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Editorial

The immune system in atherosclerosis and in acute myocardial infarction

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Acute myocardial infarction (AMI) occurs when the atheromatous process prevents total blood flow through the coronary artery. It was previously thought that progressive luminal narrowing from the continued growth of smooth muscle cells (SMCs) in the plaque was the main cause of infarction, however, angiographic studies, have identified culprit lesions that do not cause marked stenosis.

Is now evident that plaque activation, rather than stenosis, precipitates ischemia and infarction. Coronary spasm could be involved to some extent, but most cases of AMI are due to the formation of an occluding thrombus on the surface of the plaque; the two major causes of coronary thrombosis are plaque rupture and endothelial erosion. Plaque rupture is detectable in 60-70% of cases and preferentially occurs when the fibrous cap is thin and partly destroyed. One of the major challenges in modern cardiology is the knowledge of the factors that induce a silent atherosclerotic plaque shifting from a stable to a vulnerable form.

The identification of blood-borne inflammatory and immune cells inside the atheroma, led us to postulate the involvement of an immune-inflammatory mechanism in atherogenesis, from plaque formation to the induction of its complication (1). Moreover, recent studies in animal models, as well as in humans, support the hypothesis that the accumulation and modification of low density lipoprotein (LDL) in the arterial intima triggers the innate immune system, which might be the first step in the atherosclerosis process.

Hypercholesterolemia causes infiltration and retention of LDL in the arterial intima (2) where it undergoes through a progressive oxidation process leading to ox-LDL that are internalized by macrophages and initiate an inflammatory response in the artery wall by inducing endothelial cell dysfunction and smooth muscle proliferation. In addition, this modified LDL up-regulates the expression of leukocyte adhesion molecules (vascular cell adhesion molecule 1-V-CAM 1, E/P-selectin), as well as other chemokines, such as macrophage colony-stimulating factor (M-CSF) and monocyte chemoattractant protein-1 (MCP-1), in the endothelial cells. Through those mechanisms, ox-LDLs expand the inflammatory process, induce monocytes prematurely entering into the subendothelial space and differentiating into macrophages, and up-regulate the expression of scavenger receptors (SRs) and toll-like receptors (TLRs) (3, 4) on the surface of activated macrophages.

Scavenger receptors (SR-AI and AII, MARCO, CD36, CD68, SR-PSOX) recognize the structural motif shared by a wide variety of components including bacterial endotoxins, apoptotic cells and ox-LDL; which all are taken up by activated cells and are destroyed through this pathway, nevertheless, when ox-LDL internalization exceeds their elimination by macrophages these cells store lipids becoming foam cells. On the other hand, the binding of oxLDL to TLRs initiate a cascade, which induces cell activation through the transmission of transmembrane signals (5), which activate nuclear factor kappa B (NF-κB) and mitogen activated protein kinase

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(MAPK) pathways; therefore, it induces the expression of wide variety of genes, such as those encoding several cytokines, proteases, protein involved in leukocyte recruitment, production of reactive oxygen species and phagocytosis, which contribute to start and to amplify the local inflammation.

Other than from ox-LDL, TLRs can be triggered by heat shock protein (HSP) 60, bacterial wall components and virus DNA or virus RNA; therefore, the atherosclerosis process could rely on several activating stimuli (6, 7).

T-cells participate in the formation of atherosclerotic lesions as early as monocytes, and they play a key role in the arm of adaptive immunity. The cells of adaptive immunity recognize specific molecular structures exposed by antigen presenting cells in the contest of MHC determinants. The activity of those cells depends on the generation of a large number of antigen receptors, such as T-cell receptors (TCRs) and immunoglobulin, by somatic rearrangement processes in blast cells. The effector activity of the adaptive immune system includes direct attack of antigen bearing cells by cytotoxic T lymphocytes (CTL), stimulation to B-cells to produce antibody against the antigen, and induction of inflammation, with enhanced innate response, in the area near the antigen.

T-cells are always present in atherosclerotic lesions; they predominantly are CD4+, CD3 +, TCRα/β +, T-cells, which recognize protein antigens presented to them as fragments bound to major histocompatibility complex class II (MHC-II) molecules. Initial activation of "naive" T-cells requires strong activating stimuli, best provided by the dendritic cells, a specialized macrophage cell. Once successful activation has occurred, the remaining memory T-cells have a lower activation threshold; therefore, subsequent rounds of stimulation require a lesser amount of antigen. Regular macrophage, not just dendritic cells, can accomplish this less stringent function and reactivation can occur in non-lymphoid tissues such as the vessel wall.

Lesional T-cells mainly have properties of the T helper 1 (Th1) subtype (8, 9) and secrete interferon-γ (IFN-γ). IFN-γ primes macrophages, improving the efficiency of antigen presentation and lowering the threshold for TLR dependent activation; therefore, it increases tumor necrosis factor-α (TNF-α) synthesis, a cardinal proinflammatory cytokine with NF-κB activating capacity, and interlukin-1 (IL-1).

