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Low-Grade Systemic Inflammation Connects Aging, Metabolic Syndrome and Cardiovascular Disease

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Abstract

Aging is associated with immunosenescence and accompanied by a chronic inflammatory state which contributes to metabolic syndrome, diabetes and their cardiovascular consequences. Risk factors for cardiovascular diseases (CVDs) and diabetes overlap, leading to the hypothesis that both share an inflammatory basis. Obesity is increased in the elderly population, and adipose tissue induces a state of systemic inflammation partially induced by adipokines. The liver plays a pivotal role in the metabolism of nutrients and exhibits alterations in the expression of genes associated with inflammation, cellular stress and fibrosis. Hepatic steatosis and its related inflammatory state (steatohepatitis) are the main hepatic complications of obesity and metabolic diseases. Aging-linked declines in expression and activity of endoplasmic reticulum molecular chaperones and folding enzymes compromise proper protein folding and the adaptive response of the unfolded protein response. These changes predispose aged individuals to CVDs. CVDs and endothelial dysfunction are characterized by a chronic alteration of inflammatory function and markers of inflammation and the innate immune response, including C-reactive protein, interleukin-6, TNF-α, and several cell adhesion molecules are linked to the occurrence of myocardial infarction and stroke in healthy elderly populations and patients with metabolic diseases.

Aging is defined as a series of morphological and functional changes which take place over time. The term also refers to the deterioration of biological functions after an organism has attained its maximum reproductive potential [1, 2]. Aging is accompanied by a chronic inflammatory state which may contribute to metabolic syndrome (MS) and diabetes and their cardiovascular consequences. Inflammation accompanied by a proinflammatory cytokine production during aging is associated with pre-

disposing factors that include increased oxidative stress, a decrease in ovarian function, a decrease in stress-induced glucocorticoid sensitivity and an increased incidence of asymptomatic bacteriuria. Indeed, when compared with young subjects, healthy elders are more stressed and show activation of the hypothalamus-hypophysis-adrenal axis [3].

MS is a number of criteria reflecting abnormalities in lipid and glucose metabolism. These abnormalities are considered to be a cause for atherosclerosis, cardiovascular disease (CVD) and type 2 diabetes mellitus. The prevalence of CVD among patients with diabetes is 3- to 5-fold higher than in patients without it. MS demonstrates ethnic and gender variants, its frequency depends on the lifestyle and age. MS in an elderly population is a proven risk factor for cardiovascular morbidity, especially stroke and coronary heart disease and mortality. The high prevalence of MS, heart attacks and diabetes in the elderly population evidences that age is an independent risk factor for the development of metabolic abnormalities [4].

CVDs appear as a consequence of both insulin resistance and inflammatory responses which are increased during aging. Risk factors for atherosclerosis and diabetes overlap, and there is a propensity of diabetic patients to have premature atherosclerosis leading to the hypothesis that both share an inflammatory and perhaps genetic basis [5]. Low-grade inflammation caused by the secretion by adipocytes of proinflammatory cytokines due to our thrifty genotypes and alterations in the innate immune system due to our proinflammatory genotype are linked to insulin resistance, diabetes and CVD [6–8].

Aging, Diseases and the Regulation of Energy Allocation

Stress response genes and nutrient sensors regulate energy directed to cell protection, maintenance and longevity; when food is plentiful and stress levels are low, genes support growth and reproduction; in contrast, harsh conditions favor a shift in gene activity towards cell protection and maintenance extending life span. Therefore, changes in diet that lead to obesity, MS and diabetes determine longevity and alter the aging process. Important genes in extending life span include kinase mammalian target of rapamycin, AMP-activated protein kinase, sirtuins and insulin/insulin like growth factor 1 (IGF-1) signaling. These genes integrate longevity pathways and metabolic signals in a complex interplay in which life span appears to be strictly dependent on substrate and energy bioavailability [9].

IGF-1-mediated signaling is determining for longevity. Abnormalities in the insulin signaling pathway generate age-related diseases and increased mortality, whereas the growth hormone/IGF-1 axis could potentially modulate longevity in many species. Moreover in humans, an age-related decline in IGF-1 levels occurs, and at old age, low IGF-1 levels are associated with frailty, poor nutrition and cognitive decline and an increased risk of death [10, 11].

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The aging process is altered or accelerated when inflammation increases the propensity of metabolic diseases and CVD and the risk of diseases increases with age.

