

VISUALISATION OF THE ROLE OF FOXO/ β -CATENIN AGAINST TGF- β 's PROFIBROTIC CHANGES

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Aim: To visually examine the role of β -catenin/Foxo in tubular epithelial cells in protecting against TGF- β 's profibrotic changes.

Background: TGF- β is a key cytokine involved in tissue fibrosis. Activation of β -catenin/TCF is central to all TGF- β 's profibrotic signalling pathways. ICG-001, an inhibitor of β -catenin/TCF, shifts to β -catenin/ Foxo interaction which are known to enhance cell survival^(1, 2). We propose that profibrotic effects of TGF- β can be eliminated by promoting β -catenin/Foxo via inhibition of β -catenin/TCF interaction and thereby inhibiting profibrotic pathways.

Methods: Mouse tubular epithelial C1.1 cells were treated with TGF- β 1 (3ng/ml) with or without ICG-001 (5 μ M), β -catenin/TCF inhibitor. Profibrotic protein changes were examined by immunofluorescence. The β -catenin/Foxo and β -catenin/TCF interactions were examined by Duolink - Proximity Ligation Assay (PLA). Imaging was carried out using Olympus FV 1000 confocal laser scanning microscope and deconvolved images were used for analysis.

Results: Upregulated β -catenin/Foxo interaction and inhibition of β -catenin/TCF binding by ICG-001 in TGF- β treated C1.1 cells, as demonstrated by PLA showing their interaction *in situ* by confocal microscopy. The profibrotic expression of Vimentin were downregulated and E-cadherin expression were upregulated by ICG-001 and effects prevented by CRISPR/Cas9 knock out of Foxo1 gene in the TGF- β treated C1.1 cells as shown by microscopy imaging.

Discussions: These visualised results identify that β -catenin/Foxo plays protective role against TGF- β 's profibrotic activity by inhibiting β -catenin/TCF interaction via ICG-001. This may have broad therapeutic approach for fibrotic diseases.

References:

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- [2] S Hao, W He, Y Li et al. Targeted inhibition of beta-catenin/CBP signaling ameliorates renal interstitial fibrosis. J Am Soc Nephrol. 2011; 22(9):1642-53.