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POLYCYSTIC KIDNEY DISEASE

MicroRNA-17: a new drug target for ADPKD

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New data suggest that the microRNA-17 (miR-17) family promotes the progression of autosomal dominant polycystic kidney disease (ADPKD) and is a promising target for therapy. "Anti-miRs work best in the liver and kidney and have a long duration of action," explains researcher Vishal Patel. "These attributes make them ideal therapeutic agents for ADPKD, which affects these organs and requires chronic therapy."

To identify miR drug targets for ADPKD, Patel and colleagues performed miRNA microarray profiling of *Pkd1* and *Pkd2* knockout mice. They found that miR-17 was upregulated in both models. Similarly, expression of miR-17 was increased in kidney cyst samples from patients with ADPKD compared with tubule samples from healthy controls.

In mouse models of ADPKD, genetic deletion of miR-17~92 slowed cyst proliferation, reduced cyst size, improved renal function and prolonged survival. Pharmacological inhibition of the miR-17 family using an anti-miR-17 oligonucleotide also slowed cyst growth in ADPKD models. The researchers show that the primary cellular consequence of miR-17 deletion in these models is improved mitochondrial function. They identified *Ppara*, a key regulator of mitochondrial function, as a direct downstream target of miR-17.

"Metabolic rewiring (the Warburg effect) is observed in ADPKD," says Patel. "An additional component of this rewiring may be miR-17-mediated inhibition of oxidative phosphorylation through direct inhibition of *Ppara*." He concludes that miRs are feasible drug targets for ADPKD and comments that preclinical safety and efficacy studies of an anti-miR-17 drug, RGLS4326, are underway.

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ORIGINAL ARTICLE Hajarnis, S. *et al.* MicroRNA-17 family promotes polycystc kidney disease progression through modulation of mitochondrial metabolism. *Nat. Commun.* **8**, 14395 (2017)