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EDITORIAL

CHOLESTEROL: AN INFLAMMATORY COMPOUND

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Obesity is one of the main rising causes of health problems in modern society and is correlated to type 2 diabetes mellitus, hypertension, heart disease and atherosclerosis. Bacterial products, endogenous substances such as oxidized LDL (ox-LDL) and heat shock proteins mediate activation of Toll-like receptors and reinforce the view that the innate immune system plays a key role in the genesis of atherosclerosis. In addition, natural killer T (NKT) cells respond to lipids presented via CD1d on APCs, and may also be able to affect atherosclerosis. All the main cell types involved in atherosclerosis such as endothelial cells, macrophages, T cells, smooth muscle cells and platelets express proinflammatory cytokines. In addition, CD4 ligation triggers the expression of adhesion molecules, cytokines and matrix metalloprotinease. IL-6 cytokines travels to the liver where it elicits acute phase response resolving in the release of serum amyloid-A C-reactive protein, fibrogen and plasminogen activator inhibitor-1. Therefore increasing body fat mass is associated with high levels of inflammatory cytokines such as IL-1 and TNF. In this study we revisit the interrelationship between fat and inflammation.

The discovery at the end of the 20th century of Toll-like receptors (TLRs) in mammalian innate immune cells, such as macrophages and dendritic cells, has reinforced the view that the innate immune system plays a key role in inflammatory response (1). Furthermore, the discovery that, besides bacterial products, endogenous substances such as oxidized LDL (ox-LDL) and heat shock proteins (HSPs) mediate activation of TLRs has reinforced the view that the innate immune system plays a key role in the

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genesis of atherosclerosis.

Concurrent with the influx of immune cells, the role of the adaptive immune response gradually increases. Effector T cells enter the lesion and may recognize auto-antigens such as oxidatively modified low-density lipoprotein (LDL) and heat shock proteins (e.g. hsp60) that are presented by antigen-presenting cells (APCs): major histocompatibility complex class II-positive macrophages or specialized dendritic cells. An innate antibody response by B1 cells also affects atherosclerosis. In addition, natural killer T (NKT) cells respond to lipids presented via CD1d on APCs, and as a result of their versatile response to presented lipids with respect to cytokine production they may be able to affect atherosclerosis in both an anti- and pro-inflammatory way.

CD40L plays an important role in this phase of atherogenesis. All the main cell types involved in atherosclerosis, including ECs, macrophages, T cells, smooth muscle cells (SMCs), and platelets, express this proinflammatory cytokine as well as its receptor, CD40 (2-5). CD40 ligation triggers the expression of adhesion molecules and the secretion of numerous cytokines and matrix metalloproteinases (MMPs) involved in extracellular matrix degradation (6-9). Importantly, CD40L has a prothrombotic effect, inducing EC (10), macrophage (11), and SMC (12-13) expression of tissue factor, which initiates the coagulation cascade when exposed to factor VII. Accordingly, inhibition of CD40 signaling reduces experimental atherosclerosis. IFN-α secreted by activated T cells, inhibits collagen production by SMCs. T lymphocytes can also contribute to the control of collagenolysis. CD40L as well as IL-1 produced by T cells induce macrophages to release interstitial collagenases, including MMP-1, -8, and -13 (14-17). The shoulder region of plaques as well as areas of foam cell accumulation contain MMP-9, a member of the gelatinase class of the metalloproteinase family (18-22). Human plaque analysis has revealed that MMP-9 is catalytically active and may thus contribute to the dysregulation of extracellular matrix that leads to plaque rupture during the complication of atherothrombosis (23-26). Further evidence suggests that local overexpression of MMP-9 promotes intravascular thrombus formation through increased tissue factor expression and tissue factor–mediated activation of the coagulation cascade (27-30) These data support an important role for MMP-9 in several stages of atherosclerosis.

Cross-talk between T lymphocytes and other cell types present within lesions heightens the expression of the potent pro-coagulant tissue factor. Cytokines orchestrate the production of adhesion molecules, MMPs, and reactive oxygen species that may also be released from lesions. In parallel, these primary cytokines induce the expression of the messenger cytokine IL-6, particularly in smooth muscle cells. IL-6 then travels to the liver, where it elicits the acute-phase response, resulting in the release of C-reactive protein, fibrinogen, and plasminogen activator inhibitor-1. Immunization against TNF-α did not significantly affect atherosclerosis in apoE-deficient mice despite the fact that antibodies were raised that effectively blocked TNF-α (31-35). This effect did not add to the effect of the adjuvant alone, which already has a beneficial effect on atherosclerosis (36-40). All these inflammatory markers and mediators, released at different stages in the pathobiology of atherothrombosis, can enter the circulation, where they can be easily measured in a peripheral vein. Biomarkers of inflammation include adhesion molecules such as VCAM-1; cytokines such as TNF, IL-1, and IL-18; proteases such as MMP-9; the messenger cytokine IL-6; platelet products including CD40L and myeloid-related protein (MRP) 8/14; adipokines such as adiponectin; and finally, acute phase reactants such as C-reactive protein (CRP), PAI-1, and fibrinogen. Soluble VCAM-1, for example, does not predict the risk of future myocardial infarction in apparently healthy men (41-44). However, research has repeatedly and unequivocally demonstrated the essential role of VCAM-1 in experimental atherosclerotic lesion initiation and progression (45-49) .

