Update on Mechanisms of Ischemic Acute Kidney Injury

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Acute renal failure (ARF), classically defined as an abrupt decrease in kidney function that leads to accumulation of nitrogenous wastes such as blood urea nitrogen and creatinine, is a common clinical problem with increasing incidence, serious consequences, unsatisfactory therapeutic options, and an enormous financial burden to society (1–5). ARF may be classified as prerenal (functional response of structurally normal kidneys to hypoperfusion), intrinsic renal (involving structural damage to the renal parenchyma), and postrenal (urinary tract obstruction). This review focuses on intrinsic ARF, which has emerged as the most common and serious subtype in hospitalized patients and can be associated pathologically with acute tubular necrosis (ATN). Consequently, it still is common clinical practice to use the terms intrinsic ARF and ATN interchangeably. Despite decades of pioneering basic research and important technical advances in clinical care, the prognosis for patients with intrinsic ARF remains poor, with a mortality rate of 40 to 80% in the intensive care setting. Two major problems have plagued the field and hindered progress. First, well over 20 definitions for ARF have been used in published studies, ranging from dialysis requirement to subtle increases in serum creatinine (6). In an attempt to standardize the definition and reflect the entire spectrum of the condition, the term acute kidney injury (AKI) has been proposed (4). AKI refers to a complex disorder that comprises multiple causative factors and occurs in a variety of settings with varied clinical manifestations that range from a minimal but sustained elevation in serum creatinine to anuric renal failure. Prerenal azotemia and other fully reversible causes of acute renal insufficiency are specifically excluded from the spectrum of AKI. An inherent shortcoming of this term is the continued reliance on serum creatinine measurements, and the definition of AKI undoubtedly will undergo enhancements as novel early biomarkers for the identification of ARF before the rise in serum creatinine come to light (7). This review avoids the term ATN and uses the expressions AKI and intrinsic ARF transposably. The second problem is an incomplete understanding of the cellular and molecular mechanisms that underlie AKI. This review updates the reader on current advances in basic and translational research that hold promise in human ischemic AKI. Classic concepts are mentioned briefly as founding principles but expanded on only if contemporary findings substantiate or refute them. The reader is referred to recent publications that address the mechanisms that underlie other causes of intrinsic AKI, such as sepsis (8) and nephrotoxins (9). However, from the clinical viewpoint, it is acknowledged that AKI is frequently multifactorial, with concomitant ischemic, nephrotoxic, and septic components and with overlapping pathogenetic mechanisms.

Alterations in Morphology

If function depends on form, then it follows that mechanisms that are invoked to elucidate kidney dysfunction in AKI also must explain the morphologic alterations. In this regard, the term ATN is a misnomer, because frank tubule cell necrosis is rarely encountered in human ARF. This fact has once again been driven home by careful examination of protocol kidney biopsies that are obtained soon after deceased-donor transplantation (10), which represents a predictable model for ischemic AKI (11). Prominent morphologic features of ischemic AKI in humans include effacement and loss of proximal tubule brush border, patchy loss of tubule cells, focal areas of proximal tubular dilation and distal tubular casts, and areas of cellular regeneration (12). Necrosis is inconspicuous and restricted to the highly susceptible outer medullary regions. The glomeruli are usually unimpressive, unless a primary glomerular disease had caused the ARF. This apparent disparity between the severe impairment of renal function and the relatively subtle histologic changes in AKI traditionally has been bothersome. More recently, however, reconciliation has been forthcoming from a consistent finding of apoptotic cell death in both distal and proximal tubules in both ischemic and nephrotoxic forms of human AKI (9,10). In addition, a great deal of attention has been directed toward the peritubular capillaries, which display a striking vascular congestion, endothelial damage, and leukocyte accumulation (13–15). The mechanisms that underlie these newly emphasized morphologic findings and their implications for the ensuing profound renal dysfunction are detailed herein.

