Inflammation and Atherosclerosis

Group IIa and Group V sPLA₂ Are Not Redundant

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The secretory phospholipase A₂ (sPLA₂) family hydrolyzes glycerophospholipids at the sn-2 position to generate lysophospholipids and free fatty acids. Ten members have been described in mammals. These enzymes must be clearly distinguished from the intracellular phospholipase A₅ that are involved in intracellular signaling. They are also distinct from lipoprotein-associated phospholipase A₁ (Lp-PLA₂), which has been shown to be bound predominantly to LDL particles in human plasma, and hydrolizes oxidized LDL to generate lysophosphatidylcholine and oxidized nonesterified fatty acids. Group IIa sPLA₂, which was originally isolated from rheumatoid arthritis fluids, is considered to be the prototypic inflammatory sPLA₂. Its expression is markedly elevated in many cell types in response to proinflammatory stimuli. The concentration of Group IIa sPLA₂ in sera or exudating fluids correlates well with the severity of inflammatory disease. In humans, Group IIa and Group V sPLA₂ are tightly linked on chromosome 1 and their gene regulation and functions have largely been viewed as overlapping. Indeed, cross-reactivity of antibodies and molecular probes for these related enzymes has led to confusion in older literature. The study by Rosengren et al, reported in this issue, provides new insights into the expression and functional activity of Group IIa and Group V sPLA₂ in the context of atherosclerosis.¹

A role for sPLA₂s in atherogenic processes has been suggested by epidemiological studies showing that in humans, serum concentrations of Group IIa sPLA₂ is an independent risk factor for coronary artery disease and a predictor of cardiovascular events.³,⁴ However, because it is well recognized that this enzyme is highly induced in a number of tissues during inflammation, there was uncertainty as to whether this association merely reflected the fact that Group IIa sPLA₂ is a marker for inflammation. Whether Group V sPLA₂ is an acute phase protein that appears in the plasma during inflammation is less certain. New evidence provided by Rosengren et al² that Group V sPLA₂, unlike Group IIa, is not induced in mice treated with lipopolysaccharide (LPS) is consistent with other findings in humans indicating that sera from patients experiencing inflammatory diseases contain Group IIa sPLA₂, and not Group V sPLA₂.⁵ It seems reasonable to propose that the major contribution of Group V sPLA₂ to the pathogenesis of atherosclerosis would be effected at the level of the vessel wall. The finding in 1999 that transgenic expression of human Group IIa sPLA₂ in C57BL/6 mice (this strain lacks the expression of endogenous Group IIa sPLA₂) leads to spontaneous atherosclerotic lipid deposition even in the absence of dyslipidemia provided compelling evidence that sPLA₂ may play a causal role in atherosclerosis and is not just a marker for the disease.⁶ Subsequent studies showing that macrophage expression of human Group IIa sPLA₂ accelerates atherosclerosis in mice highlighted the possibility that the mechanism of the pathogenic effect of sPLA₂ may be located within the vessel wall, independent of systemic effects.² Recent studies, including the accompanying article,² establish that at least 3 different members of the sPLA₂ family are present in atherosclerotic lesions (Group IIa, Group V, and Group X sPLA₂). This suggests the intriguing possibility that multiple enzymes may contribute locally to atherosclerotic processes, and raises the question: Are these enzymes redundant, or do they provide separate functions?

Rosengren et al² report that Group V sPLA₂, but not Group IIa sPLA₂, hydrolyzes lipoprotein phospholipids in the presence of complete serum. This is consistent with earlier reports indicating that Group V sPLA₂ is more potent in hydrolyzing HDL and LDL compared with Group IIa sPLA₂.⁸,⁹ However, despite this convincing in vitro data, the large body of evidence pointing to the importance of Group IIa sPLA₂ in modulating HDL metabolism in vivo should not be ignored. When induced during inflammation, this isozyme associates selectively with HDL and appears to modify the HDL particle. Transgenic mice expressing human Group IIa sPLA₂ have lower plasma concentrations of HDL cholesterol and apoA-I compared with normal mice, and HDL particles in the transgenic mice are markedly smaller and relatively phospholipid depleted compared with normal mouse HDL.⁶ Furthermore, HDL from transgenic mice is markedly depleted of paraoxonase activity, an enzyme that is believed to be partly responsible for the protective effects of HDL.⁶ The decreased plasma HDL levels in Group IIa sPLA₂ transgenic mice appears to be attributed to enhanced HDL catabolism, a phenomenon which is associated with altered tissue uptake of HDL cholesterol ester and apoA-I.¹⁰,¹¹ The relevance of these findings in mice to the human condition seems likely, given the markedly reduced HDL levels in rheumatoid arthritis patients, who have increased plasma Group IIa sPLA₂ and accelerated atherosclerosis.

The significance of Group IIa or Group V sPLA₂ hydrolisis on HDL function in the vessel wall is not clear. On the one hand, hydrolysis by sPLA₂ results in a significant decrease in the capacity of HDL to mediate cellular cholesterol efflux from...
lipid-loaded macrophages. On the other hand, phospholipid depletion by sPLA₂ has a major impact on HDL remodeling by cholesteryl ester transfer protein (CETP). Compared with remodeling by CETP alone, the combined action of sPLA₂ and CETP enhances the generation of pre-beta migrating, lipid-free/lipid-poor apoA-I, the preferred substrate for ABCA1-dependent cellular cholesterol efflux. This effect on HDL remodeling is intriguing and raises the possibility that during inflammation, sPLA₂ may fundamentally alter the ratio between HDL-bound and free apolipoproteins. If this is the case, this scenario can be envisaged to promote both the effluxing capacity and catabolism of HDL.

Accumulating evidence suggests that LDLs hydrolyzed by sPLA₂ acquire proatherogenic properties. Rosengren et al demonstrate for the first time that Group V sPLA₂ activity toward LDL is significantly enhanced in the presence of proteoglycans. Thus, extracellular matrix (ECM) proteoglycans play an active role in lipid accumulation in the vessel wall by not only mediating the retention of LDL particles, but also by modulating the activity of LDL hydrolytic enzymes. Interestingly, recent data suggests that hydrolysis by Group V sPLA₂ promotes the interaction of LDL particles with cell-surface proteoglycans, and thereby promotes their uptake by macrophages. Thus, in regions where LDL is being accumulated, the colocalization of LDL, proteoglycans, and Group V sPLA₂ leads to a self-perpetuating cascade of events that culminates in atherosclerosis.

Are Group IIa and Group V sPLA₂ redundant with respect to atherogenesis? In vivo data suggests that the acute phase Group IIa sPLA₂ plays the predominant, if not exclusive, role in modulating systemic lipoprotein metabolism, despite its relatively weak ability to hydrolyze LDL and HDL in vitro. Whereas Group IIa sPLA₂ is induced by proinflammatory cytokines, novel data presented by Rosengren et al suggest that Group V sPLA₂ may be upregulated by bioactive lipids. The presence of Group V sPLA₂ in lipid-rich regions of human and mouse atherosclerotic lesions, its potent activity toward LDL, and its activation by proteoglycans, all point to this enzyme as an important player in the generation of proatherogenic LDL. Clearly, the enzymes investigated by Rosengren et al profoundly influence lipoprotein structure. The functional and pathogenetic implications, particularly during inflammation, merits further study.

**Disclosure(s)**

None.

**References**


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