TRiPPing the sensors: The osmosensitive pathway of polycystin-2

Karla M. Márquez Nogueras, PhD;[1] Ryne M Knutila, BS[1]; Virdjinia Vuchkovska, BS[1]; Ivana Y Kuo, PhD[1]
Department of Cell and Molecular Physiology, Loyola University Chicago

Autosomal Dominant Polycystic Kidney Disease (ADPKD) is characterized by the formation of renal cysts. Cyst formation occurs within the collecting duct region of the nephron that contributes to the kidney's ability to concentrate urine. As pathological mutations can occur to the gene encoding for the cation conducting channel, polycystin 2 (PC2), many of the calcium dependent signaling pathways are impaired in ADPKD patients. PC2 allows for cytosolic calcium increase via the endoplasmic reticulum (ER). It remains under debate what activates the channel activity of PC2, limiting our understanding of the biological role of this protein in its native environment. PC2 in collecting duct cells reside in an environment subjected to a wide range of osmotic shifts, thus we hypothesized that osmotic changes may contribute to PC2-mediated cytosolic calcium increase. We generated CRISPR/Cas9 PC2 KO iMCD3 cells and measured intracellular calcium responses to hyperosmotic changes. Hyperosmotic changes induced cytosolic calcium increases, which was abolished in the PC2 KO cells. We identified that PC2 interacted with a microtubule binding protein (MAP4), allowing the cells to respond to these extracellular changes. To test the biological relevance of these findings, we measured the insertion of the water channel Aquaporin 2 in the membrane of renal cells and in mice with PC2 KO. Disruption of the interaction between MAP4 and PC2 leads to decreased AQP2 localization in the membrane induced by hyperosmotic challenges in PC2 KO cells. Similar findings were observed in distal and collecting duct tubules in PC2 KO mice impairing the ability to concentrate urine. These findings suggest that the osmosensing pathway of renal cells is mediated through the tethering of the microtubules to the ER via the interaction of PC2 and MAP4. The characterization of these pathways provides new insights into the signaling pathways that contribute to urine concentration in ADPKD patients.

Funding sources: Research reported in this publication was supported by the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health under Award Numbers U2CDK129917 and TL1DK132769 (KMMN).