6-2 Sphingolipids and Lung Vascular Barrier Regulation

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Summary. Long thought to function primarily as the structural components of lipid membranes, sphingolipids are now also recognized as vitally important signaling mediators regulating a diverse range of functions. We recently described the potent vascular barrier-regulating properties of one of these sphingolipids, the lipid and angiogenic factor sphingosine 1-phosphate (S1P) (Garcia et al, 2001). Since disruption of vascular barrier integrity commonly occurs in highly morbid inflammatory lung conditions, a better understanding of the mechanism of barrier regulation would have important clinical implications. In this chapter, we provide a brief overview of vascular barrier regulation before detailing the mechanisms underlying potent barrier-enhancing effects of S1P in vitro and in vivo in models of acute lung injury (ALI) syndromes. The potential ramifications of these findings for the development of specific therapeutic interventions for patients with ALI syndromes are then discussed.

Keywords. permeability, endothelium, sphingosine 1-phosphate, acute lung injury, cytoskeleton

1. Overview of vascular barrier regulation

The vasculature is lined by endothelial cells (EC) which provide a semi-permeable barrier between circulating vascular contents and the surrounding tissues perfused by these vessels. Disruptions in vascular barrier integrity significantly increases permeability to fluid, protein, and cir-
culating cells. This is the central pathophysiological mechanism for many inflammatory disease processes. The lung is particularly sensitive to this type of injury, given the large surface area needed for alveolar gas exchange. Pulmonary EC vascular leak leads to alveolar flooding during inflammatory conditions such as ALI/ARDS (acute lung injury/acute respiratory distress syndrome) and sepsis. This phenomenon contributes significantly to the morbidity of those clinical syndromes. Therefore, we focus here on the pulmonary endothelium as a model for vascular barrier regulation.

EC permeability is primarily determined by the EC cytoskeleton, cell-cell connections, and cell-matrix connections. Accumulated evidence supports a critical role for the endothelial cytoskeleton in dynamic modulation of vascular barrier function. The EC cytoskeleton itself is composed of actin filaments, intermediate filaments, and microtubules (for review, see Dudek & Garcia, 2001). Actin cytoskeleton can rapidly be rearranged into filaments of various shapes and sizes that closely regulate the overall shape, motility, and contractile status of the EC. This dynamic rearrangement is controlled by various actin binding, capping, nucleating, and severing proteins regulating filament size and shape. The primary role of actin filaments in EC permeability was demonstrated in early observations that cytochalasin D, which disrupts the actin cytoskeleton, increased EC permeability while phallacidin, an actin stabilizer, prevented barrier disruption by various agonists (Phillips et al. 1989). Actin filaments interact with myosin to generate EC tensile force that, in turn, drives cell shape changes and barrier regulation. When cellular contraction occurs along the a cell's actin stress fibers, gaps form between adjacent cells and paracellular permeability increases. In addition, the actin microfilament system participates in EC barrier enhancement through focal linkages to multiple membrane adhesive proteins that connect the system to cell-cell (adherens junctions, tight junctions) and cell-matrix (focal adhesion) junctions as well as anchor the endothelium. The functional roles of microtubule and intermediate filament cytoskeletal components in EC barrier regulation are less well defined. However, microtubule disrupting agents, such as nocodazole, induce rapid rearrangement of actin filaments and focal adhesions, cellular contraction, and increase permeability across EC monolayers while microtubule stabilization attenuates these effects (Verin et al. 2001). This suggests that actin filament-microtubule crosstalk is important in EC barrier regulation.

Cell-cell and cell-matrix contacts provide tethering forces essential for EC mechanical stability and barrier maintenance. The primary cell-cell contacts in EC are adherens junctions, consisting of extracellular cadherins