The Role of NF-E2 in Regulating Chemotherapeutic Metabolite Acrolein-Induced Nephrotoxicity

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Cisplatin cures cancers but increases mortality due to its nephrotoxicity. My in vitro studies led to the hypothesis that mice treated with acrolein or cisplatin will promote kidney fibrosis by modulating NF-E2 expression. C57BL/6 mice were exposed to filtered air or acrolein (1.0 ppm; 12-weeks). Acrolein decreased NF-E2 expression, enhanced CTGF expression and induced renal cell apoptosis. Sirius-red staining demonstrated enhanced collagen deposition, and H&E staining demonstrated greater cellularity and acellular renal tubules in acrolein treated kidneys, suggestive of inflammation, fibrosis and damage. Cisplatin and its metabolite acrolein, modulate sodium-phosphate co-transport in renal cells, of which sodium-hydrogen exchange regulatory cofactor-1 (NHERF-1) is a key mediator. Thus, effects of cisplatin on WT and NHERF-1-knock-out (KO-NHERF-1) mice kidneys were examined. Cisplatin (20 mg/kg body weight; 72 h) decreased NF-E2 expression, increased CTGF expression and increased renal cell apoptosis. Renal NF-E2 expression decreased in KO-NHERF-1 mice, which decreased further after cisplatin treatment, while cleaved-Cas-3 and CTGF expression increased further. Cisplatin treatment resulted in loss of NF-E2 expression from the renal brush-border membrane in WT mice kidneys which was decreased further in cisplatin treated KO-NHERF-1 mice. Interestingly, NF-E2 was detected in the plasma of KO-NHERF-1 mice which was enhanced after cisplatin treatment. NF-E2 could serve as a biomarker of AKI alleviating need for biopsies. The two-pronged approach increasing intracellular NF-E2 expression, while blocking extracellular actions of NF-E2, will provide new therapies to treat AKI halting its progression to ESRD, in addition to potentially blocking cisplatin’s nephrotoxic effects.

Awards Won:

Second Award of $2,000