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PGC-1α attenuates hydrogen peroxide-induced apoptotic cell death by regulating the p38/GSK3β/Nrf-2 axis in HK-2 cells

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Objectives : Ischemia/reperfusion injury triggers acute kidney injury (AKI) by aggravating oxidative stress mediated mitochondria dysfunction. The peroxisome proliferator-activated receptor gamma coactivator 1α (PGC-1α) is a master player that regulates mitochondrial biogenesis and the antioxidant response. We postulated that PGC-1α functions as cytoprotective effector in renal cells and that its regulation mechanism is coordinated by nuclear factor erythroid 2-related factor 2 (Nrf-2).

Methods : In this study, to understand the effect and molecular mechanisms of PGC-1α, we developed an empty vector or PGC-1α-overexpressing stable cell lines in HK-2 cells (Mock or PGC-1α stable cells).

Results : PGC-1α overexpression increased the viability of cells affected by H2O2 mediated injury, protected against H2O2-mediated apoptotic events (e.g., increase of phosphor-p53 at Ser15, activation of caspase 3, and release of cytochrome C from the mitochondria to the cytosol), and inhibited reactive oxygen species accumulation in the cytosol and mitochondria as compared to that in Mock cells. The cytoprotective effect of PGC-1α was related to Nrf-2 upregulation, which was counteracted by Nrf-2-specific knockdown. Using inhibitor of p38, we found that regulation of the p38/glycogen synthase kinase 3β (GSK3β)/Nrf-2 axis was involved in the protective effects of PGC-1α.

Conclusions : Taken together, we suggest that PGC-1α protects human renal tubule cells from H2O2-mediated apoptotic injury by upregulating Nrf-2 via GSK3β inactivation mediated by activated p38.

Keywords : PGC-1a, apoptosis, Nrf-2, reactive oxygen species