Researchers uncover new clues to origins of the most common pediatric kidney cancer

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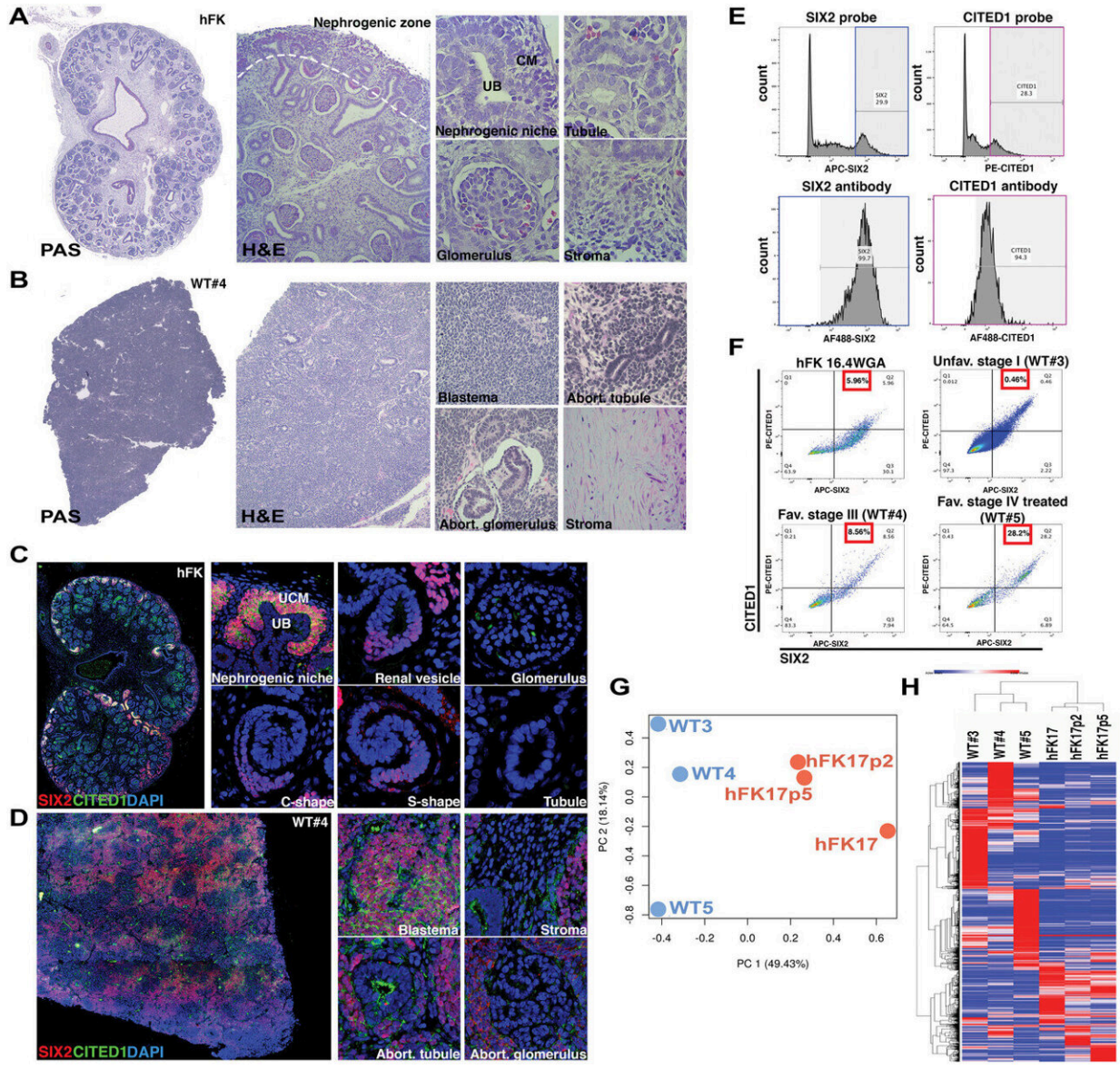

SIX2+CITED1+ cells in hFK and WT have different transcriptional signatures.

