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INCREASED INFLAMMATORY RESPONSE IN UNSTABLE ANGINA

Abstract. The article offers contemporary perspectives on how inflammation contributes to atherogenesis. The study reviewed research on the function of endothelium local factors, including the build-up of smooth muscle cells, T and B lymphocytes, macrophages, matrix metalloproteinase (MMP), and high-sensitivity C-reactive protein (CRP). In coronary artery disease (CAD), oxidized low-density lipoprotein (OLDL) and CRP are directly linked to inflammatory arterial damage. Monocyte chemoattractant protein (MCB-1) and MMP-1 activate monocytes in inflammatory regions, which contribute significantly to the rupture of atherosclerotic plaque and the subsequent emergence of acute coronary problems. MMPs, tumor necrosis factor α (TNF-α), and granulocyte-macrophage colinear stimulating factor (GM-CSF) are all synthesized more when CRP and SLDL are present.
Keywords:vischemic heart disease, atherosclerosis, acute coronary syndrome, inflammation markers.

One of the leading causes of death and disability in developed nations is coronary heart disease (CHD). Although numerous risk factors for the onset and progression of CHD have been investigated, the primary cause and trigger for acute coronary problems remain unclear. Atherosclerosis and thrombosis are the primary processes that cause acute coronary syndrome (ACS) [1]. The so-called susceptible atherosclerotic plaques are typically the target of inflammation. Endothelial cells, SMC, monocytes, neutrophils, platelets, macrophages, T-lymphocytes, and B-lymphocytes are the primary active constituents of loose connective tissue.

Early on in the development of arterial disease, as well as throughout the phase of AB instability and destruction, there are indications of a local nonspecific inflammatory process in atherosclerosis. The involvement of inflammation in the process of AB destabilization has been examined to a larger extent and it has been demonstrated that lipids are not engaged in the mechanism of AB degradation [1].

The inflammatory response in atherosclerotically altered arteries includes circulating leukocytes in addition to the equivalent arterial wall cells. Both macrophages and lymphocytes are essential to this process [3].

The innate (non-specific) and adaptive immune systems work together to maintain the delicate balance between the inflammatory and anti-inflammatory states when the immune system is active. The capacity to alter receptor expression for novel autosomal or foreign substances is a hallmark of the adaptive immune system. Its role is to control the immune response and to preserve humoral and cellular immunity. T-helpers (CD4+), cytotoxic T-killers (CD8+), and B-lymphocytes are among the cells that make up the adaptive immune system. CD4+ T cells can develop into at least three categories following antigen activation: 1) Th1, which produces proinflammatory cytokines like γ-interferon (IFNγ) and is important in cellular immunity; 2) interleukin-2 (IL-2), lymphotoxin, and Th2, which preserve humoral resistance and release anti-inflammatory cytokines like IL-4 and IL-10;

Macrophages may congregate in a central core in the typical atherosclerotic plaque where they can undergo apoptosis producing the "necrotic core" of the atherosclerotic lesion or release MMPs which degrade the extracellular matrix promoting plaque rupture. Coronary spasm due to smooth muscle hyperreactivity is the predominant cause of myocardial infarction in patients with a history of vasospastic angina, although this event is rare. However, coronary vasoconstriction and thrombosis are deeply interrelated. On the one hand occlusive coronary spasm and distal blood stagnation are known to cause a transient several fold increase of fibrinopeptide A in systemic blood. On the other serotonin, a substance released by activated platelets, is known to produce occlusive spasm in patients with variant angina and ischemia due to distal vessel constriction in patients with chronic stable angina.

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The cytokines secreted by activated inflammatory cells have the potential to activate the endothelium transforming its antiadhesive and anticoagulant properties into adhesive and procoagulant properties. Indeed, endothelial cells stimulated by IL-1, TNF or endotoxin express adhesion molecules such as intercellular adhesion molecule-1 (ICAM-1) and E-selectin on their surface and secrete soluble chemoattractants such as monocyte chemoattractant protein-1 (MCP-1), monocyte colony stimulating factor (M-CSF) and IL-8. Of note, in activated endothelial cells different adhesion molecules and chemoattractants are expressed almost simultaneously, thus suggesting a concerted activation of different genes probably, related, at least partially, to the activation of the nuclear factor κB (NF-κB)[6]. The latter was initially described in lymphocytes where it controls the activation of genes which encode for the κ chains of immunoglobulins. It consists of a family of dimeric transcription factors linked to an inhibitory protein (I-κB). The phosphorylation of I-κB results in the translocation of active subunits in the nucleus where they link to specific sequences in the promoter regions of different genes thus activating mRNA transcription.Sequences able to link NF-κB elements have been found in several human genes, including those encoding for endothelial adhesion molecules. Thus the NF-κB system might mediate cytokine-induced endothelial synthesis of adhesion molecules and of soluble chemoattractants following endothelial activation. An increase of IL-6 and of CRP following coronary angioplasty or following the weak inflammatory stimulus of coronary angiography is observed in unstable patients with elevated baseline CRP levels[3]Accordingly, peripheral monocytes from unstable patients with elevated CRP levels (>0.3 mg/dL) hyper-respond in vitro to the stimulus of lipopolysaccharide compared to monocytes from unstable patients with low CRP levels (<0.3 mg/dL), and also from stable angina patients and healthy controls (Figure 2)[4] Furthermore, in patients with acute MI the acute phase protein response to necrosis was found to be independent from infarct size, but predicted by baseline CRP levels; in this study elevated baseline CRP levels were found in 85% of myocardial infarction preceded by unstable angina. Taken together, these findings suggest that hyperreactivity of inflammatory cells to subliminal inflammatory stimuli may contribute to cause coronary instability. In line with this hypothesis, an unusual subset of T cells expressing the $CD4^{+}$CD28 null phenotype has been identified in patients with an increased inflammatory state[5].These unusual T cells are committed to the production of IFN-δ. The chronic up-regulation of IFN-γ in unstable angina patients could lead to subsequent activation of monocytes/macrophages in the circulation as well as in tissue lesions δ. The finding that CD28 null T cells have cytolytic capability suggests that immune reactions in individuals with such T cells are deviated towards a high risk for tissue damage. Environmental as well as genetic mechanisms could underlie the perturbation of the T cell repertoire. In particular, since the defect in CD28 cell surface expression may result from chronic exposure to antigen, the expansion of $CD4^{+}$CD28null T cells may reflect a persistent immune response to microorganisms or autoantigens contained in atherosclerotic plaques.It should be emphasized that inflammation associated with ACS is widespread and not restricted to the culprit stenosis. Accordingly, previous studies showed that ACS are associated with multiple coronary thrombosis at post-mortem examination, with microvascular impairment in remote regions and with enhanced short-term progression of non culprit stenoses.

Two-thirds of ACS patients have systemic indications of inflammation, which is likely an antigen-driven immune response. An important factor in determining coronary thrombosis and vasoconstriction that cause patient symptoms in this subgroup of patients is probably the activation of inflammatory cells in the culprit stenosis. It is noteworthy that inflammation is widespread throughout the coronary circulation and is not restricted to the culprit stenosis. It is uncertain what causes coronary thrombosis in ACS patients who are unstable and do not show systemic signs of inflammation.

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