Lp-PLA₂, Plaque Inflammation and Lesion Development Vary Fundamentally Between Different Vascular Sites

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Lp-PLA₂ is also known as platelet activating factor (PAF) acetylhydrolase (PAF-AH) or PLA₂G7, owing to its hierarchical position in the PLA₂ superfamily. Lp-PLA₂ or PAF-AH was discovered based on its ability to catalyze the removal of the acetyl group at the sn-2 position of the potent inflammatory mediator PAF to generate lyso-PAF and acetate. Not surprisingly, Lp-PLA₂ was first proposed to have anti-inflammatory properties.¹ In general, Lp-PLA₂ hydrolyzes glycerophospholipids containing short chain or oxidized fatty acids at the sn-2 position. Substrate hydrolysis catalyzed by Lp-PLA₂ generates lysoPAF/lyso phosphatidylcholine (lysoPC) and short and/or oxidized fatty acids, many of which are thought to have pro-inflammatory and pro-oxidative activities.² Previous studies suggested that upregulation of the Lp-PLA₂ gene in the inflamed vascular tissue point toward a potential role of Lp-PLA₂ in the development and progression of atherosclerosis³ and led to the proposition that inhibition of the activity could offer vascular protection in addition to that afforded by cholesterol-lowering agents. However, the recently published STABILITY (Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy) trial showed that darapladib did not affect the primary composite endpoint that included myocardial infarction, stroke or time to cardiovascular death in patients with stable coronary heart disease.⁴ Likewise, results recently reported from SOLID-TIMI 52 (Stabilization of Plaques using Darapladib-Thrombolysis in Myocardial Infarction 52) showed no reduction in major coronary events when added to standard of care after an acute coronary syndrome.⁵ Based on those disappointing results, interpreting the physiologic and pathophysiologic roles of Lp-PLA₂ continues to be a challenge, and a number of issues remain to be resolved.

Fenning and colleagues⁶ now report that the role of Lp-PLA₂ in atherosclerotic plaque inflammation and lesion development varies fundamentally between vascular sites. Experiments were performed using a diabetic/high cholesterol pig model, which has an appearance of advanced lesions and cardiovascular physiology similar to that of humans.³ Fenning et al observed that despite the identical systemic exposure to hypercholesterolemia and hyperglycemia, the development of atherosclerosis markedly varied between coronary and distal abdominal arteries. These data support earlier work by the authors, where they observed more progressive lesion development and inflammation in the coronary arteries when compared with thoracic and carotid arteries.³ Also in agreement with previous work of the group,⁷ inhibition of Lp-PLA₂ with darapladib inhibited progression to advanced coronary atherosclerotic lesions. However, Fenning and colleagues now report that inhibition of Lp-PLA₂ showed no reduction of inflammation and lesion development in distal abdominal aortae, providing evidence that darapladib induced attenuation of plaque progression is site-specific. These results provide novel insights for the understanding of Lp-PLA₂ in disease. However, a direct translation from the animal model to humans should be taken with caution for the following reasons. Early coronary lesions in pigs are intimal xanthomas rather than intimal thickening, as regularly noted in humans.⁸ In humans, additional risk factors like hypertension or smoking are involved in complex lesion development. Moreover, after cholesterol feeding, pigs’ exhibit increased HDL but low triglyceride levels in the setting of very high LDL levels, whereas humans often exhibit low HDL and high triglyceride levels.⁹ Under inflammatory conditions increased Lp-PLA₂ levels associate with LDL⁹ and HDL,¹⁰,¹¹ therefore lipoprotein associated Lp-PLA₂ activities are expected to be different in animals. Of particular interest, a recent study provided a different view on the role of Lp-PLA₂ in inflammatory responses, arguing against a pro-atherogenic role of Lp-PLA₂ and its products.¹² The authors suggested that elevated enzyme levels might reflect a response to the pro-inflammatory stress that is typical of atherosclerosis and that the

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relationship between Lp-PLA₂ and PAF-like substrates and products generated to various extents in settings of inflammation is not understood. It therefore remains elusive whether Lp-PLA₂ is still a valid target for therapeutic intervention.13

Disclosures
None.

References


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