Alterations in Hemodynamics

An intense and persistent renal vasoconstriction that reduces overall kidney blood flow to approximately 50% of normal has long been considered a hallmark of intrinsic ARF, prompting the previous designation of "vasomotor nephropathy" (1). As if

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to add insult to injury, the postischemic kidney also displays peculiar regional alterations in blood flow patterns. Notably, there is marked congestion and hypoperfusion of the outer medulla that persist even though cortical blood flow improves during reperfusion after an ischemic insult (13–15). Even under normal conditions, the medullary region subsists on a hypoxic precipice as a result of low blood flow and countercurrent exchange of oxygen, although paradoxically housing nephron segments with very high energy requirements (*e.g.*, the S3 segment of the proximal tubule and the medullary thick ascending limb of Henle's loop). The characteristic postischemic congestion worsens the relative hypoxia, leading to prolonged cellular injury and cell death in these predisposed tubule segments. Sophisticated imaging techniques have documented these changes in regional renal blood flow in animals and validated them in human AKI (16). Mechanisms that underlie these hemodynamic alterations have begun to surface, and they relate primarily to endothelial cell injury (13–17). This results in a local imbalance of vasoactive substances, with enhanced release of vasoconstrictors such as endothelin and decreased abundance of vasodilators such as endothelium-derived nitric oxide (NO) (2). Endothelin receptor antagonists ameliorate ischemic AKI in animals (18), but human data are lacking. Similarly, both carbon monoxide and carbon monoxide–releasing compounds are protective in animal models of ischemic AKI (19,20), likely through vasodilation and preservation of medullary blood flow, but have not been tested in humans. All things considered, these macrohemodynamic abnormalities cannot account fully for the profound loss of renal function, and several human trials of vasodilators such as dopamine have failed to demonstrate improvement in GFR in established ARF despite augmentation of total renal blood flow (21). However, microvascular alterations now are recognized to play a major role, as discussed next.

Alterations in Tubule Dynamics

Documented derangements in tubule dynamics include obstruction, backleak, and activation of tubuloglomerular feedback. The consistent histologic findings of proximal tubular dilation and distal tubular casts in human biopsies indicate that obstruction to tubular fluid flow certainly occurs in ischemic AKI. The intraluminal casts stain strongly for Tamm-Horsfall protein, which normally is secreted by the thick ascending limb as a monomer. Conversion into an obstructing gel-like polymer is enhanced by the increased luminal sodium concentration that typically is encountered in the distal tubule in AKI (22). This provides an ideal environment for cast formation along with desquamated tubule cells and brush border membranes. However, it is unlikely that obstruction alone can account for the intense dysfunction, because human studies that used forced diuresis with furosemide (23) or mannitol (24) did not have an impact on the survival and renal recovery rate of patients with established ARF. Similarly, although movement of the glomerular filtrate back into the circulation has been shown to occur, this accounts for only a very minor component of the decrease in GFR in human ARF (2). Finally, a role for activation of tubuloglomerular feedback has been proposed on the basis of human studies (25). The increased delivery of sodium chloride to the macula densa as a result of cellular abnormalities in the ischemic proximal tubule would be expected to induce afferent arteriolar constriction *via* A1 adenosine receptor (A1AR) activation and thereby decrease GFR (26). However, recent studies have shown that a knockout of the A1AR resulted in a paradoxic worsening of ischemic renal injury, and exogenous activation of A1AR was protective (27). Therefore, tubuloglomerular feedback activation after ischemic injury indeed may represent a beneficial phenomenon that limits wasteful delivery of ions and solutes to the damaged proximal tubules, thereby reducing the demand for ATP-dependent reabsorptive processes. Any salutary effect of exogenous A1AR activation in human AKI remains to be determined.

Alterations in Tubule Cell Metabolism

A profound reduction in intracellular ATP content invariably occurs early after ischemic renal injury, which sets in motion a number of critical metabolic consequences in tubule cells (28). These events are detailed next, and their interrelationship is illustrated in Figure 1.

Alterations in Adenine Nucleotide Metabolism

Oxygen deprivation leads to a rapid degradation of ATP to ADP and AMP. With prolonged ischemia, AMP is metabolized further to adenine nucleotides and to hypoxanthine. Hypoxanthine accumulation contributes to generation of reactive oxygen molecules by mechanisms explained below. Adenine nucleotides freely diffuse out of cells, and their depletion precludes re-synthesis of intracellular ATP during reperfusion. However, although provision of exogenous adenine nucleotides or thyroxine (which stimulates mitochondrial ATP regeneration) can mitigate ischemic AKI in animal models, this approach has yielded disappointing results in human ARF (29,30).