A,B) Periodic acid Schiff (PAS, left, whole image) and H&E (right, close-up images) staining of hFK (A,10 WGA) and WT#4 (B, favorable stage III) show the nephrogenic zone (white dotted line) and differentiating structures (second panel: ureteric bud, UB; cap mesenchyme CM; tubule, glomerulus, and stroma) of hFK, and unorganized WT histology with triphasic components (second panel, stroma, blastema, and epithelial structures including abortive glomeruli and tubules). 10× images acquired and composed using Photoshop DC (Adobe) for whole images, right panels of 20X images. C,D) SIX2 (red) and CITED1 (green) immunofluorescence staining of C) hFK 10 WGA and D) WT#4. SIX2+CITED1+ co-expression in hFK (C, second panel) in the nephrogenic niche (uninduced cap mesenchyme, UCM) but absent within developing (renal vesicle, C-shape, S-shape) and mature (glomerulus and tubule) structures. SIX2+CITED1+ expression is dispersed throughout the WT (D, second panels) in blastema but not in stroma or abortive structures (glomerulus and tubule). Nuclei stained with DAPI (blue), 10× images acquired and composed using Photoshop DC (Adobe) for whole images, right panels of 20× images. E) SmartFlare technique validation by flow cytometry. SIX2-Cy5 and CITED1-Cy3 probes (top left and right panel respectively) were individually used to isolate cells from hFK (17.4 WGA). Flow cytometry confirmed that 99.7% of SIX2+ cells and 94.3% of CITED1+ cells co-express both mRNA and protein (bottom left and right panels). F) FACS sorting (by Smartflares): 5.96% of cells from hFK 16.4 WGA are SIX2+CITED1+ cells, 0.46% from WT#3 (unfavorable stage I), 8.56% from WT#4 (favorable stage III) and 28.2% from WT#5 (favorable chemotherapy-treated stage IV). G,H) Bulk RNA-seq analysis of hFK (17, 17.2, and 17.5 WGA) and WT (n = 3, as in F). PCA (principal component analysis, G) describes 49.43% and 18.14% of the variability, along PC1 and PC2 respectively, within the expression data set. SIX2+CITED1+ cells from WT cluster independently of SIX2+CITED1+ cells from hFK. H) Hierarchical clustering of total gene expression in SIX2+CITED1+ cells from hFK and WT highlights higher similarity among SIX2+CITED1+ cells from different hFK versus higher divergence of SIX2+CITED1+ cells from different WT. Credit: *Advanced Science* (2023). DOI: 10.1002/advs.202206787

While Wilms tumor—also known as nephroblastoma—is rare, it is the

most prevalent childhood kidney cancer. Researchers at Children's Hospital Los Angeles have now pinpointed a disruption in early kidney progenitor cell development that can be linked to the formation of Wilms tumor.

In a study published in *Advanced Science*, researchers at the GOFARR Laboratory in Urology compared kidney progenitor cells from a tumor with precursor cells from a healthy kidney. Normally, these precursor cells mature into kidney cells, but when their early development is dysregulated, they behave like cancer stem cells.

While most children with Wilms tumor are successfully treated, current therapies are aggressive. A minority of these patients have unfavorable prognoses or relapses; for these children, there is no existing therapy. "By achieving a more precise understanding of how Wilms tumors develop, our goal is to find new treatments for all types of Wilms tumor," says Laura Perin, Ph.D., Co-Director of the GOFARR laboratory and senior study co-author with Stefano Da Sacco, Ph.D., another researcher at the GOFARR Laboratory.

Instead of developing into kidney cells, they develop into tumor cells

"Pediatric Wilms tumor can be considered a developmental cancer," says Dr. Perin, who is also Associate Professor at the Keck School of Medicine of USC. "The normal adult kidney lacks kidney precursor cells, as they are 'exhausted' before birth. But in Wilms tumors, instead of giving rise to a functional kidney, these precursor cells persist and form the tumor mass." The researchers characterized these Wilms tumor kidney precursor cells, finding that these cells can reproduce the original tumor.

"They are aggressive, they're drug-resistant, they metastasize like cancer

cells, and they are able to create the full tumor that we see in patients," says Astgik Petrosyan, Ph.D., researcher at the GOFARR Lab and first author of the study.

Cells that are oblivious to growth signals

The kidney precursor cells that generate Wilms tumors also abnormally expressed ITGβ1 and ITGβ4, proteins that help cells communicate with their microenvironment. "This abnormal attachment to their microenvironment favors the uncontrolled replication of these cells and guides the formation of the tumor mass," says Dr. Da Sacco.

"Our findings provide a more accurate understanding of the different stages of both normal and abnormal kidney development," says Dr. Perin. "This can possibly help the diagnosis of Wilms tumor, leading to more effective treatments for these patients."

More information: Astgik Petrosyan et al, Identification and Characterization of the Wilms Tumor Cancer Stem Cell, *Advanced Science* (2023). DOI: 10.1002/advs.202206787

Provided by Children's Hospital Los Angeles