There is compelling evidence that atherosclerosis is an inflammatory disease. Increased levels of markers of systemic inflammation, such as the acute-phase reactant C-reactive protein, have been associated with acute coronary events in patients with atherosclerosis. The secretory group II phospholipase A2 (sPLA2) recently has been added to the group of acute-phase reagents, and its plasma levels are greatly increased in diseases involving systemic inflammation, such as sepsis and rheumatoid arthritis. Thus, hepatocytes synthesize and secrete this enzyme in response to inflammatory cytokines such as interleukin-6, tumor necrosis factor-α, and interleukin-1. Plasma levels of sPLA2 were found to correlate with levels of C-reactive protein in patients with atherosclerosis, and the levels of sPLA2 were found to be good predictors of coronary events. Whether sPLA2 is causally involved in the pathogenesis of atherosclerosis has been under investigation during recent years.

PLA2s are enzymes that hydrolyze the acyl group at the sn-2 position of phospholipids. This results in the formation of a free fatty acid and a lysophospholipid that can be further metabolized into lipid mediators, including eicosanoids, platelet-activating factors, and lysophosphatic acid. Mammalian PLA2s are present in both cytosolic and secreted forms. The secretory PLA2s consist of the group I enzyme secreted by the pancreas and the group II enzymes secreted by many cell types in a number of tissues. Group II sPLA2 is a 14-kDa enzyme, which contains 7 disulfide bridges that make it very stable. It is highly cationic, which allows electrostatic interaction between the enzyme and glycosaminoglycans. sPLA2 is optimally active at neutral pH and has an absolute requirement for the presence of millimolar concentrations of calcium, which means that it is optimally active under the conditions prevailing in the extracellular fluids.

When secreted by cells in response to inflammatory stimuli, sPLA2 is thought to augment the inflammatory process by catalyzing the production of lipid mediators. sPLA2 is virtually inactive toward intact cell surfaces. Intact cell surfaces lack the phospholipids (phosphatidylglycerol, phosphatidylethanolamine, and phosphatidylserine) that are good substrates for sPLA2 and contain sphingomyelin, which inhibits sPLA2. Intact cell surfaces also have a high surface pressure that inhibits the enzyme.

Evidence is accumulating that circulating sPLA2 is not only a marker of systemic inflammation but can also alter plasma lipoprotein metabolism. Thus, in human apoB transgenic mice, sPLA2 expression was found to decrease the levels of HDL but did not alter the levels of apoB-containing lipoproteins, suggesting that the primary target of the enzyme is HDL. Moreover, in vitro experiments have shown that altered forms of human HDL particles generated during the acute-phase response after surgery, which contain serum amyloid A, are preferentially hydrolyzed by this enzyme. In vitro experiments have also shown that sPLA2 can hydrolyze phospholipids of LDL particles and generate small, dense LDL particles. This finding is of interest because patients with rheumatoid arthritis, who have high levels of circulating sPLA2, have a low HDL concentration and small, dense LDL particles in their plasma.

Recent studies of sPLA2 in the arterial wall add important novel aspects to the mechanisms by which sPLA2 could contribute to the development and progression of atherosclerotic lesions. Although virtually no sPLA2 has been found in the normal arterial intima, sPLA2 has consistently been found in atherosclerotic plaques, where it is associated with both smooth muscle cells and macrophages. In an elegant series of experiments, Hurt-Camejo and colleagues have studied the association of sPLA2 with the various components of the extracellular matrix. Originally, the group observed that sPLA2 is associated with collagen fibrils in the intima. Later, they studied the binding of sPLA2 to collagen-associated proteoglycans in vitro and found that sPLA2 binds to the glycosaminoglycan chains of biglycan. In this issue of Circulation Research, the investigation group reports that sPLA2 can bind to both the core protein and the glycosaminoglycan chains of decorin in vitro. This result was strengthened by immunohistochemical demonstration of an association between sPLA2 and decorin in the human arterial intima.

The collagen-associated proteoglycans decorin and biglycan have recently attracted interest in the field of atherosclerosis research because lipid droplets in the arterial intima have been shown to accumulate initially on the fibrils extending from collagen fibers. We have shown that decorin can link native LDL to collagen, and moreover, that lipoprotein lipase can strongly link both native and oxidized LDL to decorin-coated collagen. That sPLA2 also binds to decorin is interesting because PLA2 has been shown to induce fusion of glycosaminoglycan-bound LDL particles. Thus, it...
is possible that decorin is a key factor in the initiation of extracellular lipid accumulation because of its ability to attract not only LDL particles but also various enzymes capable of modifying them. In this issue of Circulation Research, Wight and colleagues point to another important function of decorin in the arterial intima.21 They show that local expression of decorin by cell-mediated gene transfer reduces neointima formation in balloon-injured rat carotid arteries by reducing the amount of the extracellular matrix components versican and fibronectin accumulating in the neointima. According to the results of their cell culture experiments, this effect of decorin likely results from the known ability of decorin to inhibit transforming growth factor-β activity.22

What could be the substrates of sPLA₂ in the arterial wall? Although sPLA₂ can hydrolyze native LDL particles, this hydrolysis proceeds at a very slow rate (≈1/100 000 of the rate of Escherichia coli membrane hydrolysis).23 However, lipolysis of LDL by sPLA₂ can still be significant in atherosclerotic lesions because the local concentration of LDL is very high and a fraction of the particles are modified in forms that render the particles a better substrate for sPLA₂. Indeed, aging and even minimal oxidative modification of LDL greatly enhance the ability of sPLA₂ to hydrolyze LDL particles.23 Moreover, a similar effect can also be expected from other types of modification that perturb the surface structure of LDL particles such as sphingomyelin hydrolysis by the arterial secretory sphingomyelinase.24

Modification of LDL in the arterial wall by sPLA₂ has a number of potentially atherogenic effects. Thus, PLA₂-modified LDL particles have increased affinity to proteoglycans, which can lead to enhanced retention and extracellular accumulation of the particles.25,26 The modified particles are more susceptible to lipid peroxidation,25 generation of bioactive phospholipids,26 and hydrolysis by secretory sphingomyelinase.27 PLA₂ modification of LDL has also been suggested to lead to enhanced uptake of the lipolyzed particles by macrophages, with ensuing intracellular lipid accumulation.28 In addition, both lysophosphatidylcholine and free fatty acids, the products of phospholipid hydrolysis, can be carried to arterial cells either by the lipolyzed particles themselves or by albumin and so induce proatherogenic changes in cells of the arterial wall.29

Mice expressing human sPLA₂ were recently shown to have enhanced formation of fatty streak lesions.30 Whether this effect is due to sPLA₂ in the circulation, sPLA₂ in the arterial wall, or both is not known. According to current knowledge, sPLA₂ could be proatherogenic both in the circulation and arterial wall. Future work is necessary to improve our understanding of how sPLA₂ is involved in the pathogenesis of atherosclerosis.

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