From the extracellular matrix to cell and tissue function in the alveolar epithelium

The alveolar epithelium is made up primarily of alveolar type II and alveolar type I (ATII and ATI, respectively) cells that have a distinctive location within the alveolus: the typical ATII cell is located in the corner of the alveolus and is surrounded by neighboring ATI cells, which cover over 90% of the alveolar surface area. In response to wounding of the airway epithelium, ATII cells can serve as stem cells to help re-form the ATI-dominated epithelial layer (reviewed in Ref. 22). Despite the observed phenotypic differentiation, we have relatively little cellular information on how the wound environment, including the cellular and extracellular changes in the lung architecture, influences the changes in solitary ATII cells to migrating masses of transdifferentiated ATII cells and, eventually, to the ATI-dominated alveolar surface area. It is likely that such groups of ATII cells have specific communication with their neighbors in order to coordinate the repair and differentiation that require induction and/or repression of cell-specific genes, migration of cells along defined axes, and the clustering of related cells to form the intact epithelium (reviewed in Ref. 4).

One method employed by many cells in the body that help coordinate cellular function into tissue or organ function is the communication of metabolites, second messengers, or other small molecules to neighboring cells using intercellular tunnels called gap junctions (reviewed in Refs. 3, 20). A single gap junction is constructed of two connexons, and each connexon is further broken down into six connexin proteins. More than 20 vertebrate connexin isoforms have been identified to date, a number likely to increase with recent genome sequencing projects. Cellular connexin expression is highly variable, with some tissues expressing a limited number of connexin protein isoforms and others expressing a variety of isoforms (reviewed in Ref. 5).

Several investigators (e.g., Refs. 1, 11, 13) have used a variety of techniques to elucidate connexin expression patterns in freshly isolated and cultured rat ATII cells and demonstrated that ATII cells can express at least six known connexin isoforms. The identification of connexin expression patterns is not entirely consistent among reports; in fact, the results point to a complex expression of connexins in response to growth conditions, growth factors, and phenotypic state of the alveolar epithelial cells. From work in other cell systems, differential expression of connexins has been shown to be associated with differential transfer of cellular second messengers (16) and/or metabolites (8). It is logical to conclude that this selective transfer of cytosolic contents may influence differences in coordinated cell physiology. With this in mind, understanding the triggers for differential connexin expression is vitally important if we are to understand how cells coordinate their functions.

It is well established that regulation of cell growth and differentiation can be profoundly altered by both soluble and insoluble macromolecules that comprise the extracellular matrix (ECM). Much attention has been focused on the makeup of the lung ECM, which includes a complex and transient makeup of structural molecules permeated by growth factors and other functional molecules (reviewed in Ref. 7). The structural data on the lung ECM have additionally shown that healthy lungs can withstand transient or permanent changes in response to disease or damage that can help guide inflammatory responses (6, 18) as well as transdifferentiation of ATII to ATI cells (reviewed in Refs. 15, 17, 19). Fibronectin is a small but important factor in the protein makeup of healthy lung ECM; however, in many lung disorders or after lung injury, fibronectin is readily increased (reviewed in Ref. 14). Many of the specific roles for fibronectin in lung repair have not been defined, but by analogy to developmental systems and by in vitro modeling of wound repair in the upper airway epithelium (10), fibronectin may be a necessary matrix component for directed cell migration.

Studies in hepatocytes (21) and keratinocytes (12) have demonstrated that alterations in the ECM can result in altered connexin expression, highlighting the link between substrate recognition and potential changes in intercellular communication. In this issue of the American Journal of Physiology-Lung Cellular and Molecular Physiology, Guo et al. (9) illustrate a similar link between ECM changes and connexin expression in cultured ATII cells. Specifically, they show the effects of manipulation of fibronectin molecules on ATII phenotype and the differential expression of connexin proteins. This link between a fundamental ECM protein and the expression of proteins involved in coordinating cellular functions may be an important part of coordinating cellular physiology among ATII cells. That is, signals inherent to a changing lung ECM in

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vivo (e.g., those seen immediately after epithelial damage) may serve as signals to halt ATI to ATII communication [e.g., coordinated intracellular calcium concentration signaling (2)] and induce the coordinated responses necessary for ATII cell division, migration, and differentiation required for wound repair. This recent work (9) also points to further experiments to elucidate other players in the signaling pathways that link the ECM to connexin expression and the identification of signaling molecules that may then allow us to better understand and control ATII cell function in vivo.

REFERENCES


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