Lipoprotein-associated phospholipase A2, a marker of vascular inflammation and systemic vulnerability

Thomas Münzel* and Tommaso Gori

II Medizinische Klinik für Kardiologie/Angiologie, Langenbeckstrasse 1, D-55131 Mainz, Germany

Online publish-ahead-of-print 30 August 2009

This editorial refers to ‘Expression of lipoprotein-associated phospholipase A2 in carotid artery plaques predicts long-term cardiac outcome’, by J. Herrmann et al. on page 2930

As interventional cardiologists, we are sometimes prone to believe that plaque quantity, more than plaque biology, is a determinant of patients’ prognosis. This concept is unfortunately challenged in daily practice, as accelerated progression of atherosclerosis, rupture of a plaque that was not critical at angiography, and/or dynamic phenomena such as spasm contribute to determine the patient’s prognosis. That the extent and severity of coronary artery disease at angiography is a strong prognostic index for the risk of subsequent (cardio)vascular events is not under discussion. However, our understanding of plaque progression and instability remains far from complete. In line with this concept, Lavi et al. recently reported that the presence of an abnormal coronary reactivity to an endothelium-dependent stimulus identifies areas occupied by plaques with a larger necrotic core, i.e. at higher risk for rupture. In addition, a number of studies and anecdotal evidence have shown that endothelial dysfunction and/or oxidative stress, systemic or local, may predict disease progression/instability and overall patient prognosis. Although it needs to be acknowledged that the best therapeutic strategy for plaques that are histologically vulnerable but cause no severe stenosis at angiography remains unexplored, the search for new markers and techniques that help in detecting vulnerable plaques and vulnerable patients should be considered a priority of modern cardiology.

An effort in this direction is presented by Herrmann et al. who describe the important role of lipoprotein-associated phospholipase A2 (Lp-PLA2) levels and activity, as measured at the level of carotid plaques, in predicting future cardiovascular events. This concept provides further support for the idea that atherosclerosis is a systemic disease, and that plaque activation in a given vascular district is associated with a global increased cardio- or cerebrovascular risk.

Lp-PLA2s belong to a superfamily that contains 15 separate groups and a number of subgroups characterized on the basis of sequence, molecular weight, disulfide bonds, requirement for Ca\(^{2+}\), and other molecular and functional features. Five major categories of PLA2s are usually described: these include the secreted small molecular weight sPLA2, the larger cytosolic Ca\(^{2+}\)-dependent cPLA2, the Ca\(^{2+}\)-independent iPLA2, the platelet-activating factor acetylhydrolases, and the lysosomal PLA2. In general, PLA2s hydrolyse the fatty acid from the sn-2 position of membrane phospholipids. The two compounds that result from this reaction are a polyunsaturated fatty acid that functions as substrate for a number of enzymes to form various eicosanoids and eicosanoid-related mediators and a lysophospholipid which can also have important roles in biological processes. Lysophospholipids such as lysophosphatidylcholine may also serve as markers of local LPA2 activity, although, as Herrmann et al. acknowledge, one needs to keep in mind that the production of these mediators is not exclusive to these enzymes. Thus, products of PLA2 activity may mediate a variety of biological events, and crucial roles during signalling and metabolic processes such as host defence, inflammation, and innate immunity have been described for most of the members of this superfamily.

Platelet-activating factor acetylhydrolases are composed of two PLA2 groups, and are mostly produced by macrophages and activated inflammatory cells. One member of this group is the Lp-PLA2, a 45 kDa, Ca\(^{2+}\)-independent secreted enzyme that catalyses a number of reactions of biological importance and that, notably, is able to bind to both HDL and LDL cholesterol molecules through as yet incompletely understood mechanisms. The physiological role of Lp-PLA2 and its potential role in determining cardiovascular pathology is also far from being completely understood (Figure 1), and there are lines of evidence suggesting both an anti-inflammatory and a proinflammatory function of this enzyme. In human plasma, the majority of the Lp-PLA2 activity is present as a complex with LDL and lipoprotein(a). In particular,
Lp-PLA2 appears to be particularly represented in small dense LDL particles, which are believed to be more proatherogenic and to promote Lp-PLA2 activity. Bound to these lipoproteins, according to the hypothesis recently proposed by Stafforini et al., Lp-PLA2 hydrolyses potentially dangerous oxidized phospholipids, reducing their ability to promote monocyte chemotaxis and adhesion, and it decreases the bioavailability of the prothrombotic platelet-activating factor. Thus, in a physiological state, Lp-PLA2 might actually have a protective, anti-inflammatory and antiplatelet function, as demonstrated by evidence in animal in vivo studies in which overexpression of human plasma PLA2 retarded the progression of conditions associated with cardiovascular disease, including atherosclerosis and post-ischaemic injury. Similarly, genetic deficiency of PLA2 has been associated with increased incidence and severity of cardiovascular conditions in certain (prevalently Asian) populations. Notably, Lp-PLA2 is itself hyperexpressed in the setting of inflammation, and it is inhibited by peroxynitrite (ONOO⁻). What causes this equilibrium to tip from a beneficial role for Lp-PLA2 to a proatherogenic role of the enzyme remains unknown.

