

Lysophosphatidylcholine in Platelet Microvesicles: The Grease for Cardiovascular Disease

Rory R. Koenen^{1,2} 

¹ Department of Biochemistry, Cardiovascular Research Institute Maastricht, Maastricht University, Maastricht, The Netherlands

² Institute for Cardiovascular Prevention (IPEK), LMU Munich, Munich, Germany

Address for correspondence Rory R. Koenen, PhD, CARIM, Maastricht University, P.O. Box 616, 6200 MD Maastricht, The Netherlands (e-mail: r.koenen@maastrichtuniversity.nl).

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In this issue of *Thrombosis and Haemostasis*, Diehl and Peter demonstrate that microvesicles derived from platelets are enriched in the bioactive lipid lysophosphatidylcholine (LPC), which was shown to activate platelets and which could be measured in unstable atherosclerotic plaques.¹ Extracellular vesicles (EVs) are small membrane-enclosed cell fragments. Almost every cell type, prokaryotic and eukaryotic, is able to release EV and this is often intensified after activation or during stress. Although a matter of debate, the current knowledge allows the classification of EV into three main types: (1) the exosomes, which originate from the endosomal compartments of the cell, (2) the microvesicles, which are formed after budding of the outer cell membrane, and (3) the apoptotic bodies that result after the cell undergoes apoptosis. The released EV retains many properties of their parent cells with respect to surface markers and content, providing information about the physiologic state and context of their parent cells or tissue. This makes EV highly interesting for biomedical research, for example, as biomarkers.² Unlike classical *biomolecular* biomarkers that basically contain information solely about concentration and type, EVs carry information about counts, size, cellular origin, and cargo, to name a couple. It is this high information density that makes EV that attractive.³ Regarding cargo, EVs have been found to contain nucleic acids, including micro-ribonucleic acids (RNAs), proteins, and bioactive lipids. During the release process, particular constituents can be enriched in EV. Thus, EV might just function to dispose cellular waste, serve as mediators of intercellular communication,⁴ or both. Needless to say, EVs are not only in sharp focus as novel physiologic players during health and disease, but also as promising biomarkers, not in the last place for cardiovascular disease.^{5–7}

Being the first cells known to release EV, platelets are a rich source of EV in circulation. While medical textbooks will mainly discuss their essential functions in hemostasis, platelets also play an important role as immune cells.⁸ Thus, the EV released by platelets not only enhance fibrin generation⁹

and thrombosis,¹⁰ but studies have also shown that they influence the behavior and/or phenotype of endothelial cells,¹¹ monocytes,¹² macrophages,^{13,14} or smooth muscle cells,¹⁵ often skewing cellular responses toward inflammation. Binding of the EV to the recipient cells, with subsequent internalization preceded the phenotypic shifts in all of the above studies. However, the molecular factors within EV made responsible for causing the effects were different and ranged from cytokines (e.g., CXCL4¹⁵) and micro-RNAs (e.g., miRNA 126¹⁴) to bioactive lipids (e.g., arachidonic acid¹¹), reflecting the broad palette of bioactive EV cargo.

In the study by Diehl and Peter, a further active molecular constituent of platelet-derived EV (microvesicles) was identified as LPC by mass spectrometry. Interestingly, the LPC contents in microvesicles were markedly enriched after platelet activation, in particular by thrombin, compared with the LPC contents of the platelets themselves. Also, thrombin-induced microvesicles contained more LPC than those from resting platelets. This suggests that LPC is actively formed in or transported into microvesicles after platelet activation. Addition of LPC to platelets resulted in typical responses, for example, integrin activation, exposure of P-selectin, spreading on immobilized fibrinogen, and aggregation, but also less well-established effects such as platelet–monocyte aggregate formation and migration toward a gradient of LPC. The authors could explain the response of platelets to LPC by the action of the G2A receptor, not only showing the presence of this receptor in platelets, but also demonstrating a dose-dependent inhibition of the response of platelets to LPC by an antibody against the G2A receptor. To investigate the potential of LPC as a possible biomarker, the authors measured LPC in the blood and arteries of control mice and mice with stable and unstable atherosclerosis. The largest amounts of LPC were found in specimen from mice with unstable plaques. Finally, using state-of-the-art mass spectrometry imaging on human vulnerable plaque specimen, the authors observed that LPC accumulated in areas that were considered particularly vulnerable.

