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The NRF2-Heme oxygenase-1 system modulates autophagy and inhibits high glucose induced apoptosis in renal tubular epithelial cells

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Objectives : Autophagy is a tightly regulated process in which endog¬enous cellular proteins aggregate and damaged organelles are degraded by the lysosomal pathway. This process functions to maintain intracellular homeostasis and cell integrity. Its renoprotective role in several animal models, including those used for aging and acute kidney injury, has also been demonstrated. However, The role of autophagy in diabetic nephropathy remains a largely undetermined; thus, its underlying mecha¬nisms are presently unclear.

Methods : In present study, we evaluated the effects of high glucose concentrations on the induction of autophagy in the human renal tubular epithelial cell line, HK-2 cells. We also investigated the ability of Sulforaphane(SFN, nuclear factor E2-related factor 2 (Nrf2) inhibitor) to protect HK-2 cells against apoptosis induced by high glucose levels by targeting autophagy

Results : The HK-2 cells stimulated with a high concentration of glucose for 72h exhibited an increased expression of the autophagic markers, LC3-II and Beclin 1. The level of LC3-II and Beclin 1 in cells treated with SFN was decreased compared to control cells. The level of Caspase-3 activated in tubule cells cultured in high glucose medium was also decreased. One important NRF2 target gene, Heme oxygenase-1(HO-1) is known as a key molecule of NRF2 protective function. To examine whether HO-1 can modulate autophagy and apoptosis in tubule cells like SFN, HK-2 cells cultured in 250 mM glucose medium for 1-2 days were treated with Adneovirus-HO-1 gene for 1 day. HO-1 transfection decreased the expression of Beclin1 and LC3-II associated with a decrease in the expression Caspase-3 with HG for 1-2days compared with mock-treated cells. Reactive Oxygen Species(ROS) are important inducers of autophagy and apoptosis. As expected, an increase of ROS was observed in HK-2 cells cultured in 250 mM glucose medium for 1-3 days. A decrease of ROS was observed in cells treated with SFN.

Conclusions : HO-1 and autophagy are induced after high glucose injury to overcome to oxidative stress and serve as adaptive responses to prevent cell

death. NRF2-HO-1 overexpression is able to limit ROS generation and oxidative stress during high glucose injury and thereby significantly inhibiting autophagy and apoptosis. This study is the first study to show the effect of NRF2-HO-1 system on high glucose induced autophagy and apoptosis of tubule cells. Targeting NRF2-HO-1 as a modulator of autophagy may result in novel therapeutic intervention in diabetic nephropathy.

Keywords : sulforaphane, Heme oxygenase-1, apoptosis, high glucose, HK-2 cells