


primary genes and proteins mutated in human polycystic kidney disease, the polycysts 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. 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. 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. 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, 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, HNF1β, and Pkhd1, 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.

In this issue, Veikkolainen et al. 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. 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