ing asked and the focused assays used to answer these questions. Indeed, until that time when type 1 biomarkers to detect modulation of GSK3β directly within its many cellular and signaling contexts in vivo become available, it will be difficult and prone to error to ascribe drug efficacy from targeting GSK3β in AKI to one single molecular outcome. Rather, it may be the ability of GSK3β to play dirty in AKI that will ultimately define this kinase as a highly desirable drug target.

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DISCLOSURES

None.

REFERENCES


What Drives Cyst Formation in PKD?

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Polycystic kidney disease (PKD) is the most common genetic cause of chronic kidney disease, with an incidence of 1:400 to 1,000.

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PKD is characterized by many large fluid-filled cysts in the kidney and often leads to end-stage renal failure. Intensive work from numerous international teams has succeeded in identifying three genes that account for almost all cases of PKD: polycystin-1 (PC-1), polycystin-2 (PC-2), and polycystic kidney and hepatic disease 1 (Pkd1). Autosomal dominant PKD is caused by mutations in PC-1 or PC-2. PC-1 encodes a protein with a large extracellular domain, 11 transmembrane domains, and a cytoplasmic tail. PC-2 encodes a transient receptor potential channel with six transmembrane domains that resembles PC-1. Autosomal recessive PKD is caused by mutations in Pkhdl, another protein with a large extracellular domain, a single transmembrane domain, and a cytoplasmic domain. Although the loci responsible for PKD are known, it is still poorly understood why mutations in PC-1, PC-2, and Pkhdl result in cyst formation. Numerous models have been proposed to account for the development of cysts. Recent notions, which raise a great deal of interest, are that ciliary function and/or planar cell polarity (PCP) is disrupted during cyst formation.

The primary cilium is an antenna-like structure that emerges from the apical surface of kidney epithelial cells, which has been found to be a key signaling center for many developmental pathways. A role for the primary cilium in cystic disease was first proposed on the basis of the surprising finding that virtually all proteins implicated in cystogenesis localize to the primary cilium. This hypothesis is strengthened by the observation that loss of cilia can induce cyst formation in the kidney accompanied by loss of oriented cell division. PCP describes the organization of cells in the plane of an epithelium. A role for PCP in preventing kidney cyst formation was first suggested on the basis of the observation that Inversin, a protein involved in another cystic kidney disease, nephronophthisis, alters PCP signaling. Interestingly, there are a number of links between the primary cilium and PCP signaling, suggesting these models may be interrelated.

A genetic pathway that is largely conserved between flies and humans regulates PCP. The PCP pathway was first discovered and is best understood in the fruit fly Drosophila melanogaster. In flies, there are two major groups of PCP genes: the core PCP genes and the Fat-Dachsous cassette. Core PCP genes include dishevelled, prickle, vang gogh, flamingo, diego, and frizzled. Because both Frizzled and Dishevelled are also involved in Wg/Wnt signaling, the PCP pathway is also referred to as the noncanonical Wnt pathway. The Fat-Dachsous cassette consists of the large atypical cadherins Fat and Dachsous (Ds), a transcriptional repressor called Atrophilin, and a Golgi-associated kinase called Four-jointed. Both the Fat-Ds and core PCP pathways are conserved to vertebrates, where they regulate planar tissue organization, notably by controlling the narrowing and elongation of tissues. PCP signaling regulates tissue elongation through oriented cell divisions (OCD) and through cell intercalations in a process known as convergent extension (CE).

