Bowman’s β-Catenin

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Wnt/β-catenin signaling plays a significant role during kidney development and maturation.1–3 β-Catenin, the canonical Wnt signal transducer, is involved in nephron induction4 and branching morphogenesis.5,6 Importantly, β-catenin modulation is necessary for full differentiation of the induced nephron as it proceeds through morphogenesis.4 These observations demonstrate β-catenin activity is used in both the positive and negative to convey patterning and cell fate information and that its actions are reused in different contexts. Aberrations in Wnt/β-catenin signaling may also contribute to dysplasia.7,8

In this issue of JASN, Grouls et al.9 describe a late role for β-catenin in the formation of the parietal epithelial cells (PECs) of Bowman’s capsule. Using TCF/lacZ reporter mice,10 the authors observed Wnt/β-catenin reporter activity in the parietal epithelial cells of Bowman’s capsule, suggesting a role for its action in these cells. By using a Pax8.Cre driver line that is active at the S-shaped body stage of developing nephrons, and therefore after the initial induction of nephron formation, they conditionally removed β-catenin to examine its subsequent role in maturation. They observed the loss of β-catenin at the S-shaped body stage results in the absence of PECs in the renal corpuscles and instead, Bowman’s capsule was populated with parietal podocytes. These cells were positive for podocyte markers (WT1, synaptopodin, and vascular endothelial growth factor), induced the formation of additional capillaries, and established a near identical structure to the glomerular podocyte-endothelium including foot processes. Because the PECs and podocytes arise from a common cellular origin, the renal vesicle/S-shaped body, these findings suggest β-catenin is required for cells to adopt the PEC fate rather than the podocyte fate. In the absence of β-catenin, the cells default to podocytes.

Mutant mice lacking PECs had reduced survival starting at 2 weeks of age and showed progressive renal disease. This raises a question about the role of PECs in the renal corpuscle of older animals. In recent work by Appel et al.,11 cell lineage tracing reveals the PECs of Bowman’s capsule as a source of replacement podocytes when some are lost from the glomerulus of healthy or injured kidneys.12 Ranconi et al.13 also describe a resident progenitor cell around the urinary pole of Bowman’s capsule and suggest these replace podocytes and proximal tubular cells lost through cell turnover or injury. Additionally, it has been shown by others that Tgf-β induces glomerular injury by inducing expression of Wnt1 that increases activated β-catenin.14 This results in depression of WT1 in a response that may be a perturbation of the response mechanism of the renal corpuscle—that is, to de-differentiate (decrease WT1) and proliferate in an effort to replace damage cells.14

One can imagine a model where Wnt/β-catenin signaling maintains the dividing parietal cells, and some of these cells exit this niche to replace failed podocytes. This is consistent with the role of Wnt/β-catenin in other adult tissues, notably the intestinal crypts surrounding each villus. In the adult intestine, Wnt/β-catenin signaling is required for stem cell maintenance and cell proliferation in the lower crypt, and some of these cells eventually exit the crypt and differentiate to replace cells lost in the villus.15 A similar activity in the renal corpuscle is not yet clear. The Wnt/β-catenin reporter mouse strains exhibit some variability in identifying active signaling.16 For example, the TCF/lacZ strain lacks detectable staining after nephrogenesis in complete,10 whereas the TOPGAL and Axin2-lacZ strains show staining at least in the medullary region of the adult kidney.17 Therefore, a close examination of Wnt/β-catenin target gene expression in the PECs of adults would be useful to confirm or eliminate the possibility of signaling activity. It would also be interesting to inactivate the β-catenin gene using the genetic system used by Appel et al.11 This would address the requirement of β-catenin for maintaining PECs and for responding to adriamycin injury.13,14

As we learn more about the developmental roles of these important pathways, we also begin to see how they may be used in maintenance systems of organs and tissues. Combined with recent data on the role of senescent cells in age-related pathogenesis,18 there is more work to be done here to understand how we may influence normal tissue renewal to aid failing kidneys and identify genes that indicate risk for certain patterns of injury.

DISCLOSURES
None.

REFERENCES

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Polarity and Renal Cystogenesis

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Epithelial cells are the building blocks of segmenting renal tubules. 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 oriented in a specific direction along the plane of the tissue. 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. 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. However, it is not clear how this loss of apical-basal polarity occurs, nor how the...