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Therapeutic Potential of Transglutaminase 2 Inhibition in Peritoneal Fibrosis Through HIF-1a Signaling Regulation

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Objectives : Peritoneal dialysis (PD) is a vital treatment for patients with chronic kidney disease (CKD), yet peritoneal fibrosis (PF) remains a significant complication. Transglutaminase 2 (TG2), a multifunctional calcium-dependent enzyme, has been implicated in fibrotic processes. This study investigates the therapeutic potential of TG2 inhibition in PF by examining the proteomic landscape, specifically focusing on its interaction with the HIF-1α signaling pathway.
Methods : Isolated primary human peritoneal mesothelial cells (hPMCs) from PD effluents were treated with rTGF-β for 48 hours to induce fibrosis, cysteamine (250 μM - 1,000 μM) for 48 hours to inhibit TG2, and H_2O_2 (1 mM) for 1 hour to induce oxidative stress. Global proteome alterations were analyzed via TMT-labeled proteomics. For in-vivo validation, C57BL/6 mouse were injected with 0.1% chlorhexidine gluconate (CG) daily to model PF.
Results : rTGF-β treatment induced fibrosis in hPMCs with elevated TG2 expression, while TG2 inhibition reduced fibrosis in a dose-dependent manner. TMT-based quantitative proteomic analysis identified 8,961 proteins, with 922 differentially expressed proteins clustering into six distinct expression patterns. Upregulated proteins in the HIF-1α signaling pathway upon rTGF-β treatment were reversed by TG2 inhibition. These results translated to western blot analyses, where TG2 inhibition reduced HIF-1α expression in the presence of rTGF-β. Moreover, TG2 inhibition decreased the production of reactive oxygen species, even at low concentrations. In CG-treated mice, significant peritoneal thickening and progression of PF positively correlated with the expression of TG2 and HIF-1α, with HIF-1α localized in fibroblasts and mesothelial cells in submesothelial zones. These findings suggest that TG2 inhibition may mitigate fibrosis and oxidative stress through modulating the HIF-1α pathway.
Conclusions : Our proteomic study demonstrates that TG2 inhibition effectively attenuates TGF-β-mediated PF by modulating the HIF-1α signaling pathway, representing a promising therapeutic approach for CKD patients needing dialysis.

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