Alterations in Intracellular Calcium

ATP depletion leads to impaired calcium sequestration within the endoplasmic reticulum as well as diminished extrusion of cytosolic calcium into the extracellular space, resulting in the well-documented rise in free intracellular calcium after AKI. Potential downstream complications include activation of proteases and phospholipases and cytoskeletal degradation (28). However, the increased cytosolic calcium dramatically induces calcium-binding proteins such as annexin A2 and S100A6, which play an important role in the cell proliferation during recovery from AKI in animal models (31). Reflective of this contradiction, a recent meta-analysis showed that calcium channel blockers may provide some protection from renal injury in the transplant setting (32), but evidence for their efficacy in other forms of human AKI is lacking.

Generation of Reactive Oxygen Molecules

There now is substantial evidence for the role of reactive oxygen species in the pathogenesis of AKI. During reperfusion, the conversion of accumulated hypoxanthine to xanthine (catalyzed by xanthine oxidase formed from xanthine dehydrogenase either as a result of proteolytic conversion or as a result of

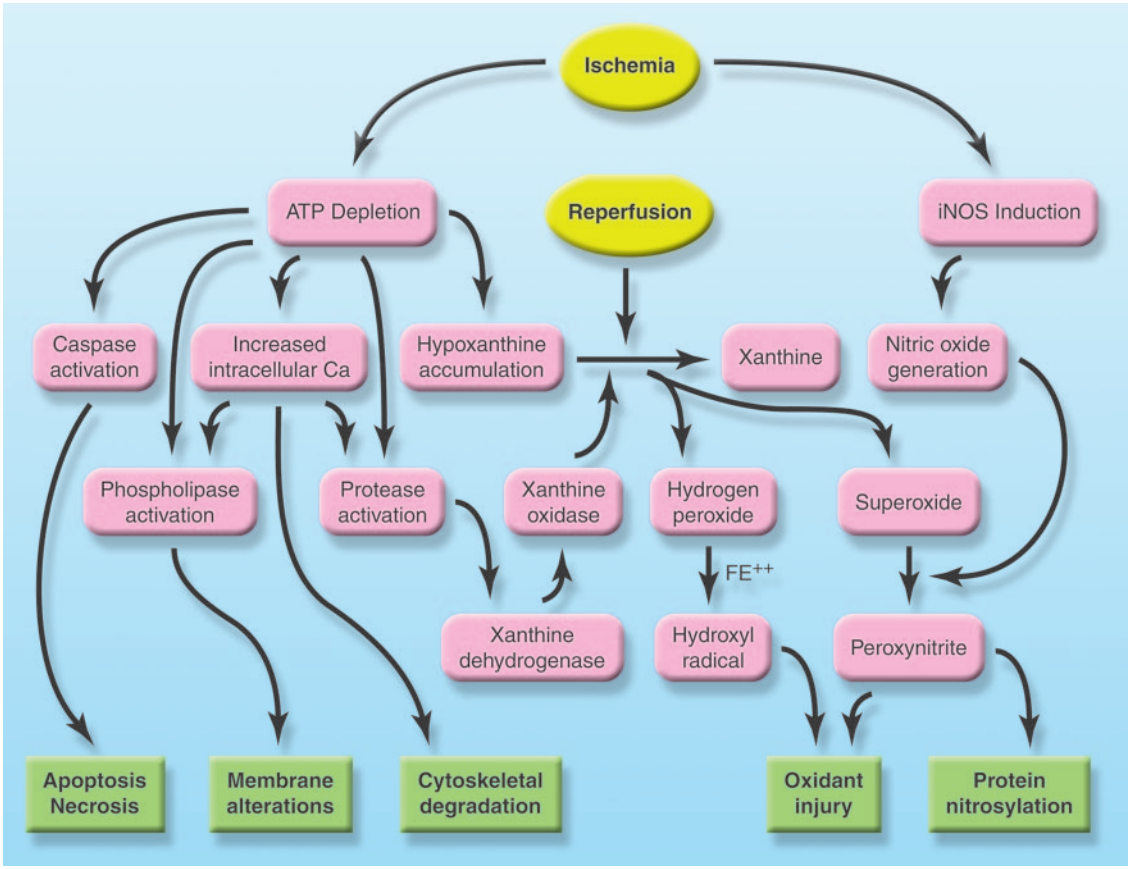

Figure 1. Alterations in tubule cell metabolism after ischemic acute kidney injury (AKI). The initiation phase is typified by profound ATP depletion, which primes the cell by activating a number of oxidative and cell death mechanisms. During the extension phase, prolonged ischemia followed by reperfusion propels these pathways to completion, resulting primarily in apoptosis and oxidant injury. Inhibition of these pathways may provide novel therapeutic approaches, as recently demonstrated with caspase inhibitors, iron chelators, and antioxidants. Illustration by Josh Gramling—Gramling Medical Illustration.