Mutations in Inversin cause cystic kidney disease in humans, and inversin knockdown results in pronephric cysts in zebrafish. Biochemical studies demonstrate that Inversin facilitates Dishevelled degradation, suggesting it acts as a molecular switch between canonical and noncanonical (PCP) pathways. Moreover, Inversin is required for CE in Xenopus laevis embryos. Subsequently, OCD was shown to be a feature of normal kidney development in rodents and may be required for correct lengthening of renal tubules during development. Importantly, OCD is lost in pck rats (a PKD rat model), as in mice that develop kidney cysts upon misexpression of HNF1b. Further support for this model comes from the analysis of Fat4−/− mice (Drosophila Fat homolog), which have dilated tubules and cysts and early loss of OCD. Genetic interaction studies show that mutations in other PCP genes, such as Vangl2, exacerbate the Fat4−/− cystic kidney phenotype, confirming a role for PCP in PKD. All of this suggests that loss of PCP and subsequent loss of OCD lead to tubular dilation and cysts.

In this issue of JASN, Nishio et al. examine various PKD mouse models to test the hypothesis that loss of OCD leads to cystic disease. The authors first examine mitotic orientation in precystic mouse models of Pkhdl, Pkd1, and Pkd2. Surprisingly, in contrast to what was found in the pck rat (mutant in PKD1), neither autosomal dominant PKD mutant had significant defects in OCD before the onset of cystogenesis. Instead, both Pkd1 and Pkd2 mouse mutants lose OCD later, during early tubular dilation. This could be due in part to species-specific differences. The authors show that tubules that have lost PC-2 protein by antibody staining still maintain OCD. A slight concern is that functional levels of PC-2 may not be detectable by immunohistochemistry.

A more dramatic blow to the simple OCD model is shown in their analysis of Pkhdl mice. In Pkhdl−/− mice, which have a hypomorphic Pkhdl allele and do not develop kidney cysts, OCD was lost in medullary collecting tubules. Importantly, however, cell lineage analyses reveal that during tubule elongation, there is a marked increase in cell migration and intercalation in Pkhdl−/− mutants. These results suggest that Pkhdl is necessary for proper OCD in mice and that disruption of OCD is not the only mechanism for cystogenesis. Loss of OCD may induce the upregulation of CE, thereby compensating for the tubule dilations resulting from defective OCD.

Recently, noncanonical Wnt/PCP signaling was also shown to regulate renal cystogenesis by control of CE. During embryonic development, Wnt9b-dependent CE movements decrease the number of cells that compose the tubule wall until a final tubule diameter is reached. Wnt9b also regulates OCD along the proximal-distal axis, leading to tubular elongation after birth. Attenuation of Wnt9b leads to errors in CE and OCD.

These findings suggest that PCP prevents cystogenesis through multiple mechanisms. It is possible that, in certain cases, OCD single-handedly maintains proper tubular elongation, thereby preventing cystic growth, whereas in other cases, CE processes...
predominate. Conversely, recent data, including those of Nishio et al., suggest that loss of OCD alone is not sufficient to produce a cystic phenotype and that CE along with OCD is required for proper tubule elongation. As such, it will be important to examine the role of CE in various cystic models, such as Fat4.

Many key questions remain unanswered. Given that loss of PKD genes results in PCP-like defects, what is the molecular nature of the genetic interactions between PKD and PCP genes? Do PCP genes control PKD gene activity or vice versa? How are spindle orientation and cell intercalation controlled by PCP and PKD? A deeper understanding of the pathogenic mechanisms that underlie cyst formation in Pkhd1, Pkd1, and Pkd2 mutants will hopefully allow targeted therapies to alleviate the morbidity and mortality associated with these devastating diseases.

DISCLOSURES
None.

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Telomere Shortening and Regenerative Capacity after Acute Kidney Injury

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With advances in modern medicine leading to improved health, the percentage of the population who are elderly is increasing. Associated with increasing age is a decline in renal function and loss of renal mass. These alterations in renal function predict increasing risk for mortality. The aging kidney also associates with multiple disease states, such as cardiovascular disease, cancer, and cognitive dysfunction, which increase susceptibility to ischemic acute kidney injury (AKI), from which the elderly are less likely to recover.

Telomere attrition is implicated in many diseases associated with aging, including cardiovascular disease; however, an association between telomere shortening and decreased renal repair and regeneration after injury is largely un-