TUBULAR DISEASE

IL-1 β switches on kidney fibrosis

IL-1 β can drive tubulointerstitial disease by inducing proximal tubule damage and fibrosis

Fibrosis and persistent inflammation are characteristics of kidney injury, but the molecular mechanisms of the crosstalk between them are unclear. Now, Lemos et al. report that in acute kidney injury (AKI), the innate immune pro-inflammatory cytokine IL-1 β induces a metabolic switch in platelet-derived growth factor receptor (PDGFR β)⁺ kidney stromal cells (SCs), which promotes tubulointerstitial fibrosis.

RNA sequencing of healthy kidney or chronic kidney disease (CKD) biopsy samples revealed a switch in metabolic gene expression from oxidative phosphorylation (OXPHOS) in healthy kidney tissue to glycolysis in fibrotic renal tissue. Furthermore, the expression of the transcription regulator *MYC* and its coactivator *MAZ* were upregulated, whereas that of the mitochondrial biogenesis regulator *PPARGC1A* was downregulated in CKD. Additionally, *MYC* protein levels were substantially elevated in the interstitial cells in CKD biopsy samples, whereas *MYC* was almost undetectable in healthy kidney tissue. Examination of metabolic gene expression in mouse kidney SCs and fibrogenic myofibroblasts in the unilateral ureteral obstruction (UVO) model of renal fibrosis confirmed that this OXPHOS–glycolysis switch during the transition from AKI to CKD occurred in vivo.

Next, the researchers analysed the transcriptome of tubulointerstitial SCs in injured mouse kidneys and found that the expression of IL-1 β and *MYC* was significantly correlated, and the expression of downstream genes in

the IL-1 receptor signalling pathway was upregulated by AKI. Stimulating primary human SCs in vitro with IL-1 β resulted in the upregulation of *MYC* and its target glycolytic proteins, which was blocked by an inhibitor of IL-1 receptor-associated kinase 4 (IRAK4). Furthermore, in a mouse model of ischaemia–reperfusion injury (IRI)-induced kidney injury, the IRAK4 inhibitor blocked the upregulation of *MYC* and reduced the proliferation of SCs after IRI. Additionally, IL-1 β treatment induced a metabolic switch and increased proliferation of primary human SCs in vitro, which was blocked by a *MYC* inhibitor. Thus, an IL-1 receptor–IRAK4–*MYC* axis regulates kidney SC proliferation and metabolism.

IL-1 receptor signalling is known to activate autophagy and, indeed, IL-1 β induced autophagosome formation and increased degradation of the cargo protein p62 in primary human SCs in vitro. Additionally, autophagy gene expression was higher in severely fibrotic human kidney tissue than in healthy kidney tissue. As p62 recognizes polyubiquitinated proteins to mediate their proteasomal degradation, *MYC* might be a direct target of p62. Deletion of the gene encoding p62 in human kidney SCs by CRISPR–Cas9 increased the levels of *MYC* and its target genes, whereas overexpression of p62 reduced *MYC* levels. Moreover, p62 and *MYC* interact and *MYC* appears to be polyubiquitinated in p62-deficient cells treated with a proteasome inhibitor. Thus, it is likely that *MYC* is a direct target of p62.

To examine the effects of modulating the IL-1 receptor–IRAK4–*MYC* axis in vivo, the researchers treated UVO mice with an inhibitor of *MYC* expression during the inflammatory phase of AKI. Interestingly, not only was SC proliferation reduced during AKI, but the number of myofibroblasts, the expression of collagen genes and collagen deposition in the tubulointerstitium (all indicative of fibrosis) were also reduced by the *MYC* expression inhibitor. The researchers next switched to using 3D human kidney organoids. “We could study multiple tissue events triggered by IL-1 β alone. This ‘single cytokine’ approach was possible because organoids lack haematopoietic innate immune cells,” Dario Lemos explains. IL-1 β stimulation induced hypertrophy of kidney organoids, proximal tubule cell atrophy and increased expression of kidney injury molecule 1, all indicators of proximal tubular damage. Additionally, increased expression of collagen genes and interstitial collagen deposition suggested that fibrosis also occurred in response to IL-1 β treatment. Importantly, these effects were blocked by inhibition of *MYC* expression. Thus, IL-1 β can drive tubulointerstitial disease by inducing proximal tubule damage and fibrosis.

“IL-1 β induces an inflammatory metabolic phenotype in fibrogenic kidney SCs, which resembles the immunometabolism of monocytes and macrophages,” explains Lemos. “Therefore, we should think of kidney SCs not just as extracellular matrix-producing cells, but also as cells that actively contribute to local inflammation.”

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