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MEK Inhibitor U0126 Ameliorates Cisplatin Induced Renal Injury by Decreasing Inflammation and Apoptosis in Mice

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Background : Although inflammation and apoptosis is known to play important roles in cisplatin nephrotoxicity, the exact intracellular signaling pathways are not well understood. Recent report that ERK 1/2 pathway mediates cisplatin induced caspase activation and apoptosis in cultured renal tubular cells led us to investigate the effect of MEK 1 inhibitor, an immediate upstream of ERK 1/2 in cisplatin induced ARF in mice.

Methods : The effect of MEK 1 inhibition on kidney TNF-α gene expression, inflammation, the activation of tissue caspases and apoptosis were examined in addition to its effects on renal function and histology in cisplatin induced ARF in mice.

Results : Pretreatment of MEK inhibitor, U0126 decreased ERK 1/2 phosphorylation following cisplatin administration with significant functional and histological protection. This beneficial effect was accompanied by decrease in TNF-α gene expression level and inflammation, as well as in caspase 3 activity and apoptosis.

Conclusion : These data provide evidence that ERK 1/2 pathway functions as an upstream signal for TNF-α mediated inflammation and caspase 3 mediated apoptosis in cisplatin induced ARF in mice and suggest that ERK 1/2 pathway can be a novel therapeutic target in cisplatin nephrotoxicity.