American Heart Association | American Stroke Association

Lp-PLA$_2$, Plaque Inflammation and Lesion Development Vary Fundamentally Between Different Vascular Sites

Gunther Marsche, PhD

Lp-PLA$_2$ is also known as platelet activating factor (PAF) acetylhydrolase (PAF-AH) or PLA2G7, owing to its hierarchical position in the PLA2 superfamily. Lp-PLA$_2$ 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-PLA$_2$ was first proposed to have anti-inflammatory properties.[1] In general, Lp-PLA$_2$ hydrolyzes glycerophospholipids containing short chain or oxidized fatty acids at the *sn*-2 position. Substrate hydrolysis catalyzed by Lp-PLA$_2$ 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-PLA$_2$ gene in the inflamed vascular tissue point toward a potential role of Lp-PLA$_2$ in the development and progression of atherosclerosis[3] 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-PLA$_2$ continues to be a challenge, and a number of issues remain to be resolved.

Fenning and colleagues[6] now report that the role of Lp-PLA$_2$ 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-PLA$_2$ with darapladib inhibited progression to advanced coronary atherosclerotic lesions. However, Fenning and colleagues now report that inhibition of Lp-PLA$_2$ 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-PLA$_2$ 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.[8] Under inflammatory conditions increased Lp-PLA$_2$ levels associate with LDL[9] and HDL,[10,11] therefore lipoprotein associated Lp-PLA$_2$ activities are expected to be different in animals. Of particular interest, a recent study provided a different view on the role of Lp-PLA$_2$ in inflammatory responses, arguing against a pro-atherogenic role of Lp-PLA$_2$ 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

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From the Institute of Experimental and Clinical Pharmacology, Medical University of Graz, Austria.

Correspondence to: Gunther Marsche, PhD, Institute of Experimental and Clinical Pharmacology, Medical University of Graz, Universitaetsplatz 4, 8010 Graz, Austria. E-mail gunther.marsche@medunigraz.at

J Am Heart Assoc. 2015;4:e001800 doi: 10.1161/JAHA.115.001800.

relationship between Lp-PLA$_2$, and PAF-like substrates and products generated to various extents in settings of inflammation is not understood. It therefore remains elusive whether Lp-PLA$_2$ is still a valid target for therapeutic intervention.[13]

Disclosures

None.

References

1. Tjoelker LW, Wilder C, Eberhardt C, Stafforini DM, Dietsch G, Schimpf B, Hooper S, Le Trong H, Cousens LS, Zimmerman GA, Yamada Y, McIntyre TM, Prescott SM, Gray PW. Anti-inflammatory properties of a platelet-activating factor acetylhydrolase. *Nature*. 1995;374:549–553.
2. Stafforini DM, McIntyre TM. Determination of phospholipase activity of PAF acetylhydrolase. *Free Radic Biol Med*. 2013;59:100–107.
3. Mohler ER III, Sarov-Blat L, Shi Y, Hamamdzic D, Zalewski A, Macphee C, Llano R, Pelchovitz D, Mainigi SK, Osman H, Hallman T, Steplewski K, Gertz Z, Lu MM, Wilensky RL. Site-specific atherogenic gene expression correlates with subsequent variable lesion development in coronary and peripheral vasculature. *Arterioscler Thromb Vasc Biol*. 2008;28:850–855.
4. STABILITY Investigators, White HD, Held C, Stewart R, Tarka E, Brown R, Davies RY, Budaj A, Harrington RA, Steg PG, Ardissino D, Armstrong PW, Avezum A, Aylward PE, Bryce A, Chen H, Chen MF, Corbalan R, Dalby AJ, Danchin N, De Winter RJ, Denchev S, Diaz R, Elisaf M, Flather MD, Goudev AR, Granger CB, Grinfeld L, Hochman JS, Husted S, Kim HS, Koenig W, Linhart A, Lonn E, Lopez-Sendon J, Manolis AJ, Mohler ER III, Nicolau JC, Pais P, Parkhomenko A, Pedersen TR, Pella D, Ramos-Corrales MA, Ruda M, Sereg M, Siddique S, Sinnaeve P, Smith P, Sritara P, Swart HP, Sy RG, Teramoto T, Tse HF, Watson D, Weaver WD, Weiss R, Viigimaa M, Vinereanu D, Zhu J, Cannon CP, Wallentin L. Darapladib for preventing ischemic events in stable coronary heart disease. *N Engl J Med*. 2014;370:1702–1711.
5. O'Donoghue ML, Braunwald E, White HD, Steen DP, Lukas MA, Tarka E, Steg PG, Hochman JS, Bode C, Maggioni AP, Im K, Shannon JB, Davies RY, Murphy SA, Crugnale SE, Wiviott SD, Bonaca MP, Watson DF, Weaver WD, Serruys PW, Cannon CP; SOLID-TIMI 52 Investigators. Effect of darapladib on major coronary events after an acute coronary syndrome: the SOLID-TIMI 52 randomized clinical trial. *JAMA*. 2014;312:1006–1015.
6. Fenning RS, Burgert ME, Hamamdzic D, Peyster EG, Mohler ER III, Kangovi S, Jucker BM, Lenhard SC, Macphee CH, Wilensky RL. Atherosclerotic plaque inflammation varies between vascular sites and correlates with response to inhibition of lipoprotein-associated phospholipase A2. *J Am Heart Assoc*. 2015;4:e001477 doi: 10.1161/JAHA.114.001477.
7. Wilensky RL, Shi Y, Mohler ER III, Hamamdzic D, Burgert ME, Li J, Postle A, Fenning RS, Bollinger JG, Hoffman BE, Pelchovitz DJ, Yang J, Mirabile RC, Webb CL, Zhang L, Zhang P, Gelb MH, Walker MC, Zalewski A, Macphee CH. Inhibition of lipoprotein-associated phospholipase A2 reduces complex coronary atherosclerotic plaque development. *Nat Med*. 2008;14:1059–1066.
8. Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. *Arterioscler Thromb Vasc Biol*. 2000;20:1262–1275.
9. Karabina SA, Liapikos TA, Grekas G, Goudevenos J, Tselepis AD. Distribution of PAF-acetylhydrolase activity in human plasma low-density lipoprotein subfractions. *Biochim Biophys Acta*. 1994;1213:34–38.
10. Birner-Gruenberger R, Schittmayer M, Holzer M, Marsche G. Understanding high-density lipoprotein function in disease: recent advances in proteomics unravel the complexity of its composition and biology. *Prog Lipid Res*. 2014;56C:36–46.
11. Marsche G, Saemann MD, Heinemann A, Holzer M. Inflammation alters HDL composition and function: implications for HDL-raising therapies. *Pharmacol Ther*. 2013;137:341–351.
12. Marathe GK, Pandit C, Lakshmikanth CL, Chaithra VH, Jacob SP, D'Souza CJ. To hydrolyze or not to hydrolyze: the dilemma of platelet-activating factor acetylhydrolase. *J Lipid Res*. 2014;55:1847–1854.
13. McConnell JP, Hoefner DM. Lipoprotein-associated phospholipase A2. *Clin Lab Med*. 2006;26:679–697, vii.

Key Words: Editorials • coronary atherosclerosis • lipoprotein-associated phospholipase A2