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Editorial

Interaction of Modified Lipoproteins with Innate and Adaptive Immunity

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Editorial

The main scientific interest of our working group rests on the pathogenesis of atherosclerosis with three main topics: i) role of modified lipoproteins for the initiation and progression of atherosclerosis (propagating an alternative hypothesis comprising both enzymatic degradation and oxidation of Low Density Lipoprotein (LDL)) ii) impact of C-reactive protein on atherosclerosis (promoted by CRP as cardiovascular risk marker, which is still a matter of lively debate) and iii) role of antioxidative enzymes in atherosclerosis.

ad i) Concerning the above mentioned hypothesis for the different impact of enzymatically degraded LDL (eLDL) and oxidized LDL (OxLDL) on atherosclerotic lesion initiation and progression, our working group proposes the following model integrating both lipoprotein modifications. Since LDL sporadically becomes entrapped in the arterial intima, a mechanism should exist to remove the stranded lipoprotein. We hypothesize that under normal circumstances, the lipoprotein is indeed enzymatically degraded in the first place by several proteases and cholesterylesterase [1] and epitopes are exposed to enable the lipoprotein to be recognized and taken up by macrophages. Indeed, in contrast to OxLDL, specific monoclonal antibodies allowed demonstration of extensive extracellular deposits of enzymatically modified LDL (eLDL) in the early atherosclerotic lesion [2], a prerequisite for sufficient cellular uptake of and foam cell formation by modified LDL. eLDL is recognized by multiple macrophage receptors and is the most potent naturally occurring foam cell inducer known to date [3]. This will lead to a sequence of events that serve to clear the vessel wall of cholesterol and is concluded by the transfer of excess cholesterol from foam cells onto HDL for reverse cholesterol transport [4-6].

ad ii) More than 30 epidemiological studies have demonstrated a significant association between elevated serum or plasma concentrations of CRP and the prevalence of atherosclerotic vascular disease, the risk of recurrent cardiovascular events among those with established disease, or the incidence of first cardiovascular events among those at risk. This strong base of epidemiological evidence has led to the hypothesis that CRP is both a marker of and a causal agent in the development of atherosclerosis. Against this background, it became logical to search for a possible link between tissue-deposited eLDL (see above), CRP, and complement activation. As a first step, we demonstrated the presence of CRP both in the early human atherosclerotic and aortic valve lesion and its colocalization with eLDL and also the terminal complement complex (C5b-9) by immunohistochemistry [8-10]. The demonstration of C5b-9 in the early human atherosclerotic lesions and its colocalization with smooth muscle cells [11] provided further evidence for a possible role of complement activation in the early stages of atherogenesis. Furthermore, we were able to demonstrate that CRP is chemotactic for human monocytes and may therefore play a major role in the recruitment of monocytes during atherogenesis [12]. Notably, further work indicated that eLDL binds to CRP and activates complement in atherosclerotic lesions *via* a CRP-dependent and CRP-independent pathway [9]. We extended this observation and demonstrated that the CRP-dependent pathway halts before the proinflammatory terminal sequence, while the CRP-independent pathway proceeds to completion with the generation of C5b-9 complexes [13]. Thus, binding of CRP to eLDL is the first trigger for complement activation in the atherosclerotic lesion, but the terminal sequence is thereby spared. This putatively protective function of CRP is overrun at higher eLDL concentrations, so that potentially harmful C5b-9 complexes are generated [13]. If the amount of insudated LDL exceeds the recycling capacity of the normal intima, or, in other words, the capacity of the system is overburdened, this will lead to an imbalance between lipoprotein and cholesterol deposition and removal with subsequent accumulation of extracellular LDL particles. If these are oxidized in the course of their prolonged residence time in the intima, among a wealth of well documented events CRP also binds to OxLDL through recognition of phopshorylcholine of oxidized phospholipids [14]. During these advanced stages of atherosclerosis, we demonstrated that uptake of labeled oxidation-specific antibodies is focally diminished in plaques displaying accepted features of plaque stability. Imaging techniques to detect the presence and depletion of OxLDL may therefore be useful in assessing plaque stabilization [15]. Conclusively, given the above mentioned examples for the role of both lipoprotein modification in early and advanced atherosclerosis, we propose that eLDL might be more important for initiation of atherosclerosis while OxLDL might be more helpful for diagnosis and prognosis of the disease. In this context, oxidative modifications in the vessel wall are considered to occur primarily as a process secondary to inflammation [5].

ad iii) Oxidative stress is defined as an imbalance between the production and degradation of reactive oxygen species (ROS). Enzymatic inactivation of ROS is achieved mainly by superoxide dismutases, catalase and the glutathione peroxidases. Glutathione and the glutathione peroxidases constitute the principal antioxidant defense system in mammalian cells. Glutathione peroxidase 1

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(GPx-1), the ubiquitous intracellular form and key antioxidant enzyme within many cells, including the endothelium, consumes reduced glutathione to convert hydrogen peroxide to water and lipid peroxides to their respective alcohols. It also acts as a peroxynitrite reductase. Due to its major role in the prevention of oxidative stress, GPx-1 may be an important antiatherogenic enzyme. In fact, we have shown in patients with coronary artery disease that a low activity of red blood cell GPx-1 is associated with an increased risk of cardiovascular events independently of traditional risk factors for atherosclerosis [16]. Furthermore, we were able to substantiate this observation by demonstrating that deficiency of GPx-1 accelerates and modifies atherosclerotic lesion progression [17,18]. The results from this study and a recent study on calcific aortic valve stenosis [19] show that modification of antioxidant defense systems may indeed add important clues to our understanding of oxidative stress in atherogenesis and may eventually redirect clinical interest towards the development of effective preventive interventions in patients at risk of cardiovascular disease.

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