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Proximal Tubular ALOX5 Links ECM Homeostasis and Collagen Remodeling in Renal Fibrosis

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Objectives : Renal fibrosis, a hallmark of chronic kidney disease (CKD), results from dysregulated extracellular matrix (ECM) turnover and collagen accumulation. Arachidonate 5-lipoxygenase (ALOX5), a key enzyme in leukotriene biosynthesis, promotes inflammation and immune activation. The proximal tubule is highly injury-prone and an early driver of tubulointerstitial fibrosis, as damaged tubular epithelial cells initiate inflammatory and profibrotic cascades. We aimed to define the role of proximal tubular ALOX5 and determine whether leukotriene signaling promote collagen deposition and ECM remodeling during renal fibrosis.

Methods : Tamoxifen-inducible proximal tubule-specific Alox5 knockout mice were subjected to unilateral ureteral obstruction (UUO). Renal fibrosis, epithelial integrity, and immune activation were assessed by histologic, immunohistochemical, molecular, biochemical, and label-free imaging analyses, including second harmonic generation (SHG) and fluorescence-lifetime imaging microscopy (FLIM). In vitro, HKC-8 cells were stimulated with Alox5-derived metabolites or TGF- β 1, while Alox5 activity was inhibited. Immune activation was further evaluated using CD11c-YFP mouse and a THP-1 co-culture system.

Results : Proximal tubular Alox5 deletion markedly reduced tubulointerstitial fibrosis and preserved epithelial integrity in UUO kidneys, accompanied by decreased expression of vimentin, CXCL12, CCL2, collagen I, and collagen III. SHG and FLIM imaging revealed that Alox5 deficiency preserved ECM organization and prevented collagen compaction. In vitro, LTD4 and 5-HETE increased total soluble collagen and inflammatory mediators (KIM-1, IL-6, CCL2, CXCL12, ICAM-1), whereas pharmacologic or genetic inhibition of Alox5 attenuated these responses and restored MMP-1 and MMP-3 expression. Furthermore, THP-1 monocyte adhesion and avidity to HKC-8 cells and 3D imaging of CD11c-YFP kidneys demonstrated reduced immune cell adhesion and infiltration, respectively, following Alox5 inhibition.

Conclusions : Proximal tubular Alox5 is a key upstream mediator linking inflammation and immune activation to ECM remodeling during renal fibrosis. Alox5 blockade attenuates fibrotic progression by restoring ECM homeostasis and reducing fibrotic collagen accumulation, supporting Alox5 as a promising upstream therapeutic target for renal fibrosis.