oxidation of sulfhydryl residues) generates hydrogen peroxide and superoxide. In the presence of iron, hydrogen peroxide forms the highly reactive hydroxyl radical. Concomitantly, ischemia induces NO synthase in tubule cells, and the NO that is generated interacts with superoxide to form peroxynitrate, which results in cell damage *via* oxidant injury as well as protein nitrosylation (28). Collectively, reactive oxygen species cause renal tubule cell injury by oxidation of proteins, peroxidation of lipids, damage to DNA, and induction of apoptosis. A recent study documented a dramatic increase in oxidative stress in humans with ARF, as evidenced by depletion of plasma protein thiols and increased carbonyl formation (33). Disappointing, intermittent hemodialysis resulted in only a limited and transient beneficial effect on the redox status of plasma protein thiol groups and no effect on protein carbonyl content (33). Several scavengers of reactive oxygen molecules (*e.g.*, superoxide dismutase, catalase, *N*-acetylcysteine) protect against ischemic AKI in animals, but human studies have been inconclusive. A promising new advance in the field is the protective effect of edaravone, a potent scavenger of free radicals and inhibitor of lipid peroxidation when administered at the time of reperfusion in a rat model of ischemic AKI (34). Edaravone has been approved for human use in the treatment of cerebral ischemia, and results of its use in human AKI are awaited with anticipation. Also, free iron that is derived from red cells or other injured cells now is recognized as one of the most potent factors in the generation of reactive oxygen species, and the iron scavenger deferoxamine does alleviate ischemia-reperfusion injury in animal models. However, the associated systemic toxicity (primarily hypotension) precludes its routine clinical use in human AKI (35). Two major advances have come to light in the area of iron chelation. The first is the availability of human apotransferrin, an iron-binding protein that protects against renal ischemia-reperfusion injury in animals by abrogating renal superoxide formation (36). Apotransferrin has been used successfully for the reduction of redox-active iron in patients who have undergone hematologic stem cell transplantation without any adverse effects (37). The second is the discovery of neutrophil gelatinase–associated lipocalin (NGAL), a major iron-transporting protein complementary to transferrin, as one of the most highly induced genes and proteins in the kidney after ischemic injury (38,39). The biology of NGAL in AKI is detailed further next. Administration of NGAL provides remarkable structural and functional protection in animal models (40,41). The potential use of both of these

endogenous agents (apotransferrin and NGAL) in human AKI currently is under investigation.

Alterations in Tubule Cell Structure

Contemporary techniques have provided novel insights into the cell biology of the proximal tubule in ischemic AKI. The structural response of the tubule cell to ischemic injury is multifaceted and includes loss of cell polarity and brush borders, cell death, dedifferentiation of viable cells, proliferation, and restitution of a normal epithelium, as illustrated in Figure 2. The mechanisms that underlie this morphologic sequence of events are complex and examined next.

Alterations in the Apical Cytoskeleton

Cellular ATP depletion leads to a rapid disruption of the apical actin cytoskeleton and redistribution of actin from the apical domain and microvilli into the cytoplasm (42). The ensuing alterations in microvillar structure lead to formation of membrane-bound, free-floating extracellular vesicles, or "blebs," that are either internalized or lost into the tubular lumen. Brush border membrane components that are released into the lumen contribute to cast formation and obstruction. These casts and vesicles that contain actin and actin depolymerizing factor (ADF; also known as cofilin) have been detected in the urine in animal as well as human AKI (42). The role of ADF/cofilin in the apical microvillar breakdown currently is under active investigation. ADF/cofilin is a cytosolic protein that normally is maintained in the inactive phosphorylated form by Rho GTPases. In cultured renal tubule cells, ATP depletion leads to Rho GTPase inactivation, with resultant activation and relocalization of ADF/cofilin to the surface membrane and membrane-bound vesicles (43,44). Concomitant, ATP depletion dissociates the actin-stabilizing proteins tropomyosin and ezrin (45), allowing the activated ADF/cofilin to bind and consequently sever actin, which in turn leads to microvillar breakdown. Another well known mechanism for ADF/cofilin activation involves families of phosphatases such as Slingshot and Chronophin

