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## POLYCYSTIC KIDNEY DISEASE

# Modulation of cystogenesis by the microenvironment

Polycystic kidney disease (PKD) is commonly caused by mutations in *PKD1* or *PKD2*, but the mechanisms of cystogenesis are not well understood. Now, Benjamin Freedman, Nelly Cruz and colleagues report a role of the microenvironment in modulating cyst formation.

The researchers previously generated a kidney organoid model of PKD from human pluripotent stem cells with targeted mutations in *PKD* genes. In their recent study they used this model to investigate cyst formation. “We started watching our PKD organoids and noticed that some tubules were beginning to detach from the culture dish,” says Freedman. “When they peeled off, they swelled up and formed cysts, which stayed tethered to the plate like balloons. This cystogenesis only happened to a minority of the organoids — around 7% — but it gave us the idea to start playing with their microenvironment.”

When cultured in suspension, more than 75% of the PKD organoids formed large free-floating cysts, but cystogenesis

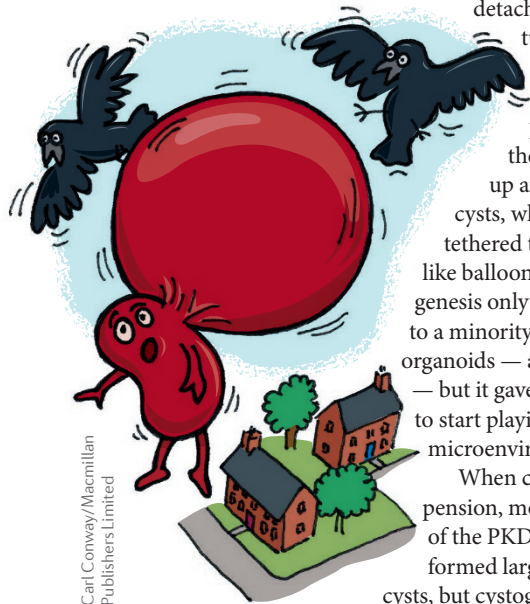
remained a very rare event in control organoids without *PKD* mutations. Culture on extracellular matrix that lacked stroma prevented cyst formation but enabled organoid cell outgrowth, whereas cAMP treatment induced cystogenesis in both PKD and control organoids.

“PKD depends as much on what’s outside the cell as it does on what’s inside, at least in mini-kidneys,” concludes Freedman. “This makes sense, because *PKD* genes encode extracellular polycystin proteins, which form a large receptor. It seems that polycystins help the whole tubule to stick together and prevent it from ballooning out and forming a cyst, so one possible way to combat PKD might be to strengthen the tubule and help it to keep together.”

The researchers now plan to further investigate the functions of polycystins in the context of their microenvironment. “One of our goals is to identify strategies to halt cyst formation,” says Cruz. “Our kidney organoids are amenable for testing candidate drugs and for detecting nephrotoxicity, getting us one step closer to finding effective therapeutic strategies for PKD.”

Ellen F. Carney

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