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TGF-β1 causes Nox4 dependent hypoxia induced apoptosis in human kidney proximal tubular epithelial cells

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Objectives:

Ischemia/reperfusion injury, resulting from hypoxic damage within a graft, is the leading cause of cell death and graft rejection. In this study, we investigated whether Nox4 have a great role in ischemic injury in a cellular model in which experimental hypoxia was induced using $CoCl_2$

Methods:

The ischemic injury induced in HK-2 cells by $CoCl_2$ was validated by reduced cell viability at different times and doses. Reverse transcription polymerase chain reaction for Nox4 and TGF-β1 was performed. Western blotting for Nox4 and Smad pathway were done. ROS production was detected using a DHE stain and Amplex red assay. HK-2 cells were transfected with siNox4 and pretreated with GKT137831(most specific Nox1/4 inhibitor). ELISA has been used to measure TGF-β1 levels. The effect of treatment with TGF-β1 type 1 tyrosine kinase inhibitor SB431542 on Nox4 expression was observed.

Results:

Expression of Nox4 in HK-2 cells significantly increased by hypoxic stimulation.TGF-β1 was secreted endogenously by hypoxic HK-2 cells. SB4315432 significantly inhibited Nox4 expression in HK-2 cells via Smad2/3 dependent cell signaling pathway. Silencing of Nox4 recued production of reactive oxygen species (ROS), downregulation of proinflammatory markers and reduced caspase 3/7 activity in hypoxic HK-2 cells. Pretreatment of GKT137831 replicated theses results.

Conclusions:

Hypoxia induces HK-2 cell apoptosis through the signaling pathway involving Nox4 dependent ROS generation and TGF-β1 via Smad pathway. Therapies targeting Nox4 may be effective against ischemia induced kidney injury.