Polarity and Renal Cystogenesis

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Epithelial cells are the building blocks of segmenting renal tubules.\(^1\) As such, there is great interest in how the differentiation, proliferation, and organization of epithelial cells into functional proximal, distal, and collecting tubules are controlled at the genetic and cellular level. One of the most critical aspects of epithelial cell biology is the establishment and maintenance of polarity, which is simply defined as the unequal distribution of cellular components along an axis in the service of functionality. Loss of epithelial cell polarity is a common thread among the many types of juvenile and adult cystic diseases of the kidneys and other tissues. Thus, understanding the molecular mechanisms that lead to the loss of epithelial cell polarity has great clinical relevance.

The common view of epithelial cell polarity in a single-cell columnar epithelium, such as a renal tubule, is organization of the cell into apical and basolateral compartments. However, there is a second aspect of polarity that requires the correct orientation of individual cells along the plane of an epithelial sheet or tube and is often critical for proper function. This macro view of polarity is called planar cell polarity, or sometimes just planar polarity, and is found in tissues where all cells are orientated in a specific direction along the plane of the tissue.\(^2\) Both apical-basal polarity and planar cell polarity have been extensively studied in the kidney and in other tissues of model organisms, as well as in human disease. Progress in identifying the many genes and proteins responsible for establishing polarity and maintaining function has been remarkable, although the interplay between the many different pathways is still unclear.

One of the first indications that apical-basal polarity was disturbed in renal cystic epithelial cells was the observation that the Na\(^+\)/K\(^+\)-ATPase was mislocalized in cells from autosomal dominant polycystic kidney disease kidneys.\(^3\) Today, the idea that disrupted apical-basal polarity drives cystogenesis through a combination of apically mislocalized growth factor receptors that promote proliferation and mislocalized ion channels that reverse fluid flow is still an attractive model to explain many aspect of cystic disease.\(^4\) However, it is not clear how this loss of apical-basal polarity occurs, nor how the


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primary genes and proteins mutated in human polycystic kidney disease, the polycystins PC1 and PC2, affect apical-basal polarity.

Within the last 5 years, several major discoveries have shifted the emphasis onto the planar cell polarity pathway as a determinant of renal cystic disease.\(^5\) Central to understanding the potential role of the planar cell polarity is the function of the primary cilia, in which nearly all of the proteins associated with cystic disease can be localized.\(^6\) Loss or shortening of cilia can be sufficient to initiate renal cysts, underscoring the importance of the cilia as a potential sensing and signaling center. Furthermore, primary cilia have been linked directly to planar polarity, particularly in the cilia that control left-right asymmetry shortly after gastrulation.\(^7\) Uniform orientation of the primary cilia and synchronized movement is critical for the presumptive establishment of the morphogenetic gradients that specify left-right asymmetry.

The basal body of the primary cilia also functions as the centrosome, which on duplication during mitosis, anchors the mitotic spindles and thus can control the axis of cell division. Both PC1 and PC2 have been associated with the centrosome and the mitotic spindles,\(^8\) with supernumerary centrosomes observed on deletion of either protein. Thus, the orientation of cell division along the axis of an epithelial tube was thought to be directly dependent on the cilia position and function and determined, at least in part, by planar cell polarity. The axis of cell division could determine whether an epithelial tube elongates or whether it forms a cyst. Indeed, through careful analysis of mitoses in several mutant mouse lines with developing renal cysts, including Wnt9b,\(^9\) HNF1β,\(^10\) and Pkhd1,\(^11\) the orientation of cell division is random, whereas normally the separation between two cells is perpendicular to the tubule, suggesting this randomization is an underlying cause of cystogenesis. However, the axis of cell division does not appear affected in mice with PKD1 or PKD2 mutations, at least not until cysts are already formed, suggesting that misoriented cell division may not be necessary or sufficient for renal cyst development.\(^12\)

In this issue, Veikkolainen et al.\(^13\) observe epithelial polarity defects in mice that carry either gain or loss-of-function mutations in the receptor tyrosine kinase ErbB4. Members of the EGF family of receptors, the ErbB proteins have been implicated as modulators of polarity in neurons and cancer. For example, activation of the ErbB2 protein disrupts the apical-basal Par3-Par6-aPKC polarity complex, which is needed for tight junction assembly.\(^14\) The ErbB4 study in the kidney suggests that a similar type of apical-basal polarity disruption may be occurring here. That the activated ErbB4 mice develop cysts and also show misorientation of the cell division axis suggests that loss of apical-basal polarity is sufficient to explain the phenomena attributed, at least in part, to planar cell polarity pathways in other cystic mutants.

Renal epithelial cells are derived from the metanephric mesenchyme and are unique in that they must undergo a mesenchymal-to-epithelial transition during development. It seems likely that establishing apical-basal polarity is a prerequisite for all other aspects of epithelial cell function, including proper localization of cilia and planar polarity. In certain cases, it appears that planar polarity may provide some feedback to maintain apical-basal polarity. How this is achieved remains unclear, but certainly provides for many avenues of further investigation.

DISCLOSURES

None.

REFERENCES
