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Mitochondrial NADP+-dependent isocitrate dehydrogenase (IDH2) for the treatment of cisplatin-induced nephrotoxicity

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Objectives : Mitochondrial NADP+-dependent isocitrate dehydrogenase (IDH2) is a major producer of NADPH, which is a critical factor for the maintenance of glutathione (GSH) redox balance in the mitochondria. Cisplatin is one of the most common anticancer drugs. However, its nephrotoxicity limits to use. With underlying mechanisms of cisplatin-induced nephrotoxicity is a reduction of intracellular levels of glutathione by formation of cisplatin-GSH complex associated. Here, we investigated the role of IDH2 in cisplatin-induced nephrotoxicity.

Methods : IDH2 gene-deleted (IDH2-/-) or wild type (IDH2+/+) mice were administrated intraperitoneally cisplatin (20 mg/kg body weight). Some mice were treated Mito-TEMPO, a mitochondria-specific antioxidant, before cisplatin injection.

Results : IDH2 deficiency aggravated cisplatin-induced renal functional and morphological impairments. Mito-TEMPO reduced those cisplatin-induced renal functional and morphological impairments in both IDH2-/- and IDH2+/+ mice. Cisplatin reduced NADPH levels in the kidney. This cisplatin-induced reduction of NADPH levels were greater in the IDH2-/- mouse kidneys than IDH2+/+ mouse kidneys. Cisplatin increased hydrogen peroxide, lipid peroxidation and mitochondrial GSSG/total GSH ratio. These increases were greater in the IDH2-/- mouse kidneys than IDH2+/+ mouse kidneys. Mito-TEMPO reduced those cisplatin-induced reduction of NADPH, and increases of hydrogen peroxide, lipid peroxidation and GSSG/total GSH ratio both IDH2-/- and IDH2+/+ mouse kidneys. In addition, mitochondrial fragmentation and renal cell death after cisplatin injection were greater in the IDH2-/- than IDH2+/+ mouse kidneys. Mito-TEMPO reduced those cisplatin-induced mitochondrial oxidative stress and cell death in the both IDH2-/- and IDH2+/+ mouse kidneys.

Conclusions : IDH2 deficiency aggravates cisplatin-induced nephrotoxicity by increasing mitochondrial oxidative stress, suggesting that IDH2 plays a crucial role in the pathogenesis of cisplatin-induced acute kidney injury (AKI).

Keywords : mitochondria, isocitrate dehydrogenase, oxidative stress, cisplatin, neprotoxicity