The study by Diehl and Peter shows that microvesicles from platelets contain bioactive lipids such as LPC. Further, this LPC

 Rory R. Koenen's ORCID is <https://orcid.org/0000-0002-9955-9730>.

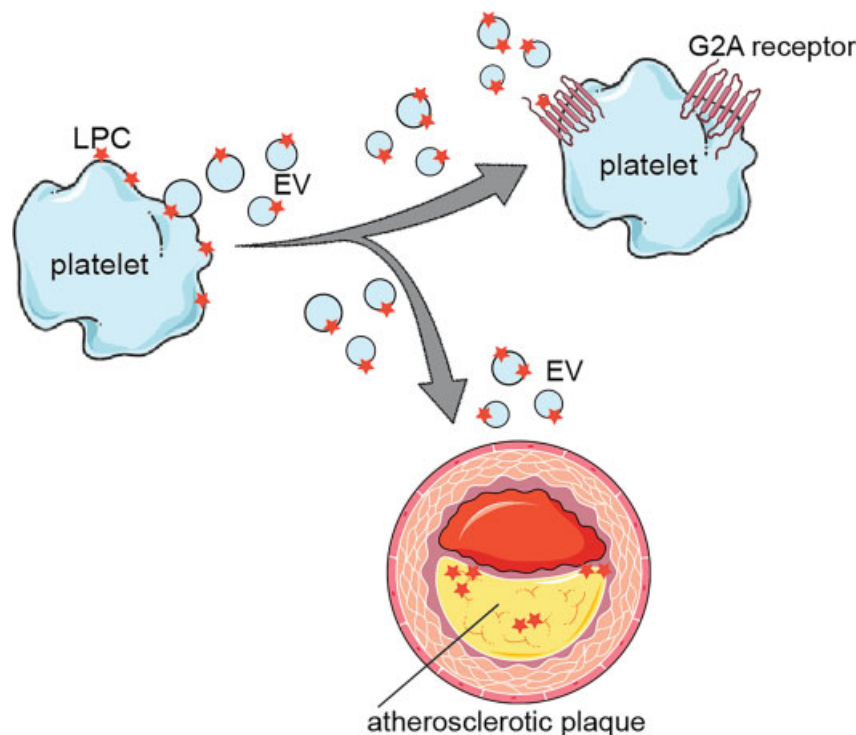


Fig. 1 Lysophosphatidylcholine (LPC) release by platelets. LPC is released into extracellular vesicles (EVs) by activated platelets. This LPC might activate platelets in an autocrine/paracrine manner through the G2A receptor. LPC was also found to accumulate in unstable areas of atherosclerotic plaques.

might not only have a function as a biomarker but might also play an active role in the development of cardiovascular disease, potentially by mediating autocrine platelet activation and by being involved in the still poorly known process of plaque destabilization (►Fig. 1). However, some open questions remain for possible future studies. For example, it is unclear to which extent the LPC that was measured in mouse plasma is associated to platelet microvesicles. Likewise, although the authors convincingly showed that LPC is enriched in unstable plaques both from mice and humans, the origin of this LPC remains to be pinpointed exactly. Similar counts for its mechanistic relevance for plaque destabilization.

Taken together, the authors have demonstrated that LPC is a novel bioactive lipid mediator of platelet microvesicle activity with potential to become the grease for the progression of cardiovascular disease.

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Conflict of Interest

None declared.

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