Autophagy boost to treat ADPKD?

Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common inheritable human diseases and leads to renal failure; however, no effective treatment exists. In a new study, Xueying Lin and colleagues used TALEN-mediated gene editing to establish a zebrafish model of ADPKD and showed that activating autophagy reduces cystogenesis and restores renal function.

“As PKD1 is the most common causative gene for PKD, we generated zebrafish pkd1a mutants,” explains Lin. These pkd1a-null fish had pronephric cysts, mTOR hyperactivation and reduced autophagic flux — a feature also present in kidney epithelial cells from PKD1-null mice and patients with ADPKD.

To pinpoint the contribution of defective autophagy to cystogenesis, the researchers reduced the levels of ATG5 — a core autophagy protein — in pkd1a-deficient fish. This inhibition of autophagy increased the incidence of cyst formation caused by pkd1a depletion at an early time point (48% versus 10%). Conversely, activation of autophagy with a short peptide of beclin-1, with carbamazepine or minoxidil, or through mTOR inhibition with rapamycin reduced cyst formation and restored renal function in pkd1a-deficient fish. “Although abnormal autophagy had previously been shown in PKD models, our study demonstrates that autophagy activation exerts therapeutic benefits in PKD,” says Lin.

Inhibition of the mTOR pathway using rapamycin is a candidate therapy for PKD but high doses of this agent are toxic and have systemic adverse effects. Here, the researchers showed that the combination of a 10-fold reduced dose of rapamycin with carbamazepine had a synergistic effect and suppressed cystogenesis as efficiently as a high dose of rapamycin.

Going forward, the researchers plan to take advantage of the zebrafish embryo, an efficient in vivo model for small molecule screening. "We plan to screen known autophagy modulators, especially those already in clinical use, to identify effective new drugs for PKD.”

Andrea Aguilar