Aging and the Immune System

Aging has been associated with immunological changes, denominated immunosenescence. An elderly immune system becomes more and more predisposed to chronic inflammatory reactions and is less able to respond to acute and massive challenges by new antigens. A young immune system has to cope quickly and efficiently with acute immunological challenges to assure survival and the reaching of reproductive age. Such reaction capability gradually burns out because of lifelong antigenic attrition. Moreover, lifelong antigenic challenges and the increasing antigenic burden determine a condition of chronic inflammation, with increased lymphocyte activation and proinflammatory cytokines [12].

Polymorphisms in the promoter regions of pro- and anti-inflammatory cytokine genes influence the level of cytokine production and the aging process. Nutrients with anti-inflammatory properties, such as vitamin E and n-3 polyunsaturated fatty acid, may reduce the level of chronic inflammation and thereby ameliorate tissue and functional loss during aging. New evidence suggests that, for the latter nutrient, gene-nutrient interactions occur that alter the effectiveness of dietary therapy [13].

Inflammation in Obesity and Metabolic Syndrome during Aging

Obesity is increased in the elderly population. Obesity is the result of a complex interaction of factors in each individual including: genetic predisposition, diet, metabolism and physical activity. The increase in the mass of adipose tissue induces a state of systemic inflammation due to an increase in secretory factors (adipokines) derived from pre-adipocytes and from macrophages constituting this tissue (fig. 1). This inflammation significantly contributes to endothelial dysfunction present in the CVD developed as a consequence of MS and diabetes [14].

Adipose tissue also provides energy for the immune system, which has a significant energy cost. The contribution of energy stores to immune function became clear from early studies noting reduced survival in subjects of low relative weight [15, 16]. Infection imposes a metabolic burden on account of the need to synthesize immunoglobulins and acute-phase proteins and other processes such as inflammation and fever. To meet these costs of infection, lipolytic factors such as cortisol, glucagon and various hormones release energy from adipose tissue [17, 18].

The immune system represents a priority function of adipose tissue during malnutrition. Adipose tissue has been previously considered as a toxic substance, but it may

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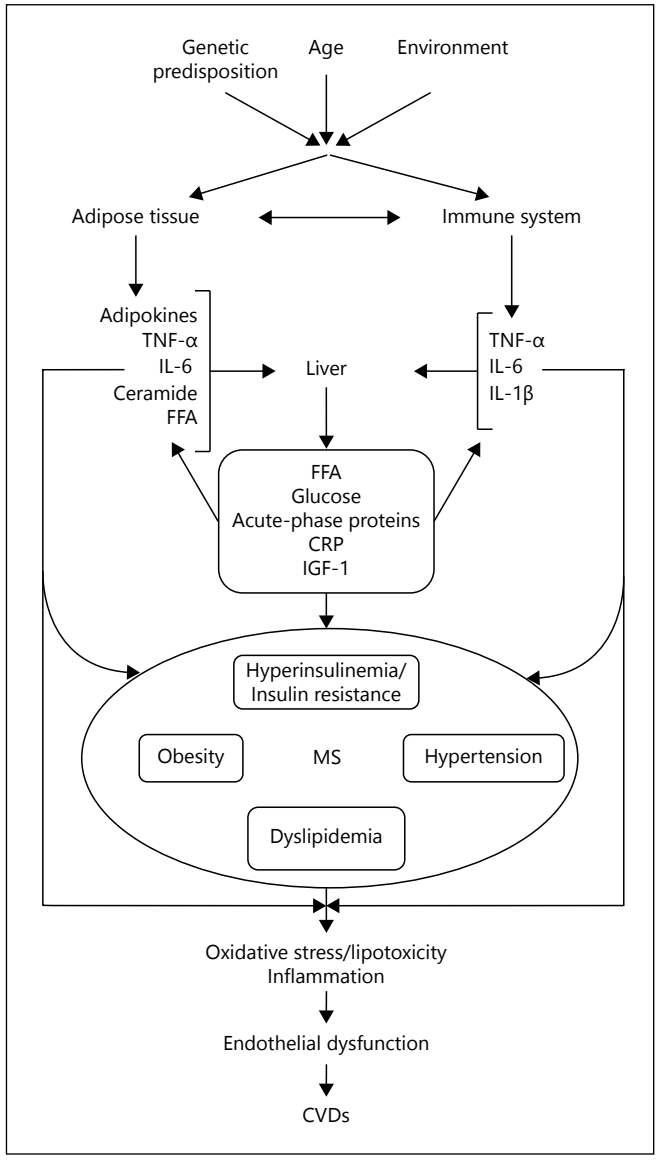

Fig. 1. Diagram of the pathophysiology of MS associated with low-grade systemic inflammation. Aging is accompanied by a chronic inflammatory state which may contribute to MS. The figure indicates the involvement of inflammatory factors derived from adipose tissue, liver and immune system cells leading to endothelial dysfunction and contributing to the development of CVDs. FFA = Free fatty acids.

be more appropriate to consider it as an activator of the immune function to increase protection against infectious diseases.

