CILIOPATHIES

Replication stress-induced DNA damage in renal ciliopathies

The association of nephronophthisis and related ciliopathies with mutations in ciliary proteins has been thought to indicate a pathogenic role for cilia dysfunction in these diseases; however, new findings show that DNA damage caused by replication stress might in fact be the driving mechanism. “Our study explored a commonly mutated ciliopathy gene at the base of the cilium, *CEP290*, and demonstrated that replication stress-induced DNA damage is the common denominator for more general renal ciliopathy phenotypes,” explain researchers Gisela Slaats and Rachel Giles.

CEP290 is mutated in various ciliopathies, including nephronophthisis and Joubert syndrome. Although the protein can localize to the nucleus, as well as to the centrosomes and the base of the primary cilium, the function of nuclear *CEP290* was unknown. Previous publications showing a potential link between ciliopathy proteins and DNA damage led Slaats and Giles to investigate the role of *CEP290* loss in the DNA

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damage response and the relevance of this pathway to ciliopathy syndromes.

The researchers found enhanced DNA damage signalling in renal cells from a patient with *CEP290*-associated Joubert syndrome, in kidneys from *Cep290*-deficient mice, and in *Cep290*-deficient zebrafish embryos. Examination of primary kidney cells from *Cep290*-deficient mice revealed increased numbers of centrioles, evidence of replication stress

and increased levels of cyclin-dependent kinases (CDKs). Intervention with a CDK inhibitor rescued DNA damage, primary cilia frequency, and centriole number in kidney cells from *Cep290*-deficient mice. “CDK inhibitors have shown promising results in renal cystic disease models but no one knew why,” says Slaats. “Our study provides the mechanism for this response and validates efficacy of CDK inhibition in murine and human primary renal cells.”

The researchers say their findings add to the rationale that nuclear functions of ciliopathy proteins participate in disease progression in renal cells and suggest that further research should focus on the role of nuclear proteins. “It is time to start looking beyond the cilium to understand the cause of renal failure in patients with ciliopathies,” notes Giles.

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Original article Slaats, G. G. *et al.* DNA replication stress underlies renal phenotypes in *CEP290*-associated Joubert syndrome. *J. Clin. Invest.* doi:10.1172/JCI80657