PLA₂-V
A Real Player in Atherogenesis
Katariina Ööri, Petri T. Kovanen

An important early step in atherosclerosis is binding of apolipoprotein B-100 (apoB-100)–containing lipoproteins (VLDL, IDL, and LDL) to the proteoglycan component of the extracellular matrix of the arterial intima.¹,² When oxidative agents or enzymes attack the proteoglycan-bound lipoproteins, they become oxidatively modified, and when various intimal proteases or lipases hydrolyze them, they become nonoxidatively modified. Whereas oxidation of proteoglycan-bound apoB-100–containing particles triggers their release and subsequent uptake by macrophages, the nonoxidative modifications do the opposite: they enhance the strength of particle binding to proteoglycans.³ In addition, such nonoxidatively modified apoB-100–containing lipoprotein particles tend to aggregate and fuse, which allows progressive extracellular accumulation of lipoprotein lipids, a key phenomenon in atherogenesis. The nonoxidative modifications can also lead to intracellular lipid accumulation and so induce foam cell formation, a hallmark of early atherogenesis.⁴ Thus, local modification of apoB-100–containing lipoproteins leads to both extra- and intracellular accumulation of lipids in the arterial intima.

In general, the nonoxidative modifications are caused by enzymes that are hydrolytic in nature, either proteolytic or lipolytic. Indeed, the arterial intima contains many different types of hydrolytic enzymes capable of lipoprotein modification. Unfortunately, however, it is currently not known which hydrolytic enzymes of the human arterial intima are actually responsible for turning the intimal lipoproteins into atherogenic particles. Among the lipolytic enzymes potentially involved in such atherogenic conversion of lipoproteins are several members of the secretory phospholipase A2 (sPLA2) family. The hydrolytic action of these enzymes on phosphatidylcholine, the major glycero phospholipid in lipoprotein particles, leads to the generation of lysophosphatidylcholine (lysoPC) and a free fatty acid (FFA).

In the current issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Bostrom et al.⁵ have examined in vivo the role of Group V sPLA₂ (sPLA₂-V) in the context of atherogenesis. The rationale for their studies derives from previous data suggesting a role for the sPLA₂ enzymes in atherosclerosis and particularly in lipoprotein modification. An important finding pointing to a role of PLA₂ enzymes in the modification of lipoprotein particles locally in the arterial intima comes from compositional analysis of lipoproteins isolated from human atherosclerotic arteries. Thus, such isolated lipoproteins have decreased phosphatidylcholine content,⁶,⁷ ie, a change that points to their hydrolysis by a PLA₂ enzyme.

Of the 10-member family of sPLA₂ enzymes, the effect of Group IIa sPLA₂ (sPLA₂-IIa) in atherosclerosis has been studied extensively, and accumulating evidence both in vivo and in vitro supports a role for this particular enzyme in atherosclerosis (reviewed by Menschikowski⁸). However, because sPLA₂-IIa has a relatively low hydrolytic activity toward phosphatidylcholines on lipoprotein surfaces, the pathophysiologic role of this enzyme in lipoprotein modification has been questioned.

Another structurally and functionally distinct type of PLA₂, the lipoprotein-associated PLA₂ (Lp-PLA₂), has also been detected in atherosclerotic lesions.⁹,¹⁰ Lp-PLA₂ is associated mainly with plasma lipoproteins, particularly with LDL, and is carried into the intima along with LDL particles. In addition, this enzyme can be synthesized and secreted within the plaque by inflammatory cells, such as macrophages, both in early and advanced atherosclerotic lesions.⁹,¹⁰ Lp-PLA₂ does not hydrolyze phospholipids on native lipoproteins, but requires oxidation of phospholipids for them to become its substrate.

The action of Lp-PLA₂ on oxidatively-modified LDL has been considered to possess both anti- and proinflammatory components.¹¹ Thus, by reducing the content of biologically active oxidized phospholipids in minimally modified LDL, Lp-PLA₂ blocks the ability of such LDL particles to promote binding of monocytes to endothelial cells in vitro.¹² On the other hand, recent experiments have clearly indicated that the hydrolytic products generated by Lp-PLA₂ and released from the modified LDL particles, ie, lysophospholipids and oxidized FFAs, elicit proinflammatory responses in various types of cells involved in atherosclerosis (reviewed by MacPhee et al.¹³). Moreover, because increased plasma concentration of Lp-PLA₂ is a biomarker of inflammation and denotes increased risk of acute coronary events,¹³ evidence favoring a proatherogenic role for Lp-PLA₂ is accumulating from several lines of studies.

