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NOX2 Inhibition as a Therapeutic Strategy for AKI-to-CKD Transition: Efficacy in Fibrosis and Cell Cycle Arrest

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Objectives : Oxidative damage is a known contributor for kidney fibrosis. This study investigates the effects of NOX inhibition on the transition from acute kidney injury (AKI) to chronic kidney disease (CKD).
Methods : A murine model for the AKI-to-CKD transition was established 4 weeks post unilateral ischemia-reperfusion injury (IRI). Mice received a NOX2 inhibitor (10 mg/kg) intraperitoneally thrice weekly following unilateral IRI for 4 weeks. Human proximal tubular epithelial cells were exposed to TMAO, a CKD-associated metabolite, to induce oxidative stress, and the inhibitory effects on NOX2 signaling were evaluated.
Results : NOX2 inhibition resulted in reduced kidney tissue fibrosis, confirmed by MT and Sirius red staining, and decreased macrophage presence (F4/80) and inflammation (P53) in kidney tissue. Notably, oxidative stress markers (8-OHDG) decreased, while phosphorylated CDK1 expression increased. Western blot analysis indicated reduced fibrosis (fibronectin, collagen-1), kidney injury (NGAL), P21, and P53, and increased phosphorylated CDK1 post-NOX2 inhibition. In vitro, TMAO induced a dose-dependent increase in ROS production and upregulated fibronectin, phosphorylated P65, Snail, and NOX2 expression. NOX2 inhibition ameliorated oxidative stress, enhanced cell viability and proliferation, reduced inflammation, and diminished kidney cell fibrosis, as demonstrated by MTS assay and decreased IL-18 and fibronectin levels. Moreover, NOX2 inhibitor dose-dependently improved apoptosis and reversed TMAO-induced G2/M cell cycle progression arrest.
Conclusions : NOX2 inhibition effectively mitigates oxidative stress, thereby attenuating kidney injury, apoptosis, cell cycle arrest, inflammation, and fibrosis during the AKI-to-CKD transition.