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POLYCYSTIC KIDNEY DISEASE

Cyst growth and cilia in ADPKD

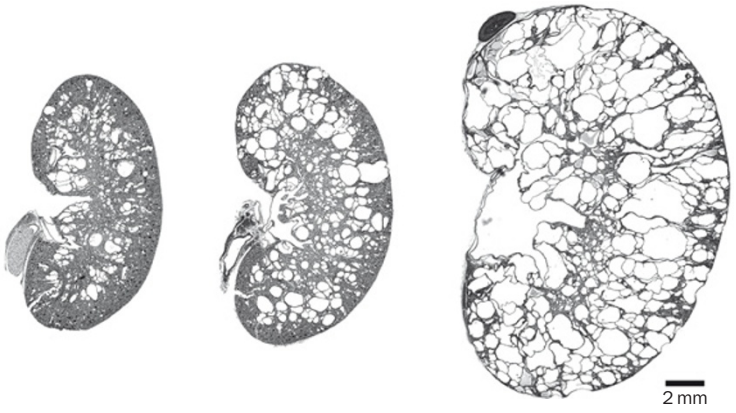
Both inactivation of polycystins in intact cilia, and cilia disruption, can lead to the formation of kidney cysts. However, the mechanism of cyst formation in autosomal dominant polycystic kidney disease (ADPKD) is not clear. Now, Stefan Somlo and colleagues report that intact cilia are required for rapid cyst growth in mouse models of ADPKD.

Somlo and colleagues previously showed that cyst progression was much faster in mice with cilia in which polycystin 1 was inactivated than in mice with complete loss of cilia. "This finding was somewhat surprising because we expected that polycystins could not function without cilia," says Somlo. In the current study, the researchers used a genetic approach to investigate the effect of cilia loss on cyst progression in mouse models of ADPKD. They found that ablation of cilia (via inactivation of genes that encode intraflagellar transport-related proteins) suppressed cyst growth in mice with conditional inactivation of polycystin 1 or 2, whereas increasing the time between polycystin inactivation and cilia ablation increased the severity of cyst growth. Further experiments suggested that the MAPK/ERK, mTOR and cAMP signalling pathways were unlikely to provide the cilia-dependent cyst growth signals.

"The fact that removing cilia abrogates rapid cyst growth in mice with polycystin inactivation indicates that intact cilia provide a positive signal for cyst growth that is repressed by polycystin function," explains Somlo. "This cilia-dependent signal is novel and does not fit any of the known signalling pathways that have been implicated in PKD. Our findings also raise the possibility that polycystins might provide a negative signal that represses the cilia-dependent signal, and that sensory input such as flow may in fact signal graded derepression of the cilia-dependent signal."

Somlo suggests that this novel cilia-dependent pathway might be an ideal target for therapy in ADPKD. "The challenge is to discover the cilia-dependent, cyst-promoting pathway that is inhibited by normal polycystin function," he says. "Once this pathway is discovered, the next step will be to target the pathway with either pharmacological or biological agents, and test these agents in preclinical, and then hopefully in clinical, studies. Similar paradigms starting out with animal models recapitulating human conditions may be applicable to other forms of chronic kidney diseases, but these efforts will require sustained investment in biomedical research."

Ellen F. Carney



Murine kidneys with ablation of cilia, ablation of cilia and polycystin 1 inactivation, and polycystin 1 inactivation alone (left to right), showing mild, intermediate and severe cyst burden, respectively. Permission obtained from Nature Publishing Group © Ma, M. *et al*. *Nat. Genet*. doi:10.1038/ng.2715.

Original article Ma, M. *et al*. Loss of cilia suppresses cyst growth in genetic models of autosomal dominant polycystic kidney disease. *Nat. Genet*. doi:10.1038/ng.2715