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Stanniocalcin-1 Inhibits ER stress and renal fibrosis via an AMP-Activated Protein Kinase-Dependent Pathway in HK2 cells

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Background: The role of endoplasmic reticulum (ER) stress in the development of renal disease is a relatively recently described, and has been suggested as a cause for the fibrotic remodeling. Therefore, modulation of ER stress could be one of the possible therapeutic approaches to renal fibrosis. Stanniocalcin-1 (STC-1) is a multifunctional glycoprotein with antioxidant and anti-inflammatory properties and regulates AMP-activated protein kinase (AMPK) activity in the kidney. Activation of AMPK may reduce ER stress. The present study aimed to investigate the effects of STC-1 in ER stress and renal fibrosis in human renal proximal tubular (HK-2) cells.

Methods : HK2 cells pretreated with STC-1 (200 ng/ml) for 1 hours followed by treatment with TGF-β (10 ng/ml) for 16 hours. To determine whether effect of STC-1 mediated by AMPK activation, pharmacological inhibitor (compound C, 5 uM) pretreated with STC-1. The protein expression of ER stress markers and fibrosis markers was determined by semiquantitative immunoblotting. The level of reactive oxygen species (ROS) was determined by fluorescent microscopy immunofluorescence.

Results : TGF-β treatment induced upregulation of glucose-related protein (GRP)78 and C/EBP homologous protein (CHOP) and STC-1 pretreatment attenuated the rise in the GRP 79 and CHOP. TGF-β treatment also induced upregulation of fibronectin and alpha-smooth muscle actin (α-SMA) and STC-1 pretreatment attenuated the TGF-β induced upregulation of fibronectin and α-SMA. STC-1 pretreatment significantly blocked TGF-β induced downregulation of AMPK and decreased level of ROS via upregulate the uncoupling protein (UCP2). On the other hand, compound C pretreatment with STC-1 before TGF-β treatment abolished the activation of AMPK, diminished the upregulation of UCP2, and aggravated ER stress and fibrosis but did not affect STC-1 expression.

Conclusions : STC-1 Inhibits ER stress and renal fibrosis via an AMPK Pathway

and STC-1 may be a therapeutic target through reducing ER stress and renal fibrosis.

Keywords : Stanniocalcin; AMP-activated protein kinase; endoplasmic reticulum stress; fibrosis