In animals the extent of atherosclerosis is reduced when the Th1 pathway is inhibited pharmacologically or genetically (10, 11), demonstrating the key role of this arm in the pathogenesis of the disease. Evidence from studies in humans supports the involvement of autoantigens in atherosclerosis.

T-cells can be isolated from fresh human plaques, cloned, expanded in culture, and finally challenged with candidate antigens. Such experiments have identified ox-LDL as a major auto-antigen in the cellular immune response of atherosclerosis (12). This finding, together with the detection of anti-ox-LDL antibodies in atherosclerotic patients and experimental animals (13), supports the concept that immune responses to ox-LDL operate in atheroma.

Several studies have linked infection to atherosclerosis and coronary artery disease (CAD). Although many questions are unanswered, it has been shown that pathogens can trigger the innate immunity by binding TLRs and could activate the adaptive immune responses through several mechanisms including the molecular mimicry, direct T-cell activation and autoimmune reactions; moreover, the infectious agents can affect the vascular biology through the direct infection of tissue. Based on this, it has been proposed that chlamydia pneumoniae and cytomegalovirus in atherogenesis can play a role in the atherosclerosis pathology (14-25).

Further antigens involved in atherosclerosis are heat shock proteins 60 and 65 (HSP60-65), a protein produced in large amounts by injured cells, which act as "chaperones" to limit denaturation of other cellular proteins. HSP60 release can not only induce specific antibodies and T-cells, but also directly activate innate immunity, binding TLR-4 receptors like a bacterial endotoxin (26, 27).

Cytokines produced by Th1 cells and macrophages produce large amounts of molecules downstream in the cytokine cascade. As a result, elevated levels of IL-1, IL-6, TNF-α, IFN-γ, and C-reactive protein (CRP) can be detected in the peripheral circulation, with high levels predicting worse prognosis. In this way, the activation of a limited number of immune cells can initiate a cascade, both in the forming lesion and systemically.

Elevated CRP levels in patients with acute coronary syndrome likely reflects this inflammatory activity in the coronary artery, rather than in ischemic myocardium (28); this finding suggests that inflammatory immune

activation in the coronary arteries initiates acute coronary syndromes, with circulating levels of inflammatory markers reflecting the clinical course of the condition.

The central lipid-rich core of the typical atherosclerotic lesion contains many lipid-laden macrophage foam cells that produce large amounts of tissue factor (TF), an extremely potent pro-coagulant, which can stimulate thrombus formation when in contact with blood (29). Therefore, coronary thromboses result frequently from a fracture in the protective fibrous cap. Ample evidence now supports the concept that the protective fibrous cap, far from being fixed and static, actually can undergo continuous and dynamic remodeling and displays considerable metabolic activity (30).

The balance between synthetic and degradative processes, closely controlled by inflammation mediators, regulates the collagen level in this structure; for example, the above-mentioned lymphokine INF-γ, can inhibit de novo synthesis of interstitial collagen by SMCs (31). Moreover, proinflammatory cytokines induce the expression of enzymes, capable of breaking down constituents of the arterial extracellular matrix (ECM); in particular, matrix metalloproteinases (MMP) can degrade the collagen fibrils that lend strength to the plaque's fibrous cap (32, 33).

SMCs also influence the levels of ECM, by the production of major isoforms of tissue inhibitors of metalloproteinases (TIMPs) (34). Fatal thrombosis sites typically have few SMCs (35, 36), since inflammatory stimuli can trigger the apoptosis of these cells (37).

As we have seen above, fatal thrombosis in coronary arteries occasionally results from the erosion of the endothelial cells, which uncovers the thrombogenic subendothelial matrix (38, 39). Inflammation can contribute to this mechanism, inducing the endothelial cells apoptosis (40, 41) and increasing the expression of TF and PAI-1 (42).

Vasospasm reducing the arterial flow can also contribute to increasing hypoxia that precipitates the endothelium dysfunction leading to the reduced production of vasodilatative factors (PG, and nitric oxide) and the increase of vasoactive substances like endothelins and tromboxane. Consequent to inflammatory stimuli, endothelial cells in atherosclerotic arteries show impaired vasodilator function, in part from the decreased production of nitric oxide while the vasospasm is increased as well as the thrombophylic state. In addition to producing vasodilatation, nitric oxide can weaken platelet aggregation and has a direct anti-inflammatory effect; moreover, augmenting the production of the inhibitor of NF-κB the inflammation results to be activated (43-45).

The above-reported elements, strongly suggest that atherosclerosis can be considered as an autoimmune or an immuno-mediated disease characterized by the imbalance among regulatory and effector mechanisms of the immune system.

The immunologic homeostasis is achieved by a physiological mechanism (peripheral immune tolerance) aimed at containing the peripheral immune system from damaging tissues by excessive reactivity and/or preventing auto-reactive T-cells, which have escaped the thymus negative selection, from causing autoimmunity.

The peripheral immune tolerance is quite a complex situation that can be achieved through several mechanisms that include ignorance, anergy, apoptosis, exhaustion, immune deviation and suppression. Thereafter, it seems logical, given the above-mentioned findings, to suggest that impairment in maintaining tolerance could contribute to the onset of atherosclerotic disease.

