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Transgultaminase-2 Inhibition Mitigates Mesangial Cells Damage by Modulating Hypertension-induced Hypoxia

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Objectives : Transglutaminase 2 (TG2), induced by hypoxia-inducible factor-1α (HIF-1α), regulates hypoxia-driven mRNA translation and oxidative stress. Previous studies suggested that a hypertension-mimicking device utilizing rotational force could induce glomerular cell dysfunction. Therefore, we investigate TG2's role in hypertension-induced hypoxia and its therapeutic potential by modulating signal transducer and activator of transcription 3 (STAT3) and HIF-1α interplay in mesangial cells.
Methods : An in vitro hypertensive platform was established using a pressurizing system. Mesangial cells were treated with 0.5 or 1 mM cysteamine, a TG2 inhibitor, for 24 or 48 hours under 4 mmHg pressure. TG2 expression and STAT3/HIF-1α crosstalk were analyzed through differentially expressed genes (DEGs), mRNA/protein profiling, and signaling pathways.
Results : Transcriptomic profiling revealed that TG2 inhibition suppressed RTK/PI3K/AKT and ROS-induced calcium signaling, upregulating the antioxidant enzyme Sod1. Subsequent KEGG analysis of 2561 downregulated genes ($p < 0.05$) identified key pathways, including HIF-1, apoptosis, and VEGF signaling. TG2 inhibition reduced STAT3-related genes (e.g., Il6st, Stat3) and HIF-1α signaling, with Akt3 linking STAT3 to HIF-1α activation and apoptosis. Cysteamine dose-dependently decreased pSTAT3, fibronectin, and HIF-1α pathway mRNA expression, reducing apoptosis (Annexin staining) while increasing oxidative degradation (ROS assay). Additionally, TG2 inhibition upregulated M-phase cell cycle genes and promoted wound healing by suppressing Cdkn1b (p27) via STAT3/HIF-1α coactivity.
Conclusions : These findings demonstrate that TG2 inhibition protects against hypertension-induced hypoxia in mesangial cells by suppressing the crosstalk between STAT3 and HIF-1α, offering a potential therapeutic approach for hypertensive nephropathy.