

Human Coronary Atherosclerotic Plaque with

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What is known about the role of immune system in development of coronary atherosclerotic plaques?

Cagatay Oktenli: Atherosclerosis is a chronic inflammatory disease in which dyslipidemia, inflammation, and the immune system play an important role (1). The spectrum of clinical syndromes caused by coronary atherosclerosis ranges from asymptomatic disease and stable angina (SA) to acute coronary syndromes (ACS), which include unstable angina (UA), myocardial infarction (MI), and sudden cardiac death.

Briefly, both the innate and adaptive arms of the immune system lead to inflammation in the developing coronary atherosclerotic plaque (2). In the atherosclerotic plaque, an antigen-specific adaptive immunity response can develop against antigens of microbial origin, oxidized LDL (OxLDL), heat shock proteins and β 2-glycoprotein I (2). The most important receptors for innate immunity in atherothrombosis are the scavenger receptors and the toll-like receptors (3). The scavenger receptors SR-A and CD36 are responsible for the uptake of oxLDL, transforming the macrophage into a foam cell (4). Macrophage/foam cells produce cytokines that activate smooth-muscle cells, resulting in extracellular formation and fibrosis.

Interleukin-6 (IL-6) is the cytokine with the most extensively studied pro-atherogenic profile. Plaques from diseased coronary arteries showed high levels of IL-6 (5). Likewise, IL-1 is also one of the first cytokines to be considered

instrumental in the propagation of vessel wall inflammation in atherosclerosis (6). IL-1 also helps in recruitment and retention of inflammatory cells such as monocytes/macrophages in the early stage of atherogenesis (7). On the other hand, tumor necrosis factor- α (TNF α), another proinflammatory cytokine, and expression has been demonstrated in both early and advanced human atherosclerotic plaques (8).

Several studies substantiate the role of IL-2 in atherogenesis (9). A possible explanation for the presumed proatherogenic effect of IL-2 may lie in its ability to induce a T-helper (Th) cell shift toward a Th1 phenotype (15). Similarly, IL-12 is also pro-atherogenic and plays an active role in regulating the immune response during the early phase of atherosclerosis (10).

Conversely, IL-4 is known to promote Th2-type responses and is found to have a protective effect against vascular injury (11). Similarly, IL-10, IL-13 and transforming growth factor- β (TGF- β) are also potentially anti-atherogenic (11). IL-10 exerts its effect on the Th1/Th2 balance by downregulating IL-12 and IL-18 production and inhibits any Th1-based immune responses (12).

IL-8 is found in human atheroma (13) and macrophages from atherosclerotic plaques show an enhanced capacity to produce IL-8 (5). Therefore IL-8 plays potential atherogenic role at focal sites in

the atherosclerotic plaque (14).

C-reactive protein (CRP) is an acute-phase reactant that serves as a pattern recognition molecule in the innate immune system (15). CRP has been localized directly within atheromatous plaque where it precedes and mediates monocyte recruitment (16). In addition, CRP stimulates monocyte release of inflammatory cytokines such as IL-1 β , IL-6, and TNF- α (17) and may also directly act as a proinflammatory stimulus to phagocytic

cells by binding to the Fc γ RII receptor (18). CRP is also an activator of complement, and it has been shown to colocalize with the membrane attack complex in early atherosclerotic lesions (19).

Consequently, innate and adaptive immune reactions are key events in pathogenesis with the balance between proinflammatory and anti-inflammatory stimuli being crucial for the development of atherosclerotic lesions.

Are there typical indicators available of immune system activation in the atherosclerotic process?

Cagatay Oktenli: Atherosclerotic processes induce inflammatory and immune responses, are not only confined to coronary vasculature or ischemic myocardium but also include stimulation of circulating monocytes and subsequent induction of acute phase proteins. Of all the plasma markers of vascular inflammation, CRP has been the most extensively investigated in clinical studies (20,21). Apart from CRP, a wide range of cytokines and chemokines has been investigated both as risk markers but also as possible risk factors for development of atherosclerosis. Plasma levels of monocyte chemoattractant protein-1 (MCP-1) and interferon- γ (IFN- γ) have been found to be increased in patients with UA (22). Plasma TNF- α concentrations

are persistently elevated among post-MI patients at increased risk for recurrent coronary events (23). The IL-2 level was increased in patients with acute ischemic syndrome and patients with SA compared to healthy controls (24). Increased levels of interleukin IL-6 have been reported in patients with UA compared with patients with SA (25). Lower levels of IL-10, with higher proinflammatory to anti-inflammatory cytokine ratios, were observed on admission in patients with UA who subsequently had cardiovascular events (26). Serum IL-18 level was identified as a strong independent predictor of death from cardiovascular causes in patients with coronary artery disease regardless of the clinical status at admission (27).

Do you believe that IL-6 is a good marker for cardiovascular risk?

Cagatay Oktenli: As partly mentioned above, many studies showed that IL-6 plasma levels are increased in patients with UA compared to those with SA or healthy subjects (25). IL-6 plasma level is increased in patients with acute MI (28) and peaks by about 36 h after the onset of myocardial damage. Furthermore, IL-6 plasma level could reflect the extent of inflammatory reactions

in the atherosclerotic vessels (29). This could explain why IL-6 is a predictive factor of MI-coronary death but not of angina (30).

There are several reports whether IL-6 is useful as a prognostic marker for cardiovascular risk. First, it has been proposed that IL-6 is weaker a risk marker for cardiovascular diseases than CRP, data directly comparing these two inflammatory markers

are warranted (31). Second, the levels of IL-6 were increased in patients with ACS compared to patients with SA and healthy controls (24), but during follow-up IL-6 levels were not predictive for coronary events in patients with ACS (32). Third, a circadian variability, with increased IL-6 levels during the night, has been described (33). However, CRP seems to be a stable protein and plasma levels do not vary diurnally. Finally, it seems likely that IL-6 is not a good marker for cardiovascular risk.

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