

ALL-TRANS-RETINOIC ACID AFFORDS CYTOPROTECTION AGAINST REACTIVE OXYGEN SPECIES-INDUCED RENAL INJURY. Sapiro, J.M., Lord-Garcia, J.L., Jia Z, Gallegos, A.G., Canatsey, R.D., Monks, T.J., and Lau, S.S. Southwest Environmental Health Sciences Center, Dept of Pharm/Toxicol., College of Pharmacy, University of Arizona, Tucson, AZ.

ischemia reperfusion injury (IRI) and chemical-induced nephrotoxicity are major etiologies of acute kidney injury during which reactive oxygen species are released. 11-Deoxy-16,16-dimethyl-prostaglandin E₂ (DDM-PGE₂) protects against 2,3,5-tris-(glutathion-S-yl)hydroquinone (TGHQ) induced, ROS-dependent cell death in LLC-PK₁ cells. Immunoblotting and proteomics analyses revealed that DDM-PGE₂ cytoprotection was associated with a time-dependent increase in retinol binding protein (RBP) synthesis, suggesting that retinoid signaling is engaged during this process. Pharmacological manipulations that abolished the ability of DDM-PGE₂ to induce RBP abrogated its cytoprotective effects, further indicating that RBP is necessary for DDM-PGE₂ mediated cytoprotection. While both all-trans-retinoic acid (ATRA) and 9-cis-retinoic acid (9-cisRA) possess biological activity, pretreatment with ATRA, but not 9-cisRA, afforded cytoprotection in LLC-PK₁ cells following TGHQ treatment. Moreover, the cytoprotective kinetics of ATRA and DDM-PGE₂ were identical, with maximal RBP induction and cytoprotection occurring at 12 and 24 hours, respectively. Chemical hypoxia was established in LLC-PK₁ cells to recapitulate IRI conditions by exposing cells to 0.1 or 1 μM antimycin A for 4 hours in glucose free media. Consistent with the effects of ATRA on TGHQ-induced cytotoxicity, ATRA pretreatment completely protected hypoxic cells from cytotoxicity as assessed by a mitochondrial dehydrogenase enzyme activity assay (MTT). Moreover, ATRA significantly reduced 8-oxo-deoxyguanosine levels in human kidney HK2 cells after TGHQ challenge. Collectively, these data reveal that ATRA protects renal cell injury, at least in part, *via* suppression of ROS-mediated oxidative damage. Therefore, ATRA may provide an effective therapeutic strategy in chemical-induced renal injury or pathological conditions where ROS contribute to the disease progression. (ES006694, ES016578).

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