translational science

Tubular cell plasticity—new hope for autosomal dominant polycystic kidney disease?

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Autosomal dominant polycystic kidney disease (ADPKD) is the most common monogenic cause of chronic kidney disease. Typical forms of ADPKD are caused by mutations in either *PKD1* or *PKD2*, encoding polycystin (PC)-1 and PC2, respectively. The polycystins are expressed in various membrane domains, including the primary cilium, and they play multiple roles in tubular cell homeostasis. The kidney cysts observed in patients with ADPKD derive from 1% to 3% of the nephrons and may involve all tubular segments. Studies performed more than 2 decades ago revealed that cyst formation is triggered by a "two-hit" mechanism due to the stochastic occurrence of somatic mutations in the normal allele of *PKD1* or *PKD2*. The functional loss of PC1 or PC2 leads to de-differentiation and proliferation of tubular cells, as well as luminal fluid secretion, triggering cystogenesis and progressive cyst growth.[1] Subsequent studies revealed that the timing of inactivation of *Pkd* genes, the residual level of polycystins, and a number of modifying factors impact cystogenesis and disease progression.[2,3] Targeting pathways that are disturbed by the deletion of polycystins, in particular the vasopressin-cyclic AMP axis, may slow disease progression but does not reverse ADPKD.[4,5] In a recent study, Dong and colleagues went a step further and tested the hypothesis that re-expression of the affected *Pkd* gene may reverse the polycystic kidney disease (PKD) phenotype *in vivo*.[6]

What did the study show?

The authors established a mouse model in which one *Pkd* gene is selectively inactivated in the kidney and subsequently re-expressed at a later time point.[6] The studies focused on *Pkd2*, but the key findings were verified for *Pkd1* (Figure 1). The mouse model combined 2 commonly used recombinase systems, Cre recombinase-*loxP* (Cre-lox) and flippase-flippase responsive target (Flp-FRT), which both allow investigators to selectively target a specific gene or DNA sequence for deletion or other manipulation. Both recombinase systems can be constitutively active or inducible and can be targeted to specific cell types by expressing the recombinase under the control of a cell type–specific promoter. To achieve the deletion of *Pkd2* after kidney development, the authors used an established mouse line with floxed *Pkd2* and a doxycycline-inducible Cre-lox system expressing Cre recombinase under the control of the *Pax8* promoter in tubular epithelial cells. Doxycycline administration for 2 weeks in 7-week-old mice selectively inactivated *Pkd2* in the kidney tubules. The reactivation step was performed in 13-week-old mice using a tamoxifen-inducible Flp-FRT system under the control of the ubiquitous *Rosa26* promoter. For this step, the authors used a modified bacterial artificial chromosome (BAC) vector expressing a transcriptional stop sequence in *Pkd2* flanked by *FRT* sites and a hemagglutinin (HA) epitope tag sequence immediately before the termination codon. Therefore, in the absence of tamoxifen, the mice do not express PC2-HA protein, whereas tamoxifen treatment for 7 days induced the expression of PC2 in multiple organs. This system allows the precise re-expression of *Pkd* genes in mice in which adult inactivation of *Pkd2* or *Pkd1* has been previously achieved.

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