C34

Modulation of Cisplatin-induced Apoptosis by MAPK Signalling in Renal Proximal Epithelial Cells

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Although apoptotic cell death has been suggested to play an important role in cisplatin-induced acute renal failure, the precise mechanism by which cisplatin induces apoptosis is not well understood. In the present study, we determined the roles of mitogen-activated protein kinase (MAPK) signalling pathways and involvement of reactive oxygen species in regulating cisplatin-induced renal cell apoptosis. Primary cultured rabbit proximal tubules were exposed to cisplatin (50 uM) or H2O2 (0.3 mM) for various times. These compounds produced time-dependent apoptosis, which was accompanied by mitochondrial dysfunction. Cisplatin treatment resulted in activation of ERK and JNK, but not p38. PD98059, a chemical inhibitor of ERK signalling pathway, prevented apoptosis and mitochondrial dysfunction induced by cisplatin. But the inhibitors of JNK and p38 were not effective. Inhibitors of JNK, ERK, and p38 prevented partially H2O2-induced apoptosis, but not mitochondrial dysfunction. Pretreatment of H2O2 scavengers (catalase and pyruvate) did not affect cisplatin-induced apoptosis. Cisplatin treatment increased cytochrome c release and caspase-3 activity and its effect was blocked by the ERK inhibitor. These results demonstrate that ERK activation plays an active role in mediating cisplatin-induced apoptosis of renal epithelial cells and functions upstream of caspase activation to initiate the apoptotic signal and the underlying mechanism of cisplatin-induced apoptosis is different from that of H2O2.

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