p120: the guardian of endothelial junctional integrity

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THE ENDOTHELIUM, composed of the endothelial monolayer and underlying matrix, constitutes the major regulatory barrier of the vascular system by finely controlling the fluxes of macromolecules across the vessel walls. An increase in the permeability of the endothelial monolayer in the lung has been established as the major cause of acute lung injury (6, 12). It has become progressively clear that adherens junctions, composed of cadherin-catenin complexes, are the fundamental structures important for maintaining endothelial barrier function. This is because adherens junctions provide intercellular tensile strength to the endothelial cell monolayer and also have the ability to transduce signals bidirectionally to the RhogTPases and actin cytoskeleton, thereby transducing adhesive interactions into changes in cell shape (5, 10, 11, 21). The primary members of the cadherin-catenin complex include vascular endothelial (VE)-cadherin and the α-, β-, γ (plakoglobin)-, and p120 catenins. Cadherins are transmembrane glycoproteins that engage in Ca\(^{2+}\)-dependent homotypic adhesive interactions through their ectodomains. The cadherin cytoplasmic tail binds β-catenin, which in turn binds α-catenin, thereby linking this complex to the actin cytoskeleton. This interaction of cadherin with catenins enables cadherins to transduce signals bidirectionally from the membrane to the actin cytoskeleton and vice versa (5).

Classically, VE-cadherin and the α- and β-catenins have been perceived as the core constituents of the adherens junction. However, recent studies have identified p120-catenin as an additional player that regulates VE-cadherin function (1, 4, 19, 21). p120 is a member of the armadillo supergene family and was initially described as an Src substrate (16). p120 differs from β-catenin as it binds VE-cadherin exclusively at the juxtamembrane domain (JMD) and has no interaction with either α-catenin or the actin cytoskeleton (1). When p120 is overexpressed in normal cells, p120 not bound to cadherin exists in a soluble cytoplasmic pool (14, 17). Several studies showed that this cytoplasmic p120 regulates Rho-GTPase activity and thus can regulate the organization of the actin cytoskeleton (2). Whereas high levels of cytosolic p120 inhibit the activation of RhoA, a subtle increase in cytosolic p120 activates two other members of the Rho family, Rac and Cdc42. Recently, p120 has been shown to associate with kinesin, a microtubule motor that regulates p120 localization and allows p120 to traffic cadherin-catenin complexes to intercellular junctions (3, 20). Depletion of p120 by small interfering RNA (siRNA) resulted in loss of cadherin expression and adherens junctions in epithelial cells (4, 19). Together, these findings indicate that p120 is required for cell surface expression of cadherin, and depending on its cytosolic pool, it may exert its control over cadherin function, including assembly of adherens junction through its interaction with cadherin and kinesin as well as signaling to Rho-GTPases.

On the basis of its role in regulating cadherin expression and Rho-GTPase signaling, one could speculate that in endothelial cells, p120 is critical in maintaining endothelial barrier function. Apart from studies that endothelial barrier disruption is associated with alterations in p120 phosphorylation (9, 15, 18), it is not known whether p120 per se regulates cadherin function and endothelial barrier integrity. In the report from Iyer et al., the current article in focus (Ref. 8, see p. L1143 in this issue), using adenoviral-mediated gene delivery and siRNA, the authors varied the endogenous level of p120 and determined how these interventions regulated cadherin-mediated maintenance of the endothelial barrier (8). Iyer and colleagues found that overexpression of the JMD of cadherin, which is known to act as a sink for p120 and thereby depletes endogenous p120, decreased endothelial barrier function. JMD overexpression also increased actin stress fiber formation and myosin light chain (MLC) phosphorylation in the Rho kinase-sensitive manner. These findings are in accord with the previously reported findings mentioned above that p120 serves as an endogenous inhibitor of RhoA function. Because RhoA has been established as a major disruptor of endothelial barrier function by regulating actin-myosin-generated contractile tension (6, 7, 13), these findings indicate that p120 may be barrier protective by balancing RhoA activity and by maintaining stable adherens junctions. However, Iyer et al. convincingly demonstrate that this is not the case since overexpression of p120 alone, despite decreasing JMD- or thrombin-induced MLC phosphorylation, in fact disrupted barrier function. The barrier-disruptive effect of p120 occurred independently of cadherin function since cell surface expression of VE-cadherin in p120 overexpressing cells was not grossly altered. How can this barrier-disruptive effect of p120 be rationalized in the presence of reduced MLC phosphorylation and thus Rho activity? Maintenance of cell shape and thus the integrity of the endothelial monolayer is a dynamic process characterized by the integrated actions of the contractile and adhesive forces that couple cells with each other and to the extracellular matrix (Fig. 1). A basal level of Rho activity may, therefore, be required to maintain intracellular adhesive interaction by organizing actin cytoskeleton linked to the catenin-cadherin complex. However, high levels of cytosolic p120, by causing ultralow Rho activity, may have perturbed the actin-linked organization of adherens junctions, resulting in a leaky barrier. This conclusion is supported by the findings reported in this study that reveal a less apparent peripheral band of actin in p120-overexpressing cells. Although not determined in this study, it is possible that excess p120 may also perturb intercellular adhesion by modulating Rac and Cdc42 activity. Additionally, excess p120 may not be confirmationally oriented to interact properly with its binding partners, which are required for formation of stable adherens junctions (1). Thus the findings of Iyer et al. strongly suggest that p120 levels must be finely tuned to maintain barrier integrity.
Another interesting finding that has come out of the work of Iyer et al. (8) is that p120 is involved in the regulation of VE-cadherin expression. Iyer and colleagues showed that sequestration of p120 by JMD overexpression or knock down of p120 by siRNA markedly reduced VE-cadherin expression. Reduction in VE-cadherin, as expected, decreased the barrier function. Unlike as reported for epithelial cells, the reduction of VE-cadherin levels that occurred by depletion of p120 was specific since it did not perturb expression of other cadherins or catenins (4). These findings are important since they identify p120 as an important controller of VE-cadherin expression and thus a regulator of several cellular processes in endothelial cells, including adherens junctional assembly, cell migration, and proliferation. As pointed out by Iyer and colleagues, p120 might regulate cadherin expression by controlling the endocytosis of cadherin (4, 19). This is supported by findings presented by Iyer et al. that increasing the endogenous level of p120 in JMD-overexpressing cells restored cell surface VE-cadherin. It is noteworthy that restoration of cell surface VE-cadherin was, however, not sufficient to restore endothelial barrier function. Because JMD overexpression did not disrupt the expression of other cadherins or catenins, the findings of Iyer et al. very likely indicate that in addition to perturbed Rho, Rac, and Cdc42 activity, improper cadherin dimerization and/or sequestration of some unknown effectors such as the tyrosine kinase, Fer, may result in the formation of weak VE-cadherin-containing adherens junctions in endothelial cells (1). A search for these effectors and the signaling events they coordinate will most likely explain the p120 influence on maintaining junctional assembly, Rho signaling, and endothelial barrier function. In the meantime, we now know that p120 acts as a guardian for VE-cadherin and integrates signaling mechanisms to regulate Rho activity that in turn control adherens junction assembly and endothelial barrier function.

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