Lysophospholipids in the regulation of endothelial barrier function

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SERUM IS KNOWN TO CONTAIN heat-stable and trypsin-sensitive bioactive factors that possess diverse biological activities, including promotion of wound healing and tissue regeneration as well as inflammatory processes. To date, some of these factors are identified to be lysophospholipid ligands [i.e., lysophosphatidic acid (LPA) and sphingosine 1-phosphate (S1P)] that bind with high affinity to and signal through members of a subfamily of G protein-coupled receptors encoded by the endothelial differentiation genes (6). In addition to endothelial differentiation gene receptors, several other biologically active phospholipids [i.e., platelet-activating factor (PAF), lysophosphatidylcholine (8), and species of oxidized phosphatidylcholine (11)] activate the PAF receptor, another lipid ligand-specific G protein-coupled receptor (7).

Most of these lipid mediators possess potent proinflammatory properties that directly activate the vascular endothelium. Recent work shows that LPA and S1P activate the transcription factor nuclear factor-κB; generate production of the cytokines monocyte chemotactic protein-1 and interleukin-8; and upregulate expression of the adhesion molecules vascular cell adhesion molecule-1, E-selectin, and intercellular adhesion molecule-1 (14) as well as increase leukocyte adhesion to the endothelial cell surface (15). Furthermore, they are mitogenic. In particular, S1P is a potent endothelial cell chemotactic agent, and, therefore, these lipids are proposed to be critical regulators in wound healing processes. PAF and other phospholipids (8, 11) that signal through the PAF receptor are also highly proinflammatory. It is well known that PAF increases vascular epithelial as well as endothelial permeability, leukocyte extravasation, and promotion of cytokine production and is implicated in several vascular diseases including vasculitis and asthma (3, 9).

With the exception of PAF, the regulation of endothelial barrier function by these lipid mediators is not well known. LPA and S1P appear to promote endothelial barrier restrictiveness (1, 4, 10), a surprising property in light of their proinflammatory and angiogenic actions. But LPA is also shown to impair endothelial barrier function (16, 17a), thus underscoring the incomplete understanding of the function, regulation, and physiological role of these lipids in vascular biology. The paper by Minnear et al. (12) in this issue of American Journal of Physiology-Lung Cellular and Molecular Physiology adds further support to the barrier-promoting actions of the lysophospholipids and some insight into their physiological significance. These authors provide evidence that the barrier-promoting effects of these lipids may account for the permeability-decreasing activity of platelets. S1P is primarily stored in platelets and released on cellular activation (18), whereas LPA is released by both non-stimulated and stimulated platelets as well as by activated fibroblasts, adipocytes, and tumor cells (13). LPA is also found in mildly oxidized low-density lipoprotein (17). On their generation and release, most of these lysophospholipids are bound to serum proteins such as albumin or lipoproteins. A key finding by Minnear et al. (12) is that platelet-derived lipids form a complex with albumin, which then confers barrier-promoting effects to the endothelium. The identity of the responsible lipid(s) has yet to be determined.

An interesting finding by Minnear et al. (12) is that LPA was not detected from the lipid-albumin complexes in one of the two platelet batches examined despite the fact that the lipid-albumin fraction from both batches yielded potent permeability-decreasing activity. This finding strongly suggests that other lipids associated with albumin in addition to LPA play a role in the promotion of barrier function. Furthermore, in the in vivo situation, LPA bound to albumin is derived from multiple sources including platelets. Therefore, the barrier-promoting property attributable to LPA from platelets is likely to be less than that of those lipids derived predominantly from platelets, such as S1P. Indeed, Yatomi et al. (18) found that activated platelets released predominantly S1P, not LPA. Furthermore, platelets in blood clots released greater amounts of SPP than platelets stimulated with thrombin, ADP, or Ca2+ ionophores in the absence of clots (5),
suggesting that lipids secreted by platelets are stimulus selective. Thus it is clear that the lipid profile associated with albumin is critically influenced by the physiological state of platelets and, therefore, is of great importance in the regulation of endothelial activities. However, in the study by Minnear et al. (12), who used nonactivated platelets, the lipid composition associated with albumin varied between the two platelet batches, indicating yet undetermined factors responsible for the difference. Thus there is a need to fully understand the determinants of lipid composition changes associated with albumin, which is fundamental to our understanding of platelet-endothelial cell biology in health and disease.

REFERENCES