Adipocytes from old mice induce a higher inflammatory response in other cells. Sphingolipid ceramide is higher in old than in young adipocytes. Reducing ceramide levels or inhibiting NF-κB activation decreases cytokine production, whereas the addition of ceramide increases cytokine production in young adipocytes to a level comparable to that seen in old adipocytes, suggesting that ceramide-induced activation of NF-κB plays a key role in inflammation [19] (fig. 1).

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The Immune System and Type 2 Diabetes

There is increasing evidence that an ongoing cytokine-induced acute-phase response is closely involved in the pathogenesis of type 2 diabetes mellitus and associated complications such as dyslipidemia and atherosclerosis. Elevated circulating inflammatory markers such as C-reactive protein (CRP) and interleukin-6 (IL-6) predict the development of type 2 diabetes mellitus, and several drugs with anti-inflammatory properties (aspirin and thiazolidinediones) lower both acute-phase reactants and glycemia and possibly decrease the risk of developing type 2 diabetes mellitus (statins). Among the risk factors for type 2 diabetes mellitus, which are also known to be associated with activated innate immunity, are age, inactivity, certain dietary components, smoking, psychological stress, and low birthweight. Other features of type 2 diabetes mellitus, such as fatigue, sleep disturbance and depression, are likely to be at least partly due to hypercytokinemia and activated innate immunity [20].

The Liver and Inflammation in Metabolic Syndrome

The liver plays a pivotal role in the metabolism of nutrients, drugs, hormones, and metabolic waste products, thereby maintaining body homeostasis. The liver is central to glucose and lipid homeostasis as well as steroid biosynthesis and degradation. This organ also has a major impact on health and homeostasis through its control of serum protein composition. Concomitant with morphological changes, the liver exhibits important alterations in global gene expression profiles with age. In mice, aging is accompanied by changes in expression of genes associated with increased inflammation, cellular stress, fibrosis, altered capacity for apoptosis, xenobiotic metabolism, normal cell-cycle control, and DNA replication. These changes predispose aged individuals to CVD [21].

Hepatic steatosis and its related inflammatory state (steatohepatitis) are the main hepatic complications of obesity and metabolic diseases. Hepatic steatosis is a disorder characterized by fat infiltration and excessive accumulation of lipids such as triglycerides in the liver (nonalcoholic fatty liver, NAFLD). The accumulation of fat in hepatocytes is a consequence of three principle sources: de novo lipogenesis in the liver; nutritional uptake from the small intestine; and free fatty acid release from visceral white adipose tissue.

Hepatic steatosis is accompanied by an increased liver/body weight ratio and higher plasma levels of enzyme markers of liver damage (alanine aminotransferase, γ-glutamyltransferase, and alkaline phosphatase). This pathology, which is often associated with obesity, hyperinsulinemia, and insulin resistance, shows an inflammatory state, characterized by increased hepatic and plasma levels of several proinflammatory cytokines, particularly TNF-α, which may play a crucial role in the progress of steatohepatitis to hepatic necrosis, fibrosis, cirrhosis and cancer (fig. 1).

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It has been observed that 70% of the adult patients and 25.5% of the pediatric patients with MS have NAFLD. The prevalence of NAFLD increases with age, but the underlying molecular mechanisms need to be further investigated. Indeed, aged mice both under standard diet conditions or a high-fat diet will develop hepatic steatosis.

Hepatocytes, like other secretory cells, are rich in endoplasmic reticulum (ER). The ER is a highly dynamic organelle that has essential roles in multiple cellular processes that are required for cell survival and normal cellular functions. ER stress contributes to the pathology of many human diseases. Cell death, a physiological consequence of chronic ER stress, is key to the pathogenesis of many diseases including obesity, insulin resistance, hepatic steatosis, inflammation, neurodegenerative disorders and cancer.

The ER responds to environmental stress such as hyperlipidemia, hyperhomocysteinemia, hyperglycemia, and inflammatory cytokines, triggering a series of signaling cascades known as the unfolded protein response (UPR). The primary signal that activates the UPR is the accumulation of misfolded proteins in the ER lumen. As a consequence, the UPR regulates the size, shape and components of the ER to accommodate fluctuating demands on protein folding, as well as other ER functions in coordination with different physiological and pathological conditions. ER stress activates NF-κB and JNK, with downstream effects on inflammatory recruitment, phosphorylation of insulin receptor signaling intermediates (to worsen insulin resistance), lipogenesis, and oxidative stress. Hence, it is important to seek strategies to improve the antioxidant capacity in subjects who suffer from NAFLD as a consequence of MS.

Aging-linked declines in expression and activity of key ER molecular chaperones and folding enzymes compromise proper protein folding and the adaptive response of the UPR [22].

Fatty acids acting through toll-like receptors (TLR) in hepatocytes increase inflammation. TLR receptors are important pattern recognition receptors in the immune system that identify bacterial pathogens, but recently their participation in hypertension and insulin resistance has been recognized. Eight TLRs are expressed in mammalian liver (TLRs 1, 2, 4, 6–10). Individual TLRs interact with different combinations of adapter proteins and activate transcription factors such as NF-κB and JNK/activator protein 1. JNK activation is a key injury and inflammatory pathway in MS-related NAFLD [23].

Inflammatory Function, Atherosclerosis and Other Cardiovascular Consequences

Inflammation is one of the main mechanisms underlying endothelial dysfunction, and therefore it plays an important role in atherosclerosis and other CVDs such as hypertension. Recent investigations of atherosclerosis have focused on inflammation, providing new insight into mechanisms of the disease. Atherosclerosis is a disorder characterized by a chronic alteration of inflammatory function, and key markers of inflammation and the innate immune response, including CRP, IL-6, TNF-α, and several cell

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adhesion molecules are linked to the occurrence of myocardial infarction and stroke in both healthy populations and among those with known coronary disease [24] (fig. 1).

Inflammatory cytokines involved in vascular inflammation stimulate the generation of endothelial adhesion molecules, proteases, and other mediators, which may enter the circulation in soluble form. The concept of the involvement of inflammation in atherosclerosis has spurred the discovery and adoption of inflammatory biomarkers for cardiovascular risk prediction. CRP is currently the best validated inflammatory biomarker; in addition, soluble CD40 ligand, adiponectin, IL-18, and matrix metalloproteinase 9 may provide additional information for cardiovascular risk stratification and prediction.

An enhanced immune response also increases plaque vulnerability. Enhanced inflammation might prove to be an evolutionary determinant of atherogenesis, plaque rupture, platelet aggregation, and acute thrombosis.

Aging and hyperglycemia contribute to reduced mitochondrial biogenesis and mitochondrial dysfunction. These mitochondrial abnormalities can predispose a metabolic cardiomyopathy characterized by diastolic dysfunction. Mitochondrial dysfunction and resulting lipid accumulation in skeletal muscle, liver, and pancreas also impede insulin metabolic signaling and glucose metabolism, ultimately leading to a further increase in mitochondrial dysfunction [25].

Free oxygen radicals are involved in alcoholic cardiomyopathy, ischemia-reperfusion injury and aging. The myocardial cells are an important source of free radicals. When this organ suffers from diminished blood supply to an area as a result of diverse conditions such as a stroke, ischemia produces oxidative stress and structural damage, and the affected tissues die due to necrosis. Reperfusion may reverse the lethal process, but often not without taking its toll in the form of injury to the tissues. This is due to calcium re-entry to the cell, and this also generates an important amount of free radicals which are linked to alterations in mitochondrial function. There are specific alterations in heart mitochondrial function which occur as a result of ischemia and reperfusion and they involve the electron transport complexes, ATP concentration, ADP/ATP translocase, permeability transition and uncoupling [26].

Conclusion

Aging is associated with immunological changes, denominated immunosenescence, and is accompanied by a chronic inflammatory state which may contribute to MS and diabetes and their cardiovascular consequences. Inflammation is enhanced in the elderly population since there is increased obesity that increases fat-produced cytokines and alterations in hepatic function that lead to inflammation. Risk factors for CVDs and metabolic diseases overlap, and therefore the hypothesis that they share an inflammatory basis has been proposed, suggesting that low-grade systemic inflammation connects aging, MS and CVD.

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References

1 Guarner V, Rubio-Ruiz ME: Metabolic syndrome: early development and aging. J Diabetes Metab DOI: 10.4172/2155-6156.S2-002.
2 Guarner-Lans V, Rubio-Ruiz ME: Aging, metabolic syndrome and the heart. Aging Dis 2012;3:269–279.
3 Bauer ME: Stress, glucocorticoids and ageing of the immune system. Stress 2005;8:69–83.
4 Tereshina EV: Metabolic abnormalities as a basis for age-dependent diseases and aging? State of the art. Adv Gerontol 2009;22:129–138.
5 Stern MP: Diabetes and cardiovascular disease: the common soil hypothesis. Diabetes 1995;44:369–374.
6 Pickup JC: Inflammation and activated innate immunity in the pathogenesis of type 2 diabetes. Diabetes Care 2004;27:813–823.
7 Festa A, D'Agostino R Jr, Howard G, Mykkänen L, Tracy RP, Haffner SM: Chronic subclinical inflammation as part of the insulin resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRAS). Circulation 2000;102:42–47.
8 Kobayasi R, Akamine EH, Davel AP: Oxidative stress and inflammatory mediators contribute to endothelial dysfunction in high-fat diet induced obesity in mice. J Hypertens 2010;28:2111–2119.
9 Kenyon CJ: The genetics of aging. Nature 2010;464: 504–512.
10 Rincon M, Rudin E, Barzilai N: The insulin/IGF-1 signaling in mammals and its relevance to human longevity. Exp Gerontol 2005;40:873–877.
11 Rozing MP, Westendorp RGJ, Frölich M, de Craen AJM, Beekman M, Heijmans BT, Mooijaart SP, Blauw GJ, Slagboom PE, van Heemst D; Leiden Longevity Study (LLS) Group: Human insulin/IGF-1 and familial longevity at middle age. Aging 2009;1: 714–722.
12 Gersh BJ, Tsang TS, Seward JB: The changing epidemiology and natural history of nonvalvular atrial fibrillation: clinical implications. Trans Am Clin Climatol Assoc 2004;115:149–160.
13 Grimble RF: Inflammatory response in the elderly. Curr Opin Clin Nutr Metab Care 2003;6:21–29.
14 Frigolet ME, Torres N, Tovar AR: White adipose tissue as endocrine organ and its role in obesity. Arch Med Res 2008;39:715–728.
15 Lord G: Role of leptin in immunology. Nutr Rev 2002;60:S35–S38.
16 Kuzawa CW: Adipose tissue in human infancy and childhood: an evolutionary perspective. Am J Phys Anthropol 1998;(suppl 27):177–209.
17 Scrimshaw NS: Energy cost of communicable diseases in infancy and childhood; in Schurch B, Scrimshaw NS (eds): Activity, Energy Expenditure and Energy Requirements of Infants and Children. Vienna, IDECG, 1990, pp 215–237.
18 Biesel W: Metabolic response to infection. Ann Rev Med 1975;26:9–20.
19 Wu D, Ren Z, Pae M, Guo W, Cui X, Merrill AH, Meydani SN: Aging up-regulates expression of inflammatory mediators in mouse adipose tissue. J Immunol 2007;179:4829–4839.
20 Pickup JC: Inflammation and activated innate immunity in the pathogenesis of type 2 diabetes. Diabetes Care 2004;27:813–823.
21 Lebel M, de Souza-Pinto NC, Bohr VA: Metabolism, genomics, and DNA repair in the mouse aging liver. Curr Gerontol Geriatr Res DOI: 10.1155/2011/ 859415.
22 Brown MK, Naidoo N: The endoplasmic reticulum stress response in aging and age-related diseases. Front Physiol DOI: 10.3389/fphys.2012.00263.
23 Farrell GC, van Rooyen D, Gan L, Chitturi S: NASH is an inflammatory disorder: pathogenic, prognostic and therapeutic implications. Gut Liver 2012;6:149–171.
24 Packard RR, Libby P: Inflammation in atherosclerosis: from vascular biology to biomarker discovery and risk prediction. Clin Chem 2008;54:24–38.
25 Ren J, Pulakat L, Whaley-Connell A, Sowers JR: Mitochondrial biogenesis in the metabolic syndrome and cardiovascular disease. Mol Med (Berl) 2010;88: 993–1001.
26 Baños G, El Hafidi M, Franco M: Oxidative stress and cardiovascular physiopathology. Curr Topics Pharmacol 2000;5:1–17.

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