FIBROSIS

The interdependence of renal epithelial and endothelial metabolism and cell state

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In this issue of *Science Signaling*, Lovisa *et al.* demonstrate the contribution of endothelial-to-mesenchymal transition (EndMT) to kidney fibrosis development. Their studies reveal the interdependence of endothelial and epithelial metabolism in health and disease.

Epithelial-to-mesenchymal transition (EMT) (*1*) is a fundamental cellular process in which epithelial cells lose their polarity and become motile mesenchymal cells. EMT plays an important role both in kidney development and disease, including renal cell cancer and tissue fibrosis. Endothelial cells can also undergo mesenchymal transition (EndMT). EndMT is essential for heart valve development (*2*). EndMT has been detected in fibrotic organs (*3*, *4*); however, the role and contribution of EndMT to fibrosis development remain controversial. Cell state is strongly linked to metabolism (*5*, *6*). Healthy endothelial and epithelial cells depend on fatty acid oxidation (FAO) and oxidative phosphorylation (OX-PHOS), but the metabolism of mesenchymal cells is usually more glycolytic. Changes in metabolism are associated with changes in cell state (*7*). In the current study, Lovisa *et al.* (*8*) sought to analyze the role of EndMT in kidney fibrosis and metabolism.

Twist or Snail are transcription factors implicated in EndMT by in vitro studies; the authors generated mice lacking one of these transcription factors in endothelial cells. Kidney fibrosis was induced in mice by unilateral ureteric obstruction (UUO) or folic acid. In both models, the authors observed markedly lower renal fibrosis and tubular damage in mice with induced deficiency of Twist or Snail. Lineage-tracing experiments performed with Rosa26-LSL-EYFP reporter mice confirmed the reduction in EndMT in kidneys of these mice. RNA sequencing and gene set enrichment analyses of whole kidney samples indicated that abrogation of EndMT ameliorated inflammation and fibrosis at the mRNA level.

Next, the authors wanted to understand the molecular pathways driven by EndMT in the kidney. Using perfusion studies with fluorescein isothiocyanate–labeled dextran and albumin, they demonstrated that an increase in vascular leakage, consistent with altered endothelial cell-cell junctions, was a main feature of EndMT-mediated damage in fibrotic kidneys. This EndMT-mediated vascular permeability was independent of vascular endothelial growth factor receptor 2 (VEGFR2) signaling, a pathway involved in angiogenesis and vascular permeability (*9*), making this finding in and of itself an interesting avenue for further research. Gene set enrichment analysis indicated an increase in the expression of hypoxia-related markers.

In addition to tissue hypoxia, the authors also observed a relationship between FAO, OX-PHOS, and EndMT. Kidney tubular epithelial cells (TECs) heavily rely on FAO and OX-PHOS for energy production and differentiation. The authors demonstrated that a decrease in abundance of the FAO rate-limiting enzyme Cpt1a led to an increase in glycolysis. Also, they showed both in vivo and in vitro that suppression of EndMT preserved FAO in TECs. Switching from FAO to glycolysis is the classic Warburg effect, which plays an important role in dedifferentiation and proliferation of cancer cells. Indeed, the authors showed increased expression of Myc, a transcription factor involved in proliferation, which correlated with both hypoxia and kidney fibrosis. Therefore, the authors were interested to see whether Myc (*10*) was a driver of EndMT. Both a pharmacological inhibitor and genetic ablation in TECs decreased interstitial fibrosis and improved tubular health in vivo. RNA sequencing demonstrated a decrease in the expression of genes encoding Myc and glycolytic enzymes, which coincided with improved FAO and OX-PHOS. The findings were confirmed by targeted metabolomics. Although the presence and activity of myofibroblasts are hallmarks of the mesenchymal transition responsible for the deleterious effects of organ fibrosis, the authors showed that conditional deletion of *Myc* in myofibroblasts did not affect kidney damage, suggesting that up-regulation of Myc in myofibroblasts does not play a role in the emergence of kidney fibrosis.

