

Polycystic Kidney Disease: Visualizing Signals that Drive Cyst Initiation in 3D

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Autosomal dominant polycystic kidney disease (ADPKD) is a progressive disease of renal and hepatic dysfunction marked by cyst formation and organ enlargement. It is caused by mutations in two proteins, PKD1 and PKD2, that are linked to aberrations in Ca^{2+} signaling and loss of endoplasmic reticulum (ER) Ca^{2+} stores. However, the fluid secretion and cellular proliferation central to renal cyst formation depends largely on another second messenger, cyclic AMP (cAMP). How Ca^{2+} and cAMP signals are related to one another and how they drive the very first events during the formation of the nascent cyst is unknown. This is largely due to technical limitations that have precluded high resolution, long-term imaging of these signaling molecules concurrent with the relatively rare event of cyst formation in multi-cellular models of PKD. Here we propose to test a daring new hypothesis that may explain how loss of ER Ca^{2+} homeostasis in PKD mutants is linked to elevated cAMP levels, cyst formation, and epithelial cell proliferation. We will take advantage of the Zeiss Lightsheet Z.1 microscope in the HCBI core, new improved fluorescent sensors for cAMP, and 3D organ cultures to evaluate the signaling properties of individual cells lining the cysts. These methodologies will allow us to interrogate in 3D the signaling events taking place deep within the tissue over many hours. Our goal is to identify the early steps that drive cyst formation and to develop a platform for future evaluation of this process in human PKD disease variants.