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ALOX5 Regulates Renal Fibrosis Through Modulation of Matrix Remodeling and Inflammatory Responses

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Objectives : Renal fibrosis, a common pathological feature of chronic kidney disease, exhibits excessive extracellular matrix accumulation and inflammatory cell infiltration. 5-lipoxygenase (ALOX5), a key enzyme in leukotriene B4 (LTB4) biosynthesis, plays crucial roles in inflammatory cell recruitment and inflammatory responses. While ALOX5-mediated LTB4 production is known to regulate inflammatory cascade and immune cell recruitment, its specific contribution to collagen deposition and matrix remodeling in renal fibrosis remains unclear.
Methods : We investigated the role of ALOX5 in renal fibrosis using TGFβ-stimulated HKC8 cells (human proximal tubule cell) with pharmacological ALOX5 inhibition. We analyzed the expression of fibrotic markers and pro-inflammatory cytokines using Western blot and qPCR. Matrix metalloproteinases (MMPs), total soluble collagen, and collagen turnover were examined through molecular and biochemical analyses. To evaluate immune cell recruitment, we established co-culture systems with immune cells.
Results : ALOX5 inhibition effectively suppressed TGFβ-induced increases in alpha-smooth muscle actin (α-SMA) and kidney injury molecule-1 (KIM-1) expression in HKC8 cells. ALOX5 pathway modulation significantly affected TGFβ-induced collagen expression. Notably, collagen composition and turnover were affected, evidenced by the changes of the TGF-β-induced elevation in the collagen I to III ratio and reversal at different time points during the biological processes. Mechanistically, ALOX5 inhibition restored the TGFβ-suppressed expression of key collagenases (MMP1, MMP3, and MMP13) and their enzymatic activities, thereby maintaining appropriate collagen turnover. Furthermore, ALOX5 pathway blockade reduced pro-inflammatory cytokines IL-6, IL-1β, and TNF-α levels and decreased immune cell infiltration in co-culture experiments, demonstrating its regulatory role in matrix remodeling and inflammatory responses.
Conclusions : ALOX5 serves as a key mediator in renal fibrosis by regulating collagen deposition and inflammatory responses. ALOX5 pathway modulation affects multiple aspects of fibrotic progression: regulation of collagen turnover, inflammatory cytokine, and immune cell recruitment. These results show that ALOX5 can be a potential therapeutic target in renal fibrosis, particularly through its role in matrix remodeling.