TABLE 333e-3 FACTORS AND PROCESSES IMPLICATED AS PROTECTIVE MEDIATORS OF ISCHEMIC PRECONDITIONING

Adenosine
AKT (protein kinase B)
Antioxidants
Autophagy
Bradykinin
Decrease in genes regulating inflammation (cytokine synthesis, leukocyte chemotaxis, adhesion, exocytosis, innate immune signaling pathways)
Extracellular signal-related kinase (ERK)
Heat shock proteins
Hypoxia-inducible factors (HIFs)
JAK-STAT pathway
Jun N-terminal kinase (JNK)
Mitochondrial ATP-sensitive potassium channel (K^+ ATP channel)
Mitochondrial connexin 43
Nitric oxide
Opioids
Protein kinase C (PKC)
Sirtuin activity (SIRT1)

processes, most of which have been identified in the heart, involve multiple signaling pathways that affect decreased apoptosis, inhibition of mitochondrial permeability transition pores, activation of survival pathways, autophagy, and other pathways involved in reducing energy consumption or reactive oxygen production. In a study from our laboratory, inducible NO synthase was found to be an important contributor to the adaptive response to kidney injury, which results in protection against a subsequent insult. Identification of the responsible protective factor(s) mediating the advantageous adaptive response to remote ischemic preconditioning would provide a therapeutic approach for prevention of acute kidney injury or facilitation of a protective adaptation to kidney injury.

ADAPTIVE RESPONSE OF THE KIDNEY TO ACUTE INJURY

Adaptive Response to Hypoxic Injury Hypoxia plays a role in ischemic, septic, and toxic acute kidney injury. Many conditions result in a global or regional impairment of oxygen delivery. This is particularly important in the outer medulla where there is baseline reduced oxygen tension and a complex capillary network that, by its nature, is susceptible to interruption. In addition, the S3 segment of the proximal tubule is very dependent on oxidative metabolism, whereas the medullary thick ascending limb of the nephron that also traverses the outer medulla can adapt to hypoxia by converting to glycolysis as a primary energy source.

One proposed adaptive response to hypoxia is a reduction in glomerular filtration with consequent reduction in "work" requirement for reabsorption of solutes by the tubule. This was termed *acute renal success* by Thurau many years ago. The importance of this has been questioned, however, because there is no significant reduction in renal oxygen consumption in post–cardiac surgery patients with acute kidney injury in the setting of reduced GFR and renal blood flow.

If hypoxia or other influences, such as toxins, damage the proximal tubule and interfere with reabsorption of sodium and water, it is important that the kidney adapt in such a way so that there is not a large natriuresis that might compromise intravascular volume and blood pressure. This is accomplished, at least in part, by tubuloglomerular feedback (TGF). The increased distal delivery of salt and water results in a homeostatic adaptation to decrease glomerular filtration and hence decrease tubular delivery of salt and water through the glomerulus and reduce the delivery to the distal nephron. This adaptive response to acute injury is different from the role of TGF in CKD, as we have discussed previously in this chapter. In chronic disease with reduced nephron function, there is a steady-state need to increase excretion of sodium, whereas with acute injury, excretion of sodium is reduced.

Many genes are activated by hypoxia that are adaptive in serving to protect the cell and organ. With hypoxia, hypoxia-inducible factor (HIF) 1α rapidly accumulates due to the inhibition of the HIF prolyl-hydroxylases, which normally promote HIF1α proteasomal degradation. HIF1α then dimerizes with HIF1β and the dimer moves to the nucleus, where it upregulates a number of genes whose protein products are involved in energy metabolism, angiogenesis, and apoptosis, enhancing oxygen delivery and metabolic adaptation to hypoxia. This takes the form of a complex interplay among factors that regulate perfusion, cellular redox state, and mitochondrial function. For example, upregulation of NO production by sepsis results in vasodilatation and reduction in mitochondrial respiration and oxygen consumption. In addition, HIF1 activation in endothelial cells may be important for adaptive preservation of the microvasculature during and after hypoxia. Better understanding of the role that the HIFs play in protective adaptation has led to an aggressive development of HIF prolyl-hydroxylase inhibitors by biotechnology and pharmaceutical companies for clinical use.

Adaptive Response to Toxic Injury Specific to the Proximal Tubule One can model an acute kidney injury by genetically inserting a Simian diphtheria toxin (DT) receptor into the proximal tubule and then adding either a single dose of DT or multiple doses of the toxin. Repair of the kidney after a single dose of DT can be shown to be adaptive with few longer term sequelae. There is a very robust proliferative response of the proximal tubule cells to replace the cells that die as a result of the DT. Ultimately the inflammation resolves, and there is little, if any, residual interstitial inflammation, expansion, or matrix deposition.

Maladaptive Response of the Kidney to Acute Injury By contrast to the above adaptive repair that occurs after a single insult, after three doses of DT administered at weekly intervals, there is maladaptive repair with development over time of a chronic interstitial infiltrate, increased myofibroblast proliferation, tubulointerstitial fibrosis, and tubular atrophy, as well as an increase in serum creatinine (0.6 ± 0.1 mg/dL vs 0.18 ± 0.02 mg/dL in control mice) by week 5, 2 weeks after the last dose in the thrice-treated animals. There is a dramatic increase in the number of interstitial cells that expressed the platelet-derived growth factor receptor β (pericytes/perivascular fibroblasts), αSMA (myofibroblasts), FSP-1/S100A4 (fibroblast specific protein-1), and F4/80 (macrophages). In addition, there is loss of endothelial cells, interstitial capillaries, and development of focal global and segmental glomerulosclerosis.

It has become increasingly recognized as a result of large epidemiologic studies that even mild forms of acute kidney injury are associated with adverse short- and long-term outcomes including onset or progression of CKD and more rapid progression to end-stage kidney disease. Experimental models in animals, such as the DT model described above, provide pathophysiologic explanations for how the effects of acute injury can lead to chronic inflammation, vascular rarefaction, tubular cell atrophy, interstitial fibrosis, and glomerulosclerosis. Recurrent specific tubular injury leads to a pattern very typical of CKD in humans: tubular atrophy, interstitial chronic inflammation and fibrosis, vascular rarefaction, and glomerulosclerosis. The mechanisms involved in the development of glomerulosclerosis evoked by primary tubular injury may be multifactorial. Damage to nephron segments may lead to sluffing of cells into the lumen and to tubular obstruction. Progressive narrowing of the early proximal tubule near the glomerular tuft can lead to a sclerotic atubular glomerulus like those that are seen with ureteral obstruction. There may be paracrine signaling from injured and regenerating/undifferentiated epithelium to directly impact the glomerulus. Alternatively, a progressive tubulointerstitial reaction originating around atrophic and undifferentiated tubules may directly encroach upon the glomerular tuft. The loss of interstitial capillaries may lead to a progressive reduction of glomerular blood flow with ischemia to the glomerulus and to the kidney regions perfused by the postglomerular capillaries. This speaks to the fact that primary tubular injury can trigger a response that adversely affects multiple compartments of the kidney and leads to a positive feedback process, involving loss of capillaries, glomerulosclerosis, persistent ischemia, tubular atrophy, increased fibrosis, and ultimately kidney failure.