With this paper, we have come closer to establishing that blocking EndMT could potentially suppress kidney fibrosis. The authors propose a hierarchy of endothelial cell dysfunction and the ensuing hypoxia as an upstream regulator of the epithelial metabolic defect that leads to epithelial dysfunction and kidney disease. In this context, it would have been interesting to identify the upstream regulators of Snail and Twist and to determine whether oxygen sensing mechanisms in the endothelium play important roles in this process. Another important question will be to understand the pathways that mediate the cross-talk between endothelial and epithelial cells.

In conclusion, it has become evident that Twist- and Snail-mediated EndMT governs vascular damage and tissue hypoxia. This process drives kidney fibrosis by affecting metabolic reprogramming through altered Myc signaling in kidney tubules (Fig. 1). The Kalluri group has elucidated the intricate interplay between epithelial metabolism and EndMT, which is indeed important in development and wound healing but deleterious in the context of organ damage. Moreover, EndMT is critically linked to EMT and metabolic reprogramming of the epithelial cells such as switching from lipid oxidation to glucose utilization. In the future, it will be interesting to further elucidate the role of metabolic programming of endothelial and epithelial cells and whether it can be therapeutically targeted. EndMT is also itself an interesting therapeutic candidate upstream of tubular epithelial damage, and future research in this area seems warranted.

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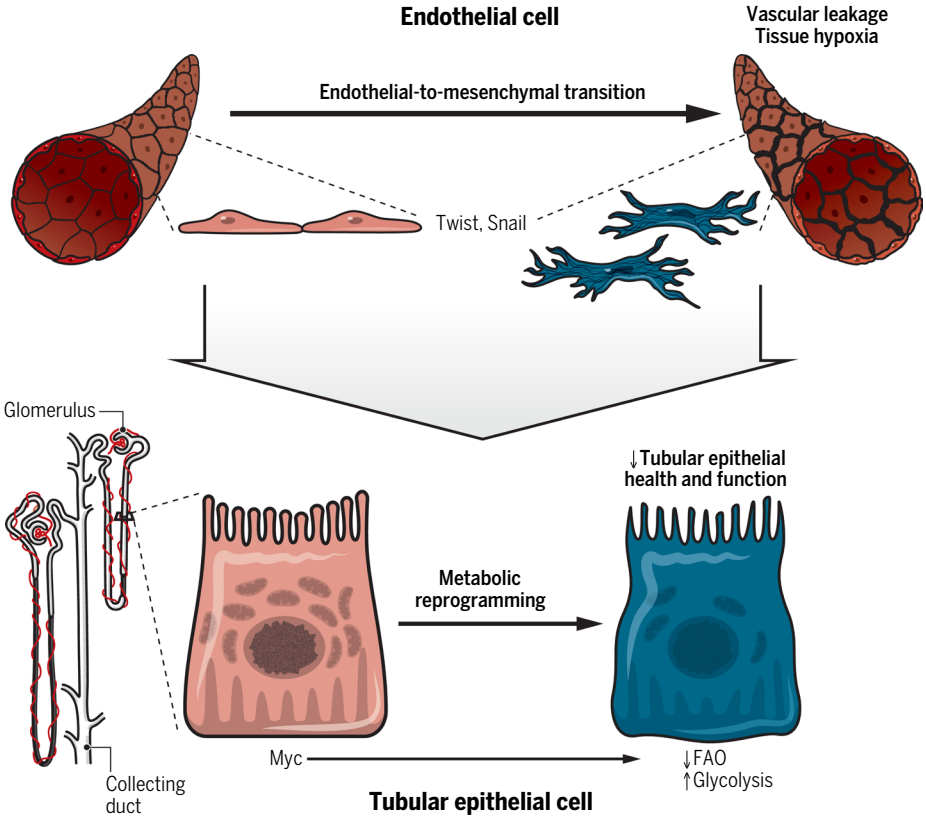

Fig. 1. EndMT links renal epithelial and endothelial metabolism. Kidney tubule cell metabolic reprogramming toward decreased fatty acid oxidation (FAO) and increased glycolysis as hallmarks of kidney disease progression depend on EndMT, which triggers vascular leakage and tissue hypoxia.

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