Role of CFTR in Kidney

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CFTR plays an important role in Polycystic Kidney Diseases (PKD): Autosomal Dominant PKD (ADPKD), caused by mutations in PKD1 or 2 and Autosomal Recessive PKD (ARPKD) caused by mutations in PKHD1. ADPKD is associated with the formation of renal cysts that grow large and ultimately destroy the kidney. ARPKD is associated with failure of the cholangiocytes to stop proliferating, leading to large cysts in the liver, and portal hypertension, and the formation of renal fusiform cysts. In normal kidney more CFTR is localized at the basolateral membrane which makes the kidney to be absorptive and not secretory as occurs in PKD. When the disease occurs in ADPKD or ARPKD, CFTR is mis-localized primarily to the apical membrane where it participates in fluid secretion and cyst expansion. We have shown in vitro and In vivo that treatment with CFTR correctors significantly reduces cyst size in ADPKD and ARPKD models. CFTR correctors are well known to enhance the processing and trafficking of CFTR to the plasma membrane. In the cystic kidneys and livers treated with CFTR correctors, CFTR moves to its normal location at the basolateral membrane creating an absorptive phenotype thereby reducing cyst size.

To evaluate further the role of CFTR in kidney and liver , we treated the ADPKD and ARPKD animal models with gene therapy using AAV1CFTR. After 3 months of treatment with one dose of AAV1CFTR we evaluated morphopathology and function of the kidney and liver in treated animals compared with untreated and normal animals. The results demonstrated indeed that CFTR plays an important role in PKD by reducing the cyst area and ameliorating kidney and liver function.

We found that ADPKD and ARPKD are associated with enhanced release of Ca^{2+} from the ER that fuels proliferation. Treatment of the cysts with CFTR correctors or AAV1CFTR reduces ER Ca^{2+} release back toward normal. We have found that CFTR binds to the PKD2 encoded TRP channel, polycystin 2, and both are highly localized to the ER in cystic epithelium where they are involved in enhanced Ca^{2+} release from the ER. CFTR correctors cause both channels to move from the ER thereby reducing Ca^{2+} release and proliferation.

In conclusion, we found that CFTR plays an important role in fluid secretion into cysts and enhances proliferation by increasing Ca^{2+} signaling by the ER. After correcting the trafficking and processing of CFTR, the area and numbers of the cysts were reduced and the clinical pathology of treated ADPKD and ARPKD animals models was improved. Funded by NIDDK.