Study: Genetic kidney disorder reversible in preclinical models

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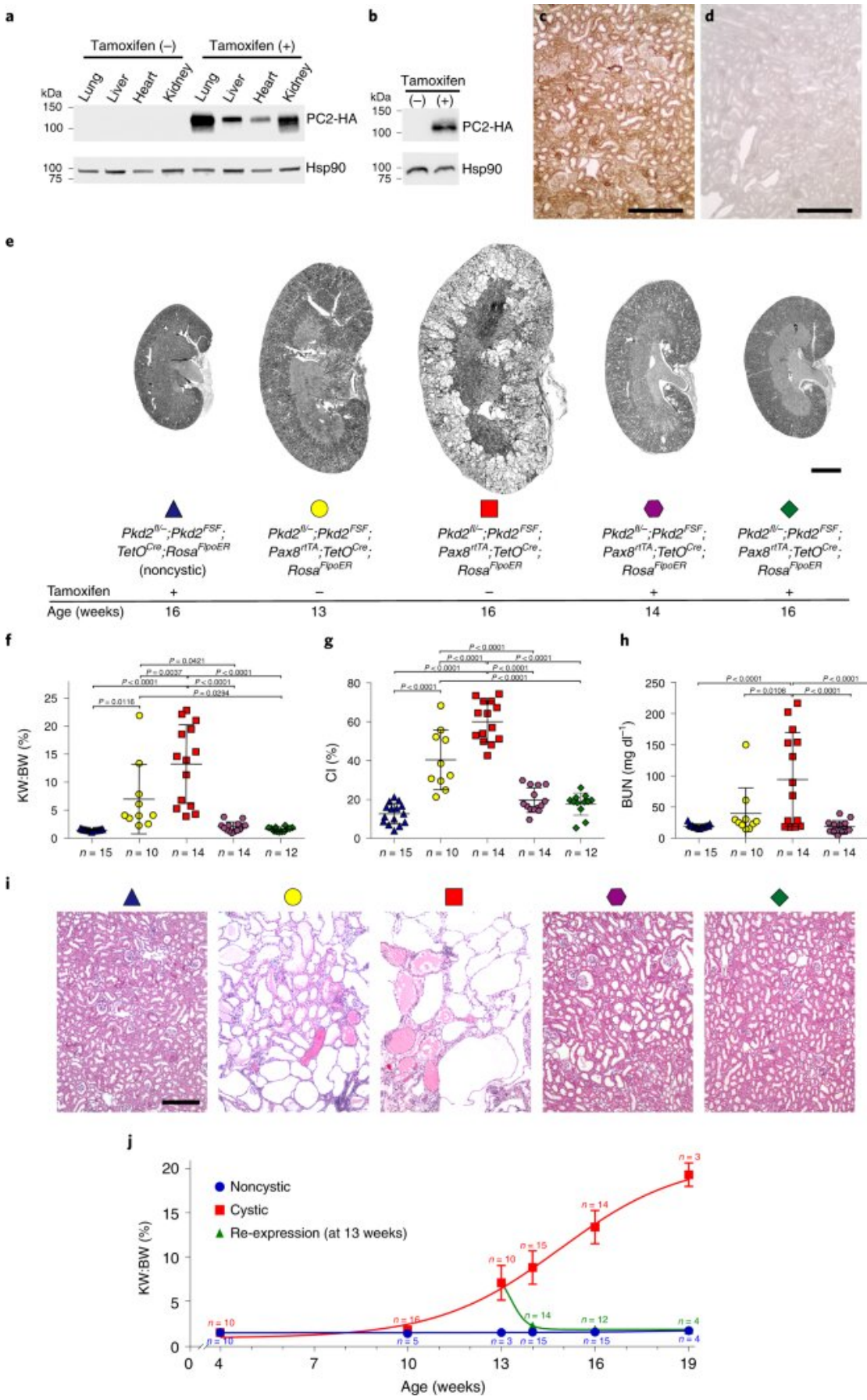
a
Tamoxifen (–)
Tamoxifen (+)
Lung
Liver
Heart
Kidney
kDa
150
100
PC2-HA
100
75
Hsp90
b
Tamoxifen
(–) (+)
c
d
e
Pkd2fl/–;Pkd2FSF;TetOCre;RosaFlpoER (noncystic)
Pkd2fl/–;Pkd2FSF;Pax8rtTA;TetOCre;RosaFlpoER
Tamoxifen + – – + +
Age (weeks) 16 13 16 14 16
f
KW:BW (%)
g
CI (%)
h
BUN (mg dl−1)
n = 15 n = 10 n = 14 n = 14 n = 12
i
j
Noncystic
Cystic
Re-expression (at 13 weeks)
KW:BW (%)
Age (weeks)

