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Ciglitazone Induces Apoptosis via Caspase-independent Mechanism in Renal Epithelial Cell: Involvement of p38-dependent AIF Nuclear Translocation

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Purpose : Peroxisome proliferators-activated receptor γ (PPAR γ) ligands have been reported to induce apoptosis in a variety of cell types including renal proximal epithelial cells. However, the molecular mechanism is poorly understood. This study was therefore undertaken to investigate the mechanisms by which PPAR γ ligands induce apoptosis in renal epithelial cells.

Methods : Opossum kidney (OK) cells, an established renal epithelial cell line, were exposed to ciglitazone, a synthetic PPAR ligand. Cell viability was measured by MTT assay and apoptosis was determined by nuclear staining and cell cycle analysis. Mitochondrial membrane potential was measured using fluorescence dye. Activation of kinases and release of cytochrome c and AIF were detected by immunoblotting. Caspase-3 activity was determined by using assay kit.

Results : Ciglitazone treatment induced cell death in a dose- and time-dependent manner and the cell death was largely attributed to apoptosis. Ciglitazone caused a transient activation of ERK and sustained activation of p38 and these effects were blocked by U0126, an inhibitor of MEK, and SB203580, an inhibitor of p38, respectively. Ciglitazone-mediated cell death was attenuated by SB203580 but not by U0126, indicating that p38 activation is involved in the ciglitazone-induced cell death. Ciglitazone induced mitochondrial membrane depolarization, cytochrome c release, and AIF nuclear translocation. These effects were prevented by SB203580. Although ciglitazone induced caspase-3 activation, the treatment of cells with the caspase-3 inhibitor DEVD-CHO did not prevent the ciglitazone- mediated cell death.

Conclusion : These results suggest that ciglitazone induces caspase-independent apoptosis through p38-dependent AIF nuclear translocation in OK renal epithelial cells. Taken together with our previous data, we assume that PPAR γ ligands exert a direct cytotoxic effect in renal epithelial cells.