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Proteomic analysis of exosomes from human tubular epithelial cells with suppressed TG2 activity under fibrotic injury

Kyuhyeon Kim[1], Kyu Hong Kim[1], Ah Ram Suh[1], Jong Joo Moon[2], Dohyun Han[3], Yong Chul Kim[2], Dong Ki Kim[1], Yon Su Kim[1], Seung Hee Yang[1]
[1]Department of Kidney Research Institute, Seoul National University Hospital, Korea, Republic of
[2]Department of Internal Medicine-Nephrology, Seoul National University Hospital, Korea, Republic of
[3]Department of Biomedical Research Institute, Seoul National University Hospital, Korea, Republic of

Objectives: Transglutaminase 2 (TG2) is a multifunctional enzyme critical in tubolointerstitial fibrosis (TIF) pathogenesis. Mounting evidence suggest that renal cell exosomes contain stress-dependent biomolecules that can easily integrate into neighboring cells to drastically alter their cytophysiology. Hence, this study aims to elucidate the impact of TG2 on the exosomal proteome from human tubular epithelial cells (hTECs) under TGF-β induced fibrosis.

Methods: hTECs were cultured in appropriate cell medium (vehicle, control group) and were treated with 2 ng/mL TGF-β (TGF-β group), or 2 ng/mL TGF-β and 2 mM cysteamine (TGF-β + cysteamine group), a competitive inhibitor of TG2. Exosomes were isolated using PEG-based precipitation. After exosome protein extraction, differentially expressed proteins (DEPs) were quantified label-free using high-resolution orbitrap mass spectrometry.

Results: In total, 6449 exosomal proteins were quantified. We identified 4 significant overlapping DEPs that had positive fold change between the control and TGF-β group (19 DEPs), and negative fold change between the TGF-β and TGF-β + cysteamine group (15 DEPs). Canstatin, KCTD12, IGFBP5, and periostin followed such trend, suggesting that the suppression of TG2 decreased the expression of these proteins associated with anti-angiogenesis and tubule $GABA_B$ receptor stability. On the other hand, we identified 3 significant overlapping DEPs that had negative fold change between the control and TGF-β group (20 DEPs), and positive fold change between the TGF-β and TGF-β + cysteamine group (9 DEPs). Fibrillin-1, tenascin, and tPA followed such trend, implying that the decreased activity of TG2 increased the expression of these pro-angiogenic proteins. In addition, plasma TG2 levels positively correlate with CKD progression, possibly further complicating the interaction between these DEPs and TG2.

Conclusions: We identified the proteomic landscape of exosomal DEPs from hTECs in response to the suppression of TG2 under TGF-β induced fibrosis. Additional research is necessary to assess the interaction of these DEPs with TG2 in TIF pathogenesis.