Fig. 1: Reactivation of Pkd2 reverses cyst formation. Credit: DOI: 10.1038/s41588-021-00946-4

Autosomal dominant polycystic kidney disease (ADPKD), a genetic disorder, causes fluid-filled cysts to develop on the kidneys, which can impair their function. As part of the growth of cysts, the kidneys develop inflammation and fibrosis, or scarring. The disease is most often caused by a mutation in one of two genes, PKD1 or PKD2, which can be passed down within families, from parent to child.

Working in mice models, Stefan Somlo, MD, C. N. H. Long Professor of Medicine (Nephrology) and Professor of Genetics; chief, Section of Nephrology, and his research team, published a study in *Nature Genetics* showing that the damage caused by ADPKD can be reversed, demonstrating the surprising plasticity of the kidney.

First, they created a mouse model that allowed inactivation followed by reactivation at a later time of PKD2. "Essentially, the mouse developed polycystic kidney disease and then we did "gene" therapy, turning on the same gene, a copy, that had been turned off to cause the disease," said Somlo.

They started with PKD2, and found that the kidney size shrunk, cysts resolved, and the tubules regained their natural form. In addition, secondary damage such as inflammation and fibrosis were substantially reversed. Researchers performed serial MRIs on each mouse to monitor the decrease in kidney size. Based on what they discovered for PKD2, they repeated the experiment focusing on PKD1 and confirmed their findings.

"One surprising finding is that this process of the kidney getting cystic and growing and then getting smaller again is actually possible. That's kind of unexpected and interesting, and it begs the question of what the polycystins normally do, because they must be regulating some feature of tubules getting bigger and smaller to accommodate maybe different physiologic conditions in normal states," said Somlo.

The researchers concluded that the re-expression of polycystins reversed alterations in cell shape and proliferation, along with inflammation and fibrosis. They found that a potentially regenerative process, autophagy, was activated as the kidneys returned to a more normal state.

Researchers also found that the timing of the therapy was critical. As demonstrated in the study, in later stage ADPKD, while the kidney size and inflammation are reduced, kidney scarring is no longer fully repairable.

The team is evaluating which molecular pathways are activated through the disease reversal, and how they work. They will then determine how best to target these pathways for possible treatments for ADPKD.

Somlo began to study ADPKD when he came to Yale School of Medicine (YSM) as a fellow around 1990. At the time, he was interested in the application to kidney disease of an upcoming technology, molecular biology. He started working on the molecular genetic aspects of disease gene identification for ADPKD, and when he established his own lab, continued expanding his studies of the disease.

Somlo is driven to learn more about kidney function and ADPKD. "There is a whole aspect of kidney function that we don't know. Even after more than two decades of research, we still need to figure out what these PKD gene proteins, polycystins, do. And I think that this study tells us that this disease is treatable, and we should try to figure it out. I think

the mouse models are actually a very powerful tool toward that end," said Somlo.

More information: Ke Dong et al, Renal plasticity revealed through reversal of polycystic kidney disease in mice, *Nature Genetics* (2021). DOI: 10.1038/s41588-021-00946-4

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