As described above, the two members of the sPLA₂ family, sPLA₂-IIa and Lp-PLA₂, are able to hydrolyze native LDL particles only poorly, or not at all. In contrast, sPLA₂-V has been shown to efficiently hydrolyze native LDL.¹⁴,¹⁵ Most importantly, sPLA₂-V is able to hydrolyze lipoproteins in complete serum,¹⁵ a finding indicative of the absence of natural inhibitors of the enzyme in serum, and also suggesting...
their absence in interstitial fluids, such as the intimal fluid, which are derivatives of blood plasma. Thus, the enzyme may also be able to act on lipoproteins in the arterial intima. Importantly, sPLA2-V has been detected in atherosclerotic lesions, but until now, direct evidence for the contribution of the enzyme in atherogenesis has not been available. In the current issue, Bostrom et al.5 in their gain-of-function and loss-of-function studies in mice show that increased expression of sPLA2-V in bone marrow–derived cells increased atherosclerosis, whereas deficiency of PLA2-V in such cells reduced atherosclerosis. The activity of PLA2 in the plasma of the variously treated mice did not change, an observation strongly supporting the idea that increased lipid deposition in mice overexpressing sPLA2-V was indeed attributable to the lipolytic activity of the enzyme within the arterial intima, the actual site of progressive lipoprotein accumulation. As discussed above, the likely substrates for sPLA2 enzymes in the arterial intima are the phosphatidylcholine molecules of the retained apoB-100–containing lipoprotein particles.14,15 Moreover, as the enzyme binds with high affinity to proteoglycans, it has the potential to hydrolyze lipoproteins retained within the proteoglycan meshwork.15 Binding of sPLA2-V to proteoglycans has been shown to actually enhance its lipolytic activity toward lipoproteins,15 so rendering it an even better candidate responsible for lipoprotein hydrolysis in the proteoglycan-rich layer of the arterial intima. Thus, we can conclude that optimal conditions appear to prevail in the arterial intima for this particular member of the family of sPLA2 enzymes.

Hydrolysis of lipoproteins in the arterial intima by sPLA2-V can potentially contribute to atherosclerosis by various mechanisms, and these options are depicted schematically in the Figure. First, phospholipolysis of lipoproteins leads to the generation of relatively high concentrations of FFAs and lysoPCs. Locally, these bioactive lipids may have vasoactive, chemotactic, and proinflammatory effects on arterial smooth muscle cells, macrophages, T cells, and endothelial cells (reviewed by Hurt-Camejo et al.16). Second, hydrolysis of the apoB-100–containing lipoproteins (VLDL, IDL, and LDL) by sPLA2 can lead to their aggregation and fusion.17 Once the phosphatidylcholine molecules on the lipoprotein surface are hydrolyzed, the lipoprotein particles become more susceptible to other types of modifications, such as oxidation18 or hydrolysis by secretory sphingomyelinase.19 Third, sPLA2-treatment enhances the binding of LDL to proteoglycans, and this may involve at least two mechanisms. Flood et al.20 have shown that sPLA2-treatment induces changes in the conformation of apoB-100, which, again, promote the interaction of LDL with the negatively charged proteoglycans. This finding is consistent with earlier studies showing that the sPLA2-generated small and dense LDL particles bind to proteoglycans more avidly than large and buoyant LDL particles.21 In addition, our laboratory has shown that particle aggregation further enhances the binding strength of the modified LDL particles to proteoglycans.3 This increase can be explained by the fact that LDL aggregates contain many copies of apoB-100, and, being multivalent, have the potential to interact with proteoglycans via more ionic interactions than their nonaggregated, native-sized counterparts. Interestingly, binding of LDL to proteoglycans promotes PLA2-induced aggregation and fusion of LDL particles,22 and an enhanced interaction of sPLA2-V–treated LDL to proteoglycans has been demonstrated by Rosengren et al.15

ApoB-100–containing lipoproteins enter the arterial intima and become entrapped within the subendothelial proteoglycan meshwork. A subendothelially located macrophage synthesizes and secretes sPLA2-V, which hydrolyzes the phosphatidylcholines on the surface of the entrapped lipoproteins. The two bioactive hydrolytic products released from the lipoproteins, lyso phosphatidylcholines (lysoPC) and free fatty acids (FFA), exert proinflammatory actions on various intimal cells. The PLA2-V–modified lipoproteins aggregate, fuse, and bind to the proteoglycans more tightly. Ultimately, the proteoglycan-bound modified lipoproteins are taken up by a macrophage, which then converts into a foam cell.
above-listed interactions between lipoproteins, sPLA₂-V, and intimal proteoglycans is likely to contribute to extracellular accumulation of lipoprotein-derived lipids. Finally, modification of LDL by sPLA₂-V can also contribute to intracellular lipid accumulation by leading to the formation of macrophage foam cells. Here, a recent mechanistic insight provides an extra flavor to the story: the increased uptake of sPLA₂-V–treated LDL appears to depend on the increased affinity of the modified LDL to the heparan sulfate proteoglycans present on the cell surface. 

The work of Bostrom et al. complements the wealth of in vitro data regarding the proatherogenic role of sPLA₂-V and provides the first in vivo support for the local action of sPLA₂-V in the arterial intima of an experimental animal. The presence of sPLA₂-V in lipid-rich regions of human and mouse atherosclerotic lesions and its potent activity toward lipoproteins, particularly in the presence of proteoglycans, both point to the possibility of this enzyme being a key player in lipoprotein modification during atherogenesis. Indeed, the road ahead for novel discoveries in this important field of scientific exploration of lipolytic pathways in atherogenesis looks quite promising.

Disclosures

None.

References


Öörni and Kovanen  

PLA₂-V: A Real Player in Atherogenesis  
447
PLA₂-V: A Real Player in Atherogenesis
Katariina Öörni and Petri T. Kovanen

doi: 10.1161/01.ATV.0000258412.58289.ee
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/27/3/445

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org//subscriptions/