O-GlcNAcylation, a modulator of metabolism and ciliogenesis, promotes autosomal dominant polycystic kidney disease (ADPKD) progression

Matthew A Kavanaugh, BS;[1, 3] Dona Greta Isai, PhD;[1, 3] Chad Slawson, PhD;[2, 3] Stephen Parnell, PhD;[2, 3] Darren P Wallace, PhD;[2, 3] Pamela V Tran, PhD;[1, 3]
[1]Department of Cell Biology and Physiology; [2]Department of Biochemistry and Molecular Biology; [3]Jared Grantham Kidney Institute, University of Kansas Medical Center, Kansas City, KS

Introduction: Altered cell metabolism is an important component of autosomal dominant polycystic kidney disease (ADPKD) pathogenesis, but drivers of these alterations are not understood. The addition of O-linked β-N-acetylglucosamine (O-GlcNAc) onto protein substrates by O-GlcNAc transferase (OGT) is a nutrient-sensitive post-translational modification that integrates multiple metabolic signals. We have reported that protein O-GlcNAcylation is increased in patient and mouse ADPKD kidneys. Thus, we hypothesize that increased O-GlcNAcylation is pathogenic in ADPKD.

Methods: We generated juvenile and adult *Pkd1* conditional knockout (cko) and *Pkd1;Ogt* double knockout (dko) mice using the HoxB7-Cre and the doxycycline-inducible Pax8rtTA;LC1-Cre recombinases (induced from 4-6 weeks of age). Juvenile and adult mouse kidneys were analyzed on postnatal day (P)14 and at 4 months of age, respectively. To identify hyper-O-GlcNAcylated proteins in ADPKD, immunoprecipitation and Western blot were performed on mouse renal tissue extracts. To examine mechanisms in human ADPKD, primary patient-derived ADPKD cells were cultured with an OGT inhibitor and *in vitro* cyst formation and cilia lengths were examined.

Results: In juvenile mice, *Ogt* deletion in *Pkd1* cko mice reduced renal cystogenesis and kidney weight:body weight ratios (KW/BW); restrained renal cilia lengths; reduced inflammation and fibrosis; increased activation of the energy sensor AMPK; and improved kidney function. Further, while *Pkd1* cko mice die between P14-P21, majority of *Pkd1;Ogt* dko mice continue to thrive beyond 6 months of age. Additionally, AMPK was found to be hyper-O-GlcNAcylated at P14 in *Pkd1* cko kidneys. In adult mice, preliminary data indicate that deletion of *Ogt* in *Pkd1* cko mice reduces KW/BW. Finally, OGT inhibition reduced primary cilia lengths and *in vitro* cyst formation of cultured human ADPKD cells.

Conclusions: In ADPKD, protein O-GlcNAcylation, including of AMPK, is increased, and deletion or inhibition of OGT reduces cyst growth and disease severity, demonstrating that O-GlcNAcylation is an important driver of ADPKD progression. We propose that targeting O-GlcNAcylation may have therapeutic potential.

Funding Sources: DoD, ASN KidneyCure