Nature Reviews Nephrology **11**, 4 (2015); published online 25 November 2014; doi:10.1038/nrneph.2014.222

POLYCYSTIC KIDNEY DISEASE

Pathogenic missense mutations result in defective trafficking of polycystin-1 to cilia

A new study suggests that missense variants in *PKD1* contribute to the pathogenesis of autosomal dominant polycystic kidney disease (ADPKD) through altered G-protein site (GPS) cleavage and aberrant cilial expression of its protein product polycystin-1. The way in which these missense mutations promote disease was previously unclear.

Yiqiang Cai and colleagues used a systematic approach to characterize the molecular effects of various mutant forms of polycystin-1 *in vitro* and analysed the pathogenic consequences *in vivo*. They developed NH_2-terminal and COOH-terminal epitope-tagged cDNA constructs of wild type and variant forms of polycystin-1 to enable differential detection of the protein fragments that result from GPS-mediated cleavage. "As anti-polycystin-1 antibodies have limited application, these molecular tools significantly advanced our study," says Cai.

Biochemical studies indicated that a subset of missense mutations perturbed trafficking of polycystin-1 to the cilia. Although GPS cleavage of polycystin-1 was necessary for normal trafficking, some variants failed to localize to cilia despite undergoing GPS cleavage. An interaction between polycystin-1 and polycystin-2 was not required for trafficking to cilia, but was necessary to maintain steady-state expression levels of the COOH-terminal fragment of polycystin-1.

> "...GPS cleavage of polycystin-1 was necessary for normal trafficking..."

The researchers used bacterial artificial chromosome (BAC)-transgenic mouse models to validate their discoveries *in vivo*. Expression of a wild-type *Pkd1* BAC transgene rescued the $Pkd1^{-/-}$ lethal phenotype; transgenic mutations that prevented GPS cleavage of polycystin-1 could not rescue the null mutation.

"We now have evidence suggesting that different mutations in *PKD1* and *PKD2* might cause various molecular and/or cellular defects that ultimately result in a common phenotype—cyst formation," says Cai. "Understanding early defects is important for a better understanding of ADPKD pathogenesis, and could lead to identification of a drug target to control the progress of cyst development."

The researchers hope to develop a high throughput cell-based system to identify agents that can improve the ciliary expression of polycystin-1 variants. They suggest that agents that assist protein folding may be candidate therapeutics to target cilia-trafficking defects.

Jessica K. Edwards

Original article Cai, Y. *et al.* Altered trafficking and stability of polycystins underlie polycystic kidney disease. *J. Clin. Invest.* doi:10.1172/JCI67273