Protection against proximal tubule necrosis with 11-deoxy-16,16-dimethyl prostaglandin E₂ in vitro

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ACUTE RENAL FAILURE IS A DEVASTATING clinical problem with limited preventive modalities. Acute renal failure frequently occurs after ischemic-reperfusion injury, toxic nephropathy, and sepsis (2, 5, 12, 13, 19). The onset of acute renal failure is frequently associated with many other life-threatening complications, including sepsis and multiorgan failure (2, 3, 7). Unfortunately, the high mortality and morbidity of acute renal failure have changed little over the past 30 years (1–3). Therefore, ways to limit acute renal failure and renal cell death are of great clinical significance. Although many studies have shown promise in vivo and in vitro, translation into successful clinical therapeutics has been limited.

Renal cell death occurs via two distinct morphological and biochemical mechanisms: necrosis and apoptosis (11, 17). Whether apoptotic or necrotic cell death occurs depends on the degree of cellular injury (e.g., severe injury leads to necrosis, whereas moderate injury favors apoptosis) and the type of cell injury (e.g., TNF-α or FasL activation of the death receptor leads to apoptosis, whereas severe ATP depletion after ischemic injury leads to necrotic death) (15, 16). Classic necrosis is a passive, non-energy-dependent process characterized by rapid cell swelling (oncosis), mitochondrial changes, and eventual cell lysis and release of the cytoplasmic contents into the interstitial surroundings, causing inflammation and even more tissue damage. In contrast, apoptosis requires energy for its programmed execution and, in most cases, initiates little inflammation.

Prostaglandins produce diverse physiological effects (e.g., modulation of vascular tone, cytotoxicity, and differentiation) in a cell-specific manner (3, 18). Several prostaglandin analogs show protective effects in several organs, including the kidney. Prostaglandin E₂ is a major mammalian metabolite of arachidonic acid in the kidney and produces renal protection in vivo and in vitro (14).

In this issue of American Journal of Physiology-Renal Physiology, the elegant report by Jia et al. (7a) from Dr. Serrine Lau’s laboratory further extends their series of studies demonstrating the cytoprotective effects of 11-deoxy-16, 16-dimethyl prostaglandin E₂ (DDM-PGE₂; an analog of PGE₂) against necrosis induced by 2,3,5-tris(glutathionyl-S-yl) hydroquinone (TGHQ; a selective nephrotoxic metabolite of hydroquinone). The current study methodically demonstrates that DDM-PGE₂ not only protects against TGHQ necrosis but also protects against H₂O₂- and iodoacetamide-induced necrosis. Interestingly, DDM-PGE₂ did not protect against TNF-α-, mercuric chloride-, or cisplatin-induced apoptosis. They have sequentially characterized the signaling pathways of renal proximal tubule (LLC-PK₁ cells) protection with DDM-PGE₂ in previous studies. They showed that DDM-PGE₂ protects against necrosis via thromboxane receptor activation through a PKC signal transduction pathway coupled to NF-κB (20). They also showed the upregulation of several potential cytoprotective proteins, including glucose-regulated protein 78 (Grp78). Grp78, a member of the heat shock protein (HSP) 70 family, is an ubiquitous and major endoplasmic reticulum (ER) chaperone protein with a major role in calcium storage and handling, protein folding, and assembly of nascent proteins (4, 9). After renal injury, increased expression of stress-inducible Grp78 may accelerate the folding and assembly of disordered proteins and may enhance renal cell recovery. In the current study, they examined LLC-PK₁ cells lacking Grp78 to test the hypothesis that Grp78 is critical in mediating cytoprotection induced by DDM-PGE₂. p38 MAPK and HSP27 signaling were also abrogated in this Grp78-lacking cell line, implicating these signaling pathways in cellular protective mechanisms.

Constitutively expressed and phosphorylated forms of HSP27 confer significantly increased cellular resistance to heat shock, oxidative stress, and a number of cytotoxic agents (1, 7). These small HSP chaperones prevent unfolded proteins from irreversible aggregation, regulate apoptosis, and stabilize the actin cytoskeleton. Increased stabilization of the actin cytoskeleton can confer resistance against stress-induced microfilament disorganization and protect against oxidant injury (8). p38 MAPK phosphorylates HSP27 and is involved in hydrogen peroxide-mediated oxidant preconditioning and upregulation of heme-oxygenase-1, a powerful protector of cell viability in many types of injury including those of the kidney (6, 10).

Protein expression analysis by proteomic technologies will no doubt deepen our understanding of adaptive and protective cellular mechanisms of acute renal failure. Jia et al. (7a) employed insightful proteomic techniques to probe answers to a highly clinically relevant question. They utilized two-dimensional gel electrophoresis coupled to matrix-assisted laser desorption ionization-time of flight analysis to further determine alterations of protein expression after DDM-PGE₂ treatment. They show that retinol binding protein, myosin light chain, and HSP27 upregulation after DDM-PGE₂ treatment were dependent on the presence of Grp78.

Selective protection by DDM-PGE₂ against necrosis but not against apoptosis is an interesting and significant finding, as necrosis is the major mechanism of renal tubular cell death in acute renal failure especially after ischemia and reperfusion injury. The protection against necrosis but not apoptosis further confirms differential pathways of these two types of cell death. It remains to be determined whether DDM-PGE₂-induced and Grp78-, HSP27-, p38 MAPK-modulated protection occurs in vivo and whether other facets of renal diseases such as acute and chronic inflammatory process are affected by these pathways. Moreover, the question remains as to whether the cytoprotective pathways of PGE₂ thromboxane receptor modulation are specific to the kidney.
ACKNOWLEDGMENTS

This work was supported by the Intramural Research Fund of the Department of Anesthesiology at Columbia University and by National Institute of Diabetes and Digestive and Kidney Diseases Grant ROI-DK-58547.

REFERENCES