Figure 1 The controversial role of Lp-PLA2. The enzyme hydrolyses a number of mediators potentially involved in atherogenesis, such as oxidized low-density lipoproteins (oxLDL) and platelet-activating factor (PAF), thus reducing their negative impact. At the same time, products of Lp-PLA2-mediated degradation of these molecules may also have proinflammatory, proliferative, and ultimately proatherogenic roles. Notably, Lp-PLA2 itself is hyperexpressed in the setting of inflammation, and it is inhibited by peroxynitrite (ONOO⁻). What causes this equilibrium to tip from a beneficial role for Lp-PLA2 to a proatherogenic role of the enzyme remains unknown.
risk has been reported in patients with stable coronary artery diseases. \(^5\,12\,13\) Collectively, these data suggest that LP-PLA\(_2\) might be a reliable biomarker of cardiovascular risk in various populations and that it might help in guiding the intensity of preventive therapy.

Since LP-PLA\(_2\) may be both a specific marker and a causal mediator of plaque progression and instability, a more exciting perspective is to test the possibility of using it as a therapeutic target. The development of the specific oral LP-PLA\(_2\) inhibitors, the azetidinones, has opened up this possibility: therapy with the LP-PLA\(_2\) inhibitor darapladib has been associated, in animal models and patients with cardiovascular disease, with a reduction (or reduced progression) of atherosclerosis and of some morphological markers of plaque instability. \(^14\,15\) Although no effect was shown on plaque deformability and other parameters of plaque instability. Thus, until further studies are performed, it needs to be acknowledged that our understanding of the role of LP-PLA\(_2\) in atherosclerosis, inflammation, and oxidative stress remains incomplete, and that most of the knowledge to date is founded on evidence of association more than causation. The study by Herrmann et al. \(^3\) adds further important information, and it emphasizes the fact that we should consider atherosclerosis as a systemic disease in which oxidative stress and inflammatory mechanisms play a central role.

In conclusion, LP-PLA\(_2\) is potentially a marker of vascular inflammation, a risk factor, a prognostic biomarker, and ultimately a target of therapy. In the perspective of further development, at least three questions are of crucial importance: the first is whether LP-PLA\(_2\)-related parameters can be used as biomarkers of inflammatory activity, with the advantage over C-reactive protein of possessing some specificity for cardiovascular disease and/or risk. It is well known that major known risk factors account for only about half of the variability in cardiovascular risk, and the quest for more accurate and more sophisticated risk scores is ongoing. To this end, it will be important to understand how much the addition of LP-PLA\(_2\)-related parameters potentiates the prognostic information that derives from conventional (more accessible) risk factors. Also, it will have to be clarified whether the additional information provided by LP-PLA\(_2\) measures can be applied in individual patients, and whether LP-PLA\(_2\)-based therapeutic strategies improve cardiovascular outcomes.

The second point is what to do to develop LP-PLA\(_2\) as a therapeutic target. LP-PLA\(_2\) levels are indirectly modified by lipid-lowering therapies, but therapies based on specific targeting of LP-PLA\(_2\) will have to be tested in terms of hard outcomes. In particular, the true role of LP-PLA\(_2\) in atherogenesis—as a mediator, a defence mechanism, or a bystander—will need to be investigated, and it will need to be clarified whether inhibition of LP-PLA\(_2\) might lead to paradoxical accumulation of proinflammatory or prothrombotic moieties.

Finally, the data from the paper of Herrmann et al. along with those previously published by the same group, \(^16\) suggest that the abundance of LP-PLA\(_2\) at the level of specific plaques might be a potent prognostic marker in our ongoing quest for the ‘vulnerable plaque’ or the ‘vulnerable patient’. Newer technologies such as virtual histology, intravascular ultrasound palpography and thermography, optical coherence tomography, and especially non-invasive techniques would definitely benefit from a molecular imaging biomarker that allows the study of plaque composition and characteristics in a safe and reliable way. In this perspective, invasive or non-invasive technologies that allow identification of biological markers of instability in single plaques are eagerly awaited.

**Conflict of interest:** None declared.

**References**