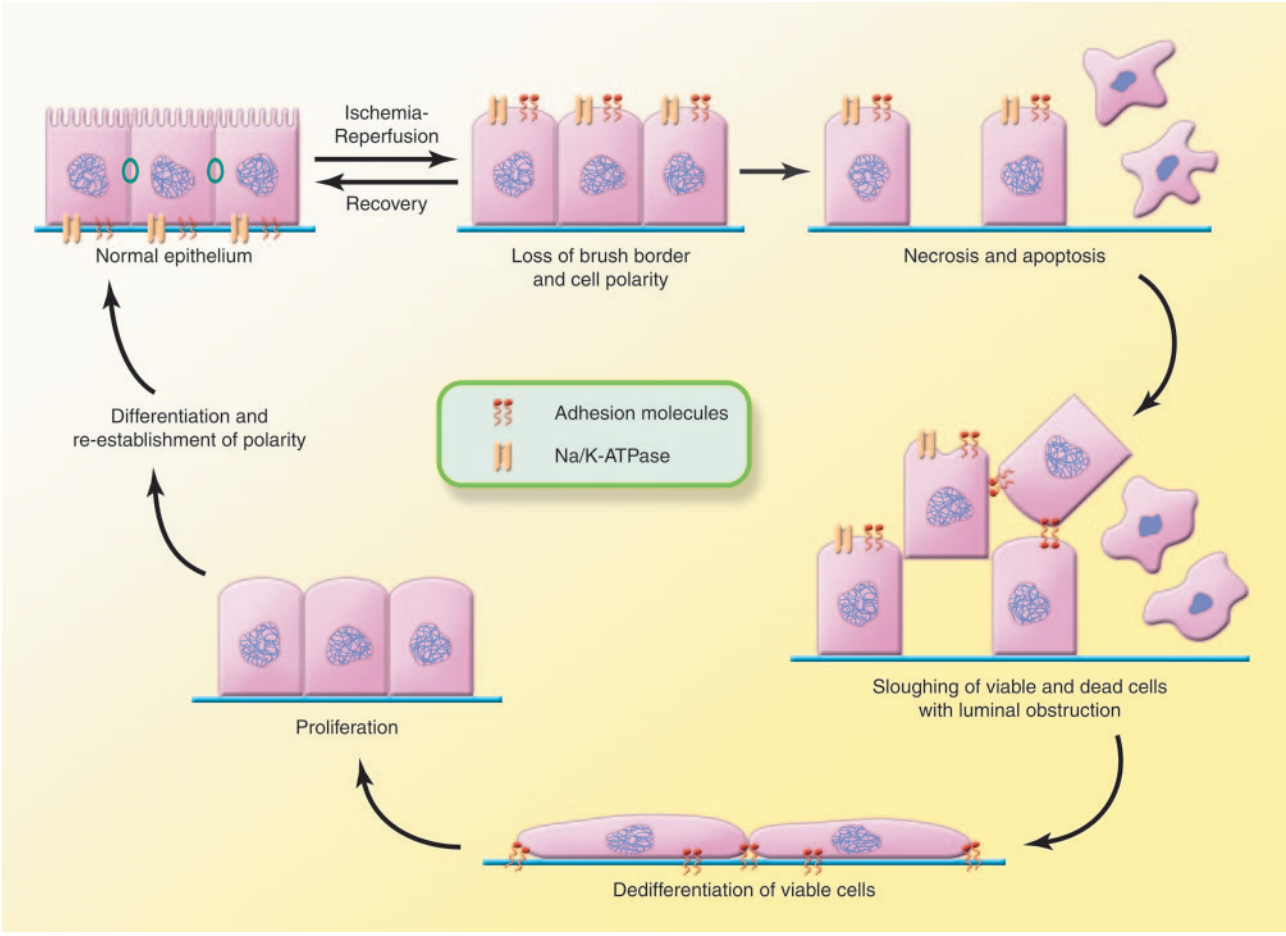

Figure 2. Alterations in tubule cell structure after ischemic AKI. The initiation phase leads to sublethal injury, with loss of brush borders and disruption of cell polarity and the cytoskeleton. If the injury is alleviated at this stage, then complete recovery ensues. If not, then the injury flows into the extension phase, with cell death, desquamation, luminal obstruction, and an inflammatory response (shown in Figure 4). Inhibition of apoptosis and inflammation at this stage may represent a powerful therapeutic approach. The maintenance phase is characterