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Omega-3 Polyunsaturated Fatty Acids Attenuate Cisplatin-induced Nephrotoxicity via Enhancement of Autophagy Flux

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Objectives: Cisplatin is one of the most effective chemotherapeutic agents used in patients with solid tumors. Omega-3 polyunsaturated fatty acids (PUFAs) enhance induction of autophagy in various tissues. Autophagy is a highly conserved pathway that has protective effects against various renal injuries including ischemic-reperfusion injury and nephrotoxic agents. We investigated the role of omega-3 PUFA-induced autophagy flux in attenuating CIN.

Methods: Male C57BL/6 mice were divided into four groups: control, control plus omega-3 PUFAs, cisplatin, and cisplatin plus omega-3 PUFAs. Real time PCR, western blot and immunohistochemistry for molecular study and H&E stain and PAS stain for histologic examination were performed. Human kidney (HK)-2, an immortalized proximal tubule epithelial cell line, cells were incubated with cisplatin (20 μg/mL). Bafilomycin A1 treatment (50 nM) was used to suppress autophagy flux in HK-2 cells.

Results: Pretreatment with omega-3 PUFAs at 24 h before cisplatin injection decreased blood urea nitrogen and serum creatinine levels. Renal damage by cisplatin was attenuated by omega-3 PUFA treatment through amelioration of oxidative stress, reduction in inflammatory cell accumulation, and decreased tubular cell apoptosis. Additionally, cisplatin significantly increased the levels of LC3, ATG7, and p62 in mice. Omega-3 PUFAs significantly increased the levels of LC3 and ATG7 and decreased the levels of p62 in cisplatin-treated mice at 96 h. Moreover, in cultured HK-2 cells, cisplatin treatment resulted in significantly increased levels of LC3, p-AMPK, and p62, whereas EPA and DHA treatment significantly increased the LC3II/LC3I ratio and decreased TUNEL-positive cells. Administration of bafilomycin A1, an inhibitor of fusion of autophagosomes with lysosomes, significantly increased PARP and TUNEL-positive cells and decreased cell viability in cisplatin plus omega-3-treated cells.

Conclusions: In conclusion, omega-3 PUFA-induced autophagy may play a renoprotective role in cisplatin-induced nephrotoxicity, which may be mediated via an increase in autophagy flux in renal tubular cells