Wnt signaling and rejuvenation of the adult kidney*

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Defects in Wnt signaling appear to underlie some forms of inherited cystic kidney disease. Knockout experiments involving the Joubertin protein now examine how Wnt activity helps repair injured renal tubules in adult mice—and show that its absence leads to the formation of cysts in the mature kidney.

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Wnt signaling is required for normal renal development [1]. It mediates the condensation of the metanephric mesenchyme surrounding the branching ureteric buds, the glial cell-derived neurotrophic factor (GDNF)-induced outgrowth of the primary nephric duct and subsequent mesenchymal-to-epithelial conversion. In canonical Wnt signaling, binding of soluble Wnt molecules to Frizzled/LDL-related protein (LRP) receptors helps β-catenin escape degradation and to translocate to the nucleus, facilitating the transcription of T-cell factor (TCF)/beta-catenin-dependent target genes (Figure 1). Persistent canonical Wnt signaling caused by increased β-catenin levels arrests renal embryogenesis and promotes cystic kidney disease in mice [8,9]. Hence, normal nephron maturation in the adult kidney depends on turning off canonical Wnt signaling.

This prevailing hypothesis is now challenged in a study that used deletion of the AHI1/Jouberin gene and unexpectedly blocked Wnt activation in adult mice [6]. Canonical β-catenin-mediated Wnt signaling persists in the kidneys of normal adult mice. Jbn-deficient mice developed kidney cysts and progressive renal impairment with increasing age, which was accelerated by injury of the organ.

Mutation in the AHI1/Jouberin gene is one cause of Joubert syndrome, a rare autosomal recessive cerebellar disease affecting one out of 100 000 people, which is associated with retinitis pigmentosa and nephronophthisis. Joubert syndrome is considered a ciliopathy [5] since Jouberin (Jbn), like many other gene products involved in cystic kidney disease, localizes to the primary cilia, a non-motile microtubular organelle attached to most body cells [3,6]. The primary cilia appears to negatively regulate canonical Wnt signaling; cilia defects impair the degradation of β-catenin and thereby facilitate canonical β-catenin-mediated Wnt signaling (reviewed in [4]). Lancaster et al. found that canonical Wnt signaling persisted in the kidneys of normal adult mice, whereas deletion of Ahi1/Jbn in mice abrogated Wnt activity in adult animals. Jbn-null mice developed cystic kidney disease at an age comparable to the relatively late onset in patients with AHI1 mutations (≥20 years of age). Furthermore, following cisplatin or ischaemia/reperfusion injury, Jbn-deficient mice failed to up-regulate Wnt signaling and consequently developed tubular dilatation, microcysts and glomerulosclerosis. Thus, Jouberin not only maintains low-level Wnt activity required for kidney homeostasis but also augments Wnt activity necessary for tissue repair in response to injury.

Although nephronophthisis is classified as a ciliopathy, renal lesions occurred in Jbn-null mice despite normal cilia morphology. Lancaster et al. show that Jbn positively modulates canonical Wnt signaling by binding β-catenin and facilitating its nuclear import (Figure 1), a function that relies on the three nuclear localization sites (NLS) of Jbn. A doubly heterozygous Ahi1 +/-; LRP6 +/- mouse partially recapitulated the Ahi1 −/− phenotype, with reduced kidney size, tubular dilatation and renal cysts, suggesting that Jbn and LRP6 act in the same signaling pathway. LRP6 is a known Frizzled co-receptor that binds soluble Wnt molecules to initiate canonical Wnt signaling (Figure 1). These observations contradict the prevailing
theory that all cystic disease associated with Joubert, Bardet-Biedl or Meckel-Gruber syndromes are caused by ciliary dysfunction.

**What can we learn from Jbn-deficient mice?**

This paper sheds light on a precarious equilibrium that governs kidney homeostasis, regeneration and tumorigenesis and suggests that, in the adult kidney, precisely regulated programmes recapitulate early renal development. A basal level of Wnt activity appears to underlie normal nephron maintenance; an additional burst is required when the kidney is injured, either by disease or environmental factors. Interestingly, Ahi1−/− kidneys were more sensitive to injury than normal kidneys, yet their function was essentially normal when unchallenged by environmental insults. Thus, a low level of Wnt activity sufficed for ongoing tubular renewal but not for extensive repair in response to injury. This has been observed in other knockout mouse models; loss of cilia due to deletion of the ciliary motor protein subunit KIF3A is minimal until ischaemia and subsequent regeneration triggers cyst formation [7]. These findings indicate that Wnt signaling remains at basal levels until needed to regenerate tubules, which is perhaps unsurprising as persistently high Wnt activity is associated with numerous cancers [2].

Nephrologists are trained to treat kidney disorders of patients who are usually referred after problems arise. Now our care needs to be even more proactive to shield genetically challenged kidneys from injury substantial enough to require regeneration. The possibility that Wnt signaling reactivates developmental signaling pathways in the adult kidney could lead to therapies that facilitate regeneration after ischaemic or toxic damage. Conversely, blocking Wnt signaling, a candidate cancer therapy currently under investigation, could cause detrimental side effects by compromising kidney homeostasis and renal function. The newly generated mouse model provides a novel basis for examining how impairment of tubular integrity proceeds to cyst formation and for devising therapies to halt the progression of cystic disease.

**Conflict of interest statement.** None declared.

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