Lipoprotein-Associated Phospholipase A$_2$

Novel Biomarker and Causal Mediator of Atherosclerosis?

Nancy Swords Jenny

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 pathophysiologic 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.

Lipoprotein-associated phospholipase A$_2$ (Lp-PLA$_2$) holds promise as a biomarker specifically associated with several key aspects of atherogenesis. Lp-PLA$_2$, also known as platelet-activating factor acetylhydrolase (PAF-AH), is an enzyme produced primarily by macrophages and lymphocytes. Although Lp-PLA$_2$ has been reported to exhibit both pro- and antiinflammatory activities, its primary role appears to be proatherogenic. In this context, Lp-PLA$_2$ hydrolyzes oxidized phospholipids such as those within oxidized LDL, generating proinflammatory moieties lysophosphatidylcholine and oxidized fatty acids. In addition, approximately 80% of circulating Lp-PLA$_2$ is sequestered on LDL particles which serve to modulate enzyme activity. Enzyme activity is reported to be increased when Lp-PLA$_2$ bound to more atherogenic small dense LDL versus larger particles.

In this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology*, Kolodgie and colleagues$^3$ and Gerber and colleagues$^4$ provide important new evidence on the role of Lp-PLA$_2$ in atherosclerosis development and prognostic value of this novel biomarker after myocardial infarction (MI). In an immunohistochemical study of Lp-PLA$_2$ expression in coronary segments from 25 sudden coronary death patients, Kolodgie et al$^3$ found strong expression of Lp-PLA$_2$ within the necrotic core and in macrophages, notably apoptotic macrophages, surrounding vulnerable and ruptured plaques. There was minimal expression of Lp-PLA$_2$, primarily in the lipid pool, detected in less advanced lesions. Localization of Lp-PLA$_2$ 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-PLA$_2$ in atherosclerosis, fibrous cap thickness was determined in part by macrophage infiltration.$^3$ In addition, Lp-PLA$_2$ was associated with apoptotic macrophages and macrophage apoptosis, in turn correlated with expansion of the lipid core. These findings suggest that Lp-PLA$_2$ may be both a specific marker and causal mediator of plaque progression and instability. The study by Kolodgie et al$^3$ 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-PLA$_2$ in atherosclerosis is of even greater interest given the findings of Gerber et al$^4$ who examined the potential role of Lp-PLA$_2$ in defining risk of adverse outcomes after MI. In a community-based study of 271 patients with acute MI, high Lp-PLA$_2$ 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-PLA$_2$. Compared with the lowest tertile, hazard ratios (95% confidence intervals) for death in the middle and upper tertiles of Lp-PLA$_2$ 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-PLA$_2$ also provided incremental predictive value over traditional risk factors and C-reactive protein. The study by Gerber et al$^4$ extends and compliments previous findings. Several studies have reported associations between Lp-PLA$_2$ and risk of developing CVD.$^5-^8$ Lp-PLA$_2$ has also been associated with adverse events in patients with clinical CVD.$^{10-13}$ Combined with the novel information on the prognostic value of Lp-PLA$_2$ after MI in the current study, these data support a role for Lp-PLA$_2$ in risk stratification following major CVD events.

Although these studies highlight both potential causal and biomarker roles for Lp-PLA$_2$ in atherosclerosis, there are still many questions to be resolved.$^{14}$ Perhaps one of the most important is whether measurement of Lp-PLA$_2$ antigen level or enzymatic activity provides the best reflection of ongoing atherosclerosis. Lp-PLA$_2$ mass, but not activity, was associated with calcified coronary plaque in the Coronary Artery Risk Development in Young Adults (CARDIA) study.$^5$ This likely reflects the complex biology of Lp-PLA$_2$; and of lipids and lipid-related moieties in general. Lp-PLA$_2$ is considered to be predominantly proatherogenic; however, the enzyme may have antiinflammatory properties as well. Lp-PLA$_2$ degrades platelet-activating factor (PAF) in vitro. Although similar activity has not been demonstrated in vivo, Lp-PLA$_2$ cleavage of minimally modified LDL likely reduces the
ability of LDL to promote monocyte chemotaxis and adhesion. In terms of proatherogenic activities, Lp-PLA₂ degradation of oxidized LDL generates proinflammatory molecules and as oxidized phospholipids themselves may have anti-inflammatory properties, Lp-PLA₂ activity would nullify these properties. 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 antiinflammatory in nature. 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. However, key questions remain to be answered in this arena as well. Statins lower Lp-PLA₂ activity, presumably through reduction of LDL levels. 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 (ie, 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 epidemiologic and clinical research.

Disclosures

None.

References

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