Lipoprotein-Associated Phospholipase A₂
Novel Biomarker and Causal Mediator of Atherosclerosis?

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Inflammation is clearly recognized as a central component in the development and progression of cardiovascular disease (CVD). What is not clear, however, is how to best identify and monitor pathophysiological inflammatory processes leading to acute coronary events. Many studies have focused on the potential of circulating biomarkers of inflammation to define risk of incident CVD events and morbidity and mortality following events.

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Lipoprotein-associated phospholipase A₂ (Lp-PLA₂) holds promise as a biomarker specifically associated with several key aspects of atherogenesis. Lp-PLA₂, also known as platelet-activating factor acetylhydrolase (PAF-AH), is an enzyme produced primarily by macrophages and lymphocytes. Although Lp-PLA₂ has been reported to exhibit both pro- and anti-inflammatory activities, its primary role appears to be proatherogenic. In this context, Lp-PLA₂ hydrolyzes oxidized phospholipids such as those within oxidized LDL, generating proinflammatory moieties lysophosphatidylcholine and oxidized fatty acids. In addition, approximately 80% of circulating Lp-PLA₂ is sequestered on LDL particles which serve to modulate enzyme activity. Enzyme activity is reported to be increased when Lp-PLA₂ bound to more atherogenic small dense LDL versus larger particles.

In this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, Kolodgie and colleagues and Gerber and colleagues provide important new evidence on the role of Lp-PLA₂ in atherosclerosis development and prognostic value of this novel biomarker after myocardial infarction (MI). In an immunohistochemical study of Lp-PLA₂ expression in coronary segments from 25 sudden coronary death patients, Kolodgie et al found strong expression of Lp-PLA₂ within the necrotic core and in macrophages, notably apoptotic macrophages, surrounding vulnerable and ruptured plaques. There was minimal expression of Lp-PLA₂ primarily in the lipid pool, detected in less advanced lesions. Localization of Lp-PLA₂ to the lipid-rich necrotic core of developing and advanced lesions likely reflects its key role in lipid hydrolysis. Products of this activity attract circulating monocytes and participate in macrophage activation. Further supporting a causal role of Lp-PLA₂ in atherosclerosis, fibrous cap thickness was determined in part by macrophage infiltration. In addition, Lp-PLA₂ was associated with apoptotic macrophages and macrophage apoptosis, in turn correlated with expansion of the lipid core. These findings suggest that Lp-PLA₂ may be both a specific marker and causal mediator of plaque progression and instability. The study by Kolodgie et al is therefore important in elucidating the numerous complex processes within the vessel wall which underlie the pathogenesis of atherosclerosis. Understanding these processes is a key step in reducing the morbidity and mortality associated with CVD.

The potential causal role of Lp-PLA₂ in atherosclerosis is of even greater interest given the findings of Gerber et al who examined the potential role of Lp-PLA₂ in defining risk of adverse outcomes after MI. In a community-based study of 271 patients with acute MI, high Lp-PLA₂ levels at the time of event were strongly and independently associated with mortality over one year of follow-up. Survival estimates (95% confidence intervals) were 92% (68% to 98%), 85% (78% to 93%), and 74% (65% to 84%) for the lowest, middle, and upper tertiles of Lp-PLA₂. Compared with the lowest tertile, hazard ratios (95% confidence intervals) for death in the middle and upper tertiles of Lp-PLA₂ were 2.2 (0.9 to 5.5) and 4.8 (2.1 to 11.6) in models adjusted for age and sex. Associations were stronger when models were adjusted for additional risk factors. Lp-PLA₂ also provided incremental predictive value over traditional risk factors and C-reactive protein. The study by Gerber et al extends and compliments previous findings. Several studies have reported associations between Lp-PLA₂ and risk of developing CVD. Lp-PLA₂ has also been associated with adverse events in patients with clinical CVD. Combined with the novel information on the prognostic value of Lp-PLA₂ after MI in the current study, these data support a role for Lp-PLA₂ in risk stratification following major CVD events.

Although these studies highlight both potential causal and biomarker roles for Lp-PLA₂ in atherosclerosis, there are still many questions to be resolved. Perhaps one of the most important is whether measurement of Lp-PLA₂ antigen level or enzymatic activity provides the best reflection of ongoing atherosclerosis. Lp-PLA₂ mass, but not activity, was associated with calcified coronary plaque in the Coronary Artery Risk Development in Young Adults (CARDIA) study. This likely reflects the complex biology of Lp-PLA₂ and of lipids and lipid-related moieties in general. Lp-PLA₂ is considered to be predominantly proatherogenic; however, the enzyme may have antiinflammatory properties as well. Lp-PLA₂ degrades platelet-activating factor (PAF) in vitro. Although similar activity has not been demonstrated in vivo, Lp-PLA₂ cleavage of minimally modified LDL likely reduces the
Potential role for Lp-PLA₂ in atherosclerosis. Circulating Lp-PLA₂ (small blue circles) is bound predominantly to LDL cholesterol particles and is carried to the intima along with LDL. Lp-PLA₂ hydrolyzes oxidized phospholipids such as those within oxidized LDL generating proinflammatory moieties lysophosphatidylcho-
line and oxidized fatty acids. In turn, these compounds function in recruitment and activation of monocyte–macrophages and are linked to macrophage apoptosis. Macrophage apoptosis likely contributes to expansion of the necrotic core of the atheroscle-
rotic lesion, thinning of the fibrous cap, and, ultimately, plaque destabilization. Reprinted with permission from Zalewski et al.\textsuperscript{17}

ability of LDL to promote monocyte chemotaxis and adhe-
sion.\textsuperscript{1} In terms of proatherogenic activities, Lp-PLA₂ degra-
dation of oxidized LDL generates proinflammatory mol-
cules and as oxidized phospholipids themselves may have antiinflammatory properties, Lp-PLA₂ activity would nullify these properties.\textsuperscript{1} The complexity of this system is further illustrated by the distribution of circulating Lp-PLA₂. 70\% to 80\% of the enzyme is associated with the apolipoprotein B moiety of LDL, in particular, with small dense LDL particles that are believed to be more proatherogenic and appear to increase Lp-PLA₂ activity. The remaining 20\% to 30\% of Lp-PLA₂ is bound to the phospholipid moiety of HDL. This association is not well characterized but may be antiinflam-
matory in nature.\textsuperscript{1} More mechanistic studies are needed to resolve the full range of Lp-PLA₂ functionality and how these actions modulate the development and progression of atherosclerosis.

Given its potentially central role in atherosclerosis, the discovery of specific Lp-PLA₂ inhibitors has rendered Lp-PLA₂ a viable therapeutic target. In this context, a clinical threshold for Lp-PLA₂ has recently been proposed.\textsuperscript{15} However, key questions remain to be answered in this arena as well.\textsuperscript{14} Statins lower Lp-PLA₂ activity, presumably through reduction of LDL levels.\textsuperscript{16} What role would specific Lp-PLA₂ inhibitors play in therapy? It is not known whether the recommended threshold for Lp-PLA₂ activity can be achieved by current therapeutic regimens (i.e., diet, exercise, statins) alone. Studies to date have focused primarily on Whites with limited data on other ethnic groups. Is the proposed clinical threshold relevant in all populations? Studies of Lp-PLA₂ genetics will also provide interesting information. These and other questions await answers in future prospective epidemi-
ologic and clinical research.

Disclosures

None.

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