Looking at this context, it is of interest to underline that atheroma lesions contain a large number of Th1 cells in contrast with the only modest quantitative of Th2 cells. Since Th2 cells, at variance of the Th1 counterpart, secrete a set of cytokines (IL-4, IL-10, tumor growth factor-β (TGF-β)) performing immunosuppressive activity, one can hypothesize that Th2 cells could be protective against atherosclerosis.

Th1 activated cells facilitate atherogenesis and produce cytokines, such as IL-12 and IL-18, which stimulate their own proliferation and inhibit the Th2 response (46-52). In contrast, IL-4 and IL-10, produced by Th2, may inhibit Th1 activity and the development of vascular disease. This hypothesis seems to be confirmed by some experimental evidence that shows that IL-10 gene targeting, as well as its pharmacologic inhibition, aggravates atherosclerosis in hypercholesterolemic mice and exacerbates coronary thrombosis (53-55). Moreover, abrogation of TGF-β signaling in T-cells, elicits a dramatic phenotype, with rapid development of large, unstable atherosclerotic plaques

(56). These findings indicate that immunity is under tonic inhibition, by TGF-β and IL-10, and that the removal of these brakes on the effector T lymphocytes accelerates the atherosclerosis process.

The antibody producing B-cell harm seems to be less involved in the atherosclerotic disease; few B lymphocytes are detectable in the lesions. In our experience, in humans, we found low circulating levels of IgG specific for ox-LDL in the serum of patients affected by AMI (57). Nevertheless, several reports suggest that B lymphocytes could exert a protective activity in the atherosclerosis diseases through different mechanisms.

First, IgG could bind and inactivate the ox-LDL antigen, which represents a chronic immunological stress for the plaque.

Secondly, the low circulating levels of IgG to ox-LDL in AMI could depend on extreme activation of the Th1 arm in the vascular lesions (see above concerning cross regulation between Th1/Th2).

Finally, it could be an indirect marker of the reduced activity of some protective cells, like B lymphocytes, whose activation is under the control of Th2 pathway.

Is not definitely known whether such athero-protective effects depend on circulating antibodies against plaque antigens or on T-B cells interaction mediated by cytokines, however, several studies lead us to prefer the first hypothesis.

Immunization in animals with ox-LDL reduces atherosclerosis in hypercholesterolemic rabbit and mice, and the transfer of immunoglobulins also inhibits disease development (58-61). Spleen B-cells, which are particularly effective atherosclerosis inhibitors, recognize phosphorylcholine, a molecule present in ox-LDL, apoptotic cell membranes and in the wall of Streptococcus pneumoniae (62, 63).

These antibodies may contribute to the elimination of ox-LDL and dead cells, as well as to the defence against pneumococcal infection; interestingly, patients who have undergone splenectomy, have increased susceptibility, not only to pneumococcal infection, but also to CAD (64).

Knowledge regarding the role of immunity and inflammation in CAD provides new insights into the pathogenesis of CAD, of acute coronary syndrome and particularly of myocardial infarction; moreover, it offers new opportunities in the diagnosis, prediction and treatment of this life threatening disease.

Immunosuppressant or anti-inflammatory agents could represent attractive treatments for acute coronary syndrome. Cyclosporine, syrolimus and tacrolimus block the activation and proliferation of T-cells, as well as of SMCs; although they are actually employed in drug eluting stents to prevent restenosis, we still do not know whether this compound family could be used systemically in the prevention and treatment of acute coronary syndrome (65-67). Moreover, the "late thrombosis" of drug eluting stents has taught physicians that the inhibition of immune-inflammatory system may be dangerous, particularly if it is not aimed at a specific target.

Equally complex is the situation of anti-inflammatory drugs; recent data showed increased incidence of cardiovascular events in patients treated with rofecoxib, a cycloxigenase-2 inhibitor which blocks the production of the anti-thrombotic compound by platelets (68).

Statins are certainly the best usable anti-inflammatory drug in clinical practice (69-77) this pleiotropic effect depends on the inhibition of isoprenoid intermediate and cholesterol production by mevalonic acid.

Isoprenoids control the activity of many signaling pathways; reduced cholesterol synthesis may interfere with the membrane composition and with the clustering of T-cell receptors during immune activation. Therefore, statins may inhibit antigen-dependent T-cell activation. The vaccine represents an attractive approach, because it could conversely induce a protective immunity (78) against a specific target. In animals, atherosclerosis was reduced by vaccination with ox-LDL or HSP60 (58, 61, 79-81) this could be due to the induction of protective auto-antibodies or T-cells.

Since better antigen preparation must be developed and more knowledge obtained before the vaccination can be tested in humans, several research groups are trying to identify the molecular properties of antigens, which may cause an immune response in atherosclerotic lesions.

Other perspectives have come from research regarding inflammatory cytokines; some of these compounds, especially TGF-β, regulate the immune response by the inhibition of T-cells, and so it looks very promising for the future management of atherosclerotic disease.

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