system).

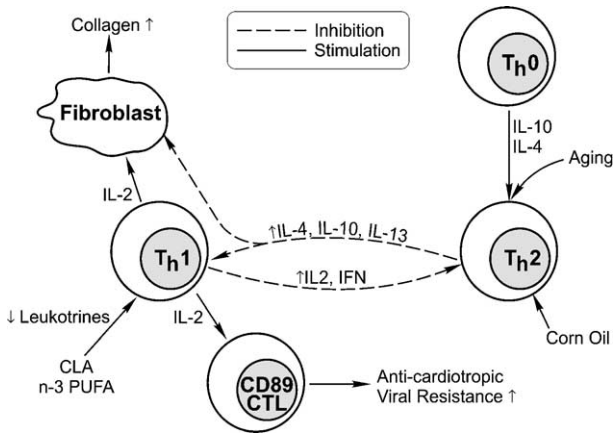

Fig. 1. Schematic representation of cytokine polarization in modulation of fibroblast activity and host resistance to protect or damage cardiac structure and function. Increased levels of Th1 cytokines promote collagen synthesis as well as activation of lymphocytes with antiviral activity. The role of nutrients such as PUFA in regulating cytokine production and hence heart structure is shown. Conjugated linoleic acid and n-3 PUFA stimulate Th1 cells, whereas n-6 PUFA in dietary corn suppress them, helping explain their known roles in heart disease in seniors.

Because cytokine polarization plays a key role in heart function in seniors, it needs to be studied and manipulated to prevent immune-mediated heart failure. Being readily available and safe, n-3 PUFA and CLA show promise to lower heart disease by cytokine depolarization in immunodeficient humans (aged, surgery, organ transplant and trauma, as well as some advanced cancer and arthritis patients). Their role in depolarizing cytokines by lowering biomarkers of inflammation and endothelial activation in people helps explain how these fatty acids can prevent cardiovascular disease [11]. A great need exists to explore this immune paradigm. Nutritional supplementation to treat or prevent cytokine polarization could restore cardiac function and structure during aging (Fig. 1).

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