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In This Issue

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By John Ashkenas, Science Editor

Cell interactions in spermatocyte apoptosis

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A new route to branching morphogenesis

(See article on pages 481–489).

Branching morphogenesis, one of the unifying themes in organogenesis, allows a cluster of epithelial cells to generate a system of branching tubules and ducts, rather than a simple, flat sheet. This event can be recapitulated in 3-dimensional culture systems, when spontaneously formed kidney, lung, or mammary cell aggregates are treated with HGF or any of several other agents. Following up on a recent report that overexpression of the renal epithelial cell membrane protein polycystin-1 stimulates branching of these cells in culture, Nickel and coworkers have now worked out some of the molecular interactions that distinguish this response from the better known pathway induced by HGF. Mutations in the human polycystin-1, or in the interacting protein polycystin-2, are the most frequent cause of polycystic kidney disease, indicating that these two proteins are required for normal kidney cell proliferation and for the structure and function of the renal epithelium. Overexpression of polycystin-1 — or, as the authors now show, of the protein's polycystin-2–interacting region — leads to greater cell motility, stimulates cell elongation and branching, and causes rounded clusters of murine inner medullary connecting duct epithelial cells to generate tubules in culture. Unlike HGF-stimulated morphogenesis, which is mediated by the Ras signaling pathway, these responses depend on activation of protein kinase C-α. Nickel et al. find that the two pathways can operate in parallel, since HGF enhances this morphological change even in the polycystin-overexpressing cell.

Ciliary proteins and polycystic kidneys

(See article on pages 533–540).

Polycystin 1 and *2* mutations represent the most common cause of dominantly inherited polycystic kidney disease. However, humans and mice are also subject to recessive disorders in which the kidneys, and sometimes the liver, pancreas, or ovaries, are subject to cyst formation. In mice, the analysis of these mutations has led to interest in the role of apical cilia in the development of these tissues and in a seemingly unrelated matter, the genesis of a left-right axis during embryogenesis. Several ciliary proteins, including one of the dynein-class motor proteins and polaris, a protein found in the basal body and the ciliary axoneme, are affected by these mutations. Hou and colleagues have now found that the mouse *cpk* gene encodes another such ciliary protein, termed cystin, a putative scaffold protein that may bind directly to the axonemal membrane. Cystin, like polaris, localizes to the axoneme of kidney cell cilia and is presumed to have a similar distribution in biliary and other epithelial cells. Mutation of *cpk* leads to renal and biliary cysts but is not reported to disrupt left-right asymmetry in development. However, the body axis formation phenotype seen, for instance, in animals with defects in polaris appears to reflect a need for motile cilia, which direct a leftward flow of extracellular fluid across an embryonic structure called the "node". In contrast, the cilia in the kidney and elsewhere are frequently nonmotile and may play other roles, perhaps in mechanosensory signaling. Whatever these roles, cystin would be predicted to be particularly needed in these structures, but perhaps not in the nodal cilia. Whether a cystin homolog is a candidate for human autosomal recessive polycystic kidney disease is still unknown, since no such sequence is identifiable in the current draft of the human genome sequence.