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Ezetimibe Mitigates Exacerbated Tubulointerstitial Fibrosis Resulting from P62 Knockout in a UUO Model: Insights from Spatial Transcriptomics and Histology

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Objectives : Tubulointerstitial fibrosis significantly contributes to the progression of chronic kidney disease. Previous research has underscored the anti-fibrotic potential of autophagy and the Nrf2-Keap1 pathway, which is pivotal in combating oxidative stress. This pathway is notably activated by p62, an autophagy adaptor protein, underscoring the intricate interplay between autophagy and oxidative stress defense mechanisms in renal fibrosis mitigation. Ezetimibe, a cholesterol-lowering agent, has been recognized for its ability to activate Nrf2-Keap1 pathway through p62 activation. Consequently, we aimed to explore the impact of p62 knockout and subsequent Ezetimibe treatment in a unilateral ureteral obstruction (UUO) mouse model, providing insight into potential therapeutic strategies for tubulointerstitial fibrosis.
Methods : A total of 48 UUO kidneys were harvested from p62 wild-type and knockout mice, each treated with either vehicle or Ezetimibe. The proportion of fibrotic tissue was quantitatively assessed using Masson's Trichrome stains. Tubulointerstitial-specific gene expression profiles were determined through spatial transcriptomics with the GeoMx Digital Spatial Profiler.
Results : P62 knockout mice treated with vehicle exhibited increased fibrosis compared to wild-type counterparts. The change was reflected at the molecular level by Gene Set Enrichment Analysis (GSEA) highlighting upregulation in the pro-fibrotic TGF-beta and NF-κB pathways, oxidative damage response, alongside downregulation in pathways related to oxidative stress response, antioxidant activity, and mitochondrial biogenesis as well as mitophagy (autophagic mitochondrial degradation), and secondary lysosome activity. Conversely, Ezetimibe treatment in knockout mice not only significantly ameliorated fibrosis compared to vehicle-treated counterparts but also favorably influenced molecular pathways, as evidenced by upregulation in pathways facilitating the detoxification of reactive oxygen species, mitochondrial gene expression and mitochondrial crista structure, while downregulating pro-fibrotic TGF-beta and NF-κB pathways, oxidative damage response.
Conclusions : P62 knockout exacerbates tubulointerstitial fibrosis in the UUO model, while Ezetimibe treatment mitigates this effect by restoring mitochondrial function, enhancing antioxidant activity and mitophagy, and suppressing pro-fibrotic pathways.