Lysophosphatidylcholine: an enigmatic lysolipid

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INCREASED ENDOTHELIAL PERMEABILITY of pulmonary microvessels is the major contributor of acute lung injury, sepsis, and acute respiratory distress syndrome (2, 7). Studies have established that change in cell shape resulting in concurrent formation of gaps between endothelial cells is a primary determinant of increase in endothelial permeability (2, 7). Proinflammatory mediators (such as thrombin, histamine, and bradykinin) and other blood-borne mediators (such as VEGF) bind endothelial cell surface receptors and activate signaling cues that induce endothelial cell contraction, forming gaps in the monolayer (2, 7). Stress fibers composed of bundles of polymerized actin and myosin filaments are the primary elements of the contractile machinery in endothelial cells (2). These fibers were shown to form in cultured endothelial cells in response to many permeability-increasing mediators. RhoA, a monomeric GTPase, upon activation is known to form stress fibers and thus plays a central role in causing the increase in endothelial permeability (2). Studies in various cell types indicate that G protein-coupled receptor agonists, such as thrombin, activate RhoA by activating G_{q12/13} and G_{q11} (5, 9, 14). G_{q12/13}-induced activation of RhoA in endothelial cells evidently requires PKCα-dependent phosphorylation of guanosine dissociation inhibitor and p115-Rho exchange factor (3, 11).

The report from Huang et al., the current article in focus (Ref. 4, see p. L176 in this issue), shows that extracellular application of lysophosphatidylcholine (LPC), which exceeded the binding capacity of albumin, activated RhoA in a PKCα-sensitive manner and impaired endothelial barrier function. LPC (2 μM) given alone also perturbed endothelial barrier function, indicating functional effects of LPC in vivo may be controlled by a balance between free form and albumin-bound form of LPC. Although endothelium was shown to be a target for LPC in several studies, it was not known whether LPC per se regulates endothelial barrier integrity. For example, LPC was shown to impair endothelial cell function by preventing the synthesis of endothelium-derived relaxing factor (12). LPC also induced oxidant production through activation of NADPH/NADPH oxidase system (16) and increased the expression of chemokines such as monocyte chemoattractant protein-1 and IL-8 in the endothelial cells (13). In addition, LPC suppressed antithrombotic property of endothelial monolayer by inhibiting expression of tissue factor pathway inhibitor (15). LPC is a normal constituent of plasma and is generated by phospholipase A2-induced hydrolysis of membrane phosphatidylcholine. Increased plasma LPC levels are reported in several inflammatory diseases such as ischemia and asthma (see references cited in Ref. 4). LPC has been shown to be a pathological component of oxidized lipoproteins (LDL) in plasma and of atherosclerotic lesions (17). Interestingly, LPC is also released into plasma upon thrombin stimulation of endothelial cells (10). Thrombin is an established edemagenic mediator and increases endothelial permeability by the PKCα-RhoA pathway (2, 3, 11). In this regard, the Huang et al. (4) studies are interesting as they indicate that LPC can increase endothelial permeability directly and LPC generated by endothelial cells in response to edemagenic agents may exacerbate barrier-disruptive response. The homologies between signaling events activated by LPC and thrombin suggest that LPC may activate Rho and subsequent barrier disruption by activating the heterotrimeric G proteins G_{q} and G_{12/13}. The orphan G protein-coupled receptor GPR4 expressed on endothelial cells has been suggested to induce LPC-mediated signaling events (8). Whether GPR4 couples to G_{q} and G_{12/13} in endothelial cells and induces Rho activation via these proteins remains to be tested.

On the basis of evidence discussed above along with the findings of Huang et al. (4), LPC appears to be a proinflammatory mediator and may be intricately involved in disrupting endothelial barrier function resulting in inflammatory responses in the vessel wall. Surprisingly, LPC is described as being protective against lung vascular injury as extracellular application of 1 μM LPC prevented injury by N-formyl-methionyl-leucyl-phenylalanine-activated neutrophils in an isolated perfused lung model (6). In another study, subcutaneous administration of LPC activated neutrophils, which protected mice against sepsis induced by cecal ligaton and puncture or intraperitoneal injection of Escherichia coli (18). Along the same lines, a study shows that chronic septic patients who presumably have tissue inflammation and leaky endothelial barrier have lower plasma levels of LPC (1). It is possible that low plasma LPC levels are the result of activation of lipases. Together, these seemingly conflicting findings indicate that LPC effects on endothelium are complex and may depend on the integrity of endothelium. Whereas LPC disrupts barrier function in naïve endothelium, it has a protective role when the barrier is leaky. It is also possible that variable effects of LPC observed in cultured endothelial cells and in vivo experimental models could be very well due to differences in length and/or saturation state of fatty acid chain. Thus further studies are needed to understand the role of this “enigmatic” lysolipid in regulating endothelial permeability and inflammatory responses in cultured cells and in vivo models.

REFERENCES


