Epithelium: sticking it out, together

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Some cells live within a community of neighboring cells, restricted in time and space, most prominently interacting with cells of similar functions. Some cells live within fixed positions, surrounded on all sides by a loose forest of matrix proteins. Some cells live as nomads, wandering throughout the body, responding to needs as they arise. Each cell is part of an elaborate orchestra, coordinated by a conductor still poorly understood.

The story of what makes a cell live within a community, or in a fixed position, or as a nomad remains the focus of active investigation. One striking feature of cells living within a community is that they express surface proteins at junctional sites that homotypically interact with similar proteins in adjacent cells. These junctional proteins facilitate cell-cell recognition and contribute to the biophysical qualities of cell-cell adhesion such as barrier strength (3, 8). Indeed, cadherins represent a superfamily of proteins that display cell-restricted expression patterns and thus provide one mechanism by which “like” cells find and interact with one another. Extracellular cadherin repeat domains are the functional interaction domains of these proteins. These repeat domains complex with calcium and through calcium binding interact with the cadherin that is expressed on an adjacent cell. Since cadherins display cell-restricted expression patterns, they play a central role in cell-cell recognition.

The epithelial form of cadherin, E-cadherin, is expressed in the two-cell stage of development in mammals and plays an important role in cell compaction by the eight-cell stage (2). In the postnatal lung, E-cadherin is responsible for tethering adjacent epithelial cells together, and it contributes to the strong epithelial barrier seen throughout the distal airways (3, 8); disruption of E-cadherin binding is sufficient to decrease barrier strength (9).

E-cadherin interacts with auxiliary proteins that ultimately link it to an actinomyosin-based cytoskeleton (3, 8). Proper tethering of this complex to the cytoskeleton, which actively holds the cell under tension, is required for the epithelial community to govern its barrier. The auxiliary proteins are not trivial but are signal transduction effectors, gears that determine whether (or how actively) to engage the transmission. When E-cadherin sits in neutral, it balances the external forces applied by interaction with a homotypic partner from the adjacent cell, with internal forces applied by the tension of actomyosin interaction. As E-cadherin is engaged, the inward force becomes a dominating influence and can ultimately displace E-cadherin from its homotypic binding partner. When such displacement occurs, the epithelial community’s barrier is lost. In the short term, such decreased barrier function can contribute to fluid accumulation in the air spaces, and, in the long term, it may promote metastasis of epithelial tumors or allow tumors to invade the community.

Given the broad relevance of E-cadherin function to the epithelial community, and to organ function on the whole, considerable efforts have been made to understand how extracellular signals disrupt E-cadherin homotypic binding. A common finding is that inflammatory first messengers, such as histamine and thrombin, act on different membrane receptors [type 1 histamine (H1) and type 2 protease-activated receptor (PAR-2), respectively] to disrupt E-cadherin-mediated adhesion. Activation of both H1 and PAR-2 receptors increases tyrosine kinase-dependent signaling, with incompletely understood physiological consequences. EGF receptor signaling (e.g., receptor tyrosine kinase activation) has been shown to disrupt cadherin-dependent adhesion (7), bringing into question how such disparate first messengers—as in histamine, thrombin, and EGF—acting through disparate receptor complexes—as in the H1 receptor, PAR-2, and EGF receptor tyrosine kinases—each decrease E-cadherin homotypic binding. A critical clue to this query comes from studies that reveal how E-cadherin is processed from the endoplasmic reticulum and inserted in the plasma membrane.

E-cadherin interacts with β-catenin in the endoplasmic reticulum; this interaction is essential for complex stabilization and, ultimately, membrane insertion (1). Indeed, disruption of the β-catenin interaction with E-cadherin results in rapid protein turnover, and appropriate barrier integrity is never achieved (4, 5, 7). Once the complex is inserted in the membrane, disruption of the β-catenin interaction with E-cadherin decreases the strength of E-cadherin homotypic binding. Hence, these findings suggest signaling events that disrupt, or dynamically alter, the nature of E-cadherin-to-β-catenin binding may, in turn, influence the strength of E-cadherin homotypic interaction.

In this issue of *AJP-Lung*, Winter and coworkers (10) report on their work to test this idea directly, that tyrosine phosphorylation of β-catenin is sufficient to disrupt the strength of E-cadherin homotypic binding. Three separate tyrosine phosphorylation sites, Y142, Y489, and Y654, were examined to determine whether the phosphorylation of these residues may independently or together act as a gear and engage the transmission in response to H1 receptor and PAR-2 activation necessary to disrupt E-cadherin-mediated adhesion. To address this question, an elegant system was devised using L cells, in which their adhesion to an immobilized E-cadherinFc could be studied. L cells do not typically express either E-cadherin or H1 receptor, and so E-cadherin and H1 were stably expressed and then stably transfected with wild-type β-catenin or one of three mutants that could not be phosphorylated at Y142, Y489, or Y654. L cells endogenously express PAR-2, and so this receptor was not transfected. Using this model system, Winter et al. (10) demonstrated that H1 receptor ligation and PAR-2

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activation (e.g., G protein-coupled receptor activation) decreased E-cadherin-dependent adhesion. In both cases, the response required the phosphorylation of β-catenin Y489 and Y654 but not Y142. Supportive results were obtained using a Madin-Darby canine kidney (MDCK) culture system in which cell resistance was measured. These findings therefore illustrate how diverse first messengers can act through different receptors and tyrosine kinases to consolidate their barrier-disrupting actions through highly conserved phosphorylation events on a common downstream protein. Indeed, the findings suggest that disruption of homotypic cadherin binding is a fundamental final common pathway necessary to decrease barrier integrity.

Although the present study of Winter and colleagues (10) provides important mechanistic insight into how different intracellular signaling cascades converge on β-catenin to control E-cadherin function, they also direct us in our future work. It is increasingly appreciated that signaling networks possess highly restricted, compartmentalized domains that facilitate proper communication. The anatomical and functional coupling between H1 receptor- and PAR-2-dependent regulation of the cadherin-catenin complex remains poorly understood. Moreover, how the many, simultaneous intracellular signals are deciphered by adhesion complexes remains incompletely resolved. The in vivo relevance of these observations must be confirmed; we do not presently know whether β-catenin Y489 and Y654 are constitutively phosphorylated or whether their phosphorylation increases during inflammation. These are critical points, as direct inhibition of tyrosine phosphorylation may possess therapeutic value. Indeed, recent work by Miyahara et al. (6) suggest Src kinase inhibition prevents the ventilator-induced increase in lung vascular permeability. Overall, the insights provided by Winter et al. (10) are significant and can help to guide our forthcoming studies to provide ever more direct insight into the functional control of cell communities, as in the case of adhesion strength among lung epithelial cells.

REFERENCES