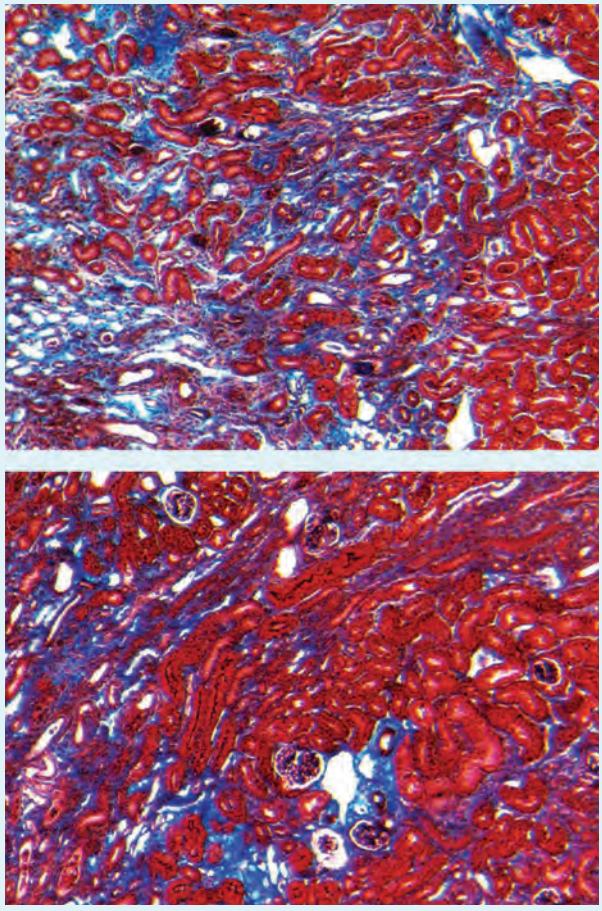
NEPHROLOGY



Metalloprotease ADAM17 mediates profibrotic factor release in the kidney

Kidney fibrosis is a frequent consequence of kidney injury or disease and can result in nephron loss and eventual kidney failure. Eirini Kefaloyianni and colleagues demonstrate that the metalloprotease ADAM17 is upregulated after kidney injury and mediates the release of pro-TNFα and the EGFR ligand amphiregulin in the proximal tubule. Deletion of *Adam17* within the proximal tubule or treatment with an ADAM17 inhibitor protected against fibrosis after acute kidney injury (AKI; see the accompanying image) or unilateral ureter obstruction (UUO) in mice. Importantly, soluble amphiregulin levels were elevated in urine samples from patients with AKI or chronic kidney disease, and ADAM17 and amphiregulin expression in kidney biopsies strongly correlated with markers of fibrosis, indicating that ADAM17 drives fibrosis in human kidney fibrosis.

ADAM17 substrate release in proximal tubule drives kidney fibrosis

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ONCOLOGY

PAX8/chromatin interactions are dramatically altered in serous ovarian carcinomas

Most high-grade serous ovarian carcinomas (HGSOCs) arise from fallopian tube secretory epithelial cells (FTSECs). PAX8 is a lineage-restricted transcription factor (TF) of the Müllerian epithelium. It gives rise to the female reproductive tract and is retained in nearly all HGSOCs. Kevin Elias and colleagues investigated alterations in the epigenetic behavior of PAX8 between FTSECs and HGSOCs. Using whole transcriptome shotgun sequencing (RNA-seq) and ChIP-seq, Elias and colleagues showed that the cistromes between FTSEC and HGSOC lines are radically altered. Additionally, genes that were significantly altered between FTSECs and HGSOCs were clustered around PAX8 binding sites. The differentially regulated genes were also near binding sites for the TEAD family of transcription factors, which mediate YAP-dependent gene induction and have been implicated in FTSEC/HGSOC transformation. Coimmunoprecipitation and proximity ligation assays confirmed that PAX8 and TEAD TFs physically interact in Müllerian cells. These results suggest that the development of HGSOC is linked to PAX8/TEAD-mediated interactions with chromatin.

Epigenetic remodeling regulates transcriptional changes between ovarian cancer and benign precursors

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http://jci.me/87988