It is now generally accepted that, in addition to hypercholesterolemia, pro-inflammatory and procoagulatory factors play a major role in atherogenesis. Risk factors such as smoking, hypertension, diabetes and renal diseases alter lipoprotein profile and composition, thus rendering them susceptible to modification. Modified lipoproteins induce local inflammation, possibly due to activation of nuclear factor (NF-)κB and subsequent expression of adhesion molecules,

release of pro-inflammatory cytokines, growth factors and mitogens, which are mediators for cell growth, proliferation and lipid deposition. Elevated CRP levels have been associated with obesity (50). Several studies have been conducted in obese subjects and in obese patients with hyperinsulinemia, diabetes, or rheumatoid arthritis (51-54). Inflammation has been increasingly recognized as an important player in the pathophysiology of numerous human disorders. Accumulating evidence has led to the conclusion that atherosclerosis is an inflammatory disease, although it was believed to be a disorder of high cholesterol levels in the bloodstream for over a century.

Obesity is a common problem that is an increasing cause of impaired health in modern society (55-58). Obese subjects are more likely to develop type 2 diabetes mellitus, gall bladder disease, hypertension, heart disease, osteoarthritis, sleep apnea, nonalcoholic fatty liver disease and potential cirrhosis, and certain forms of cancer (59-61). An accumulation of excess intra-abdominal or visceral fat is associated with insulin resistance and is a major feature of the metabolic syndrome, which confers a 1.5- to 2-fold increased risk for developing diabetes and cardiovascular disease (CVD) (62-64). Increased body fat mass, especially when centrally located, is associated with higher levels of inflammatory adipocyte cytokines (adipokines) such as IL-6 and TNF-α that may contribute to, or worsen insulin resistance and CVD (65-66).

Obese patients are prone to a procoagulant state, in part attributed to the increased levels of plasminogen activator inhibitor–1 that have been observed to accompany the obese, insulin-resistant condition.[9] High levels of plasminogen activator inhibitor–1 result in reduced fibrinolytic capability, thereby contributing to increased risk for thromboembolic events (67-71).

The accumulation of excess adipose tissue causes increased expression or suppression of certain hormones, leading to inflammation and chronic disease. Obesity, is an important risk factor for cardiovascular disorders, it is often associated with hypertension and it increases the risk of metabolic perturbations including insulin resistance, hypertriglyceridemia, and low plasma high-density lipoprotein cholesterol (HDL-C) concentrations. Managing obesity as a way to prevent its metabolic and cardiovascular complications is thus an attractive target for reducing overall cardiovascular risk (72-75).

Traditionally, the treatment of cardiovascular and metabolic risk has targeted the management of individual risk factors, such as hypertension, type 2 diabetes, hypertriglyceridemia, and low high-density lipoprotein (HDL) cholesterol levels. Atherosclerosis is a chronic disease that develops over a lifetime, with clinical manifestations that occur after decades of silent progression. Despite recent progress in the treatment of cardiovascular disease associated with a significant reduction of death rates from 1990 to 2000, atherosclerotic disease is still the leading cause of mortality in developed countries.

Aortic stiffness - an independent determinant of cardiovascular risk - relates positively to circulating MMP-9 concentrations, suggesting a role for this elastin-degrading enzyme in the development of systolic hypertension (76-78). Patients with stable coronary artery disease have higher circulating concentrations of MMP-9 than healthy controls (79-81). Plasma MMP-9 concentrations during acute coronary syndromes are increased 2- to 3-fold compared to normal. Within a week, the initial MMP-9 elevation reverses back towards the control range, supporting an active role for MMP-9 in the pathogenesis of plaque rupture (82-85).

3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or statins, have revolutionized the treatment of hypercholesterolemia. Indeed, statins are the most efficient drugs to reduce serum cholesterol levels and have demonstrated their capacity to greatly reduce coronary morbidity and mortality in both primary and secondary intervention trials (86-87). Initially shown to be effective in patients with substantially elevated cholesterol (88), the benefits of statin therapy have also been demonstrated in patients with average cholesterol levels.

Statin therapy decreases C-reactive protein levels, in association with better clinical outcomes, regardless of cholesterol levels (89) and a reduction of atherosclerosis progression associated to a decrease in C-reactive protein levels has been observed in patients under statin therapy (90-94). Various studies have demonstrated a beneficial effect of statins in pathologies thought to be independent of

cholesterol levels.

Statins not only block cholesterol synthesis but also increase endothelial nitric oxide synthase expression and thus could decrease severity of cerebral ischemia in a mouse model of ischemic stroke. Although much research is needed to elucidate the mechanisms by which weight loss results in decreased inflammation, lowering CRP levels can be attributed to a decrease in fat mass which lowers IL-6 levels, which in turn decreases CRP synthesis by the liver, and from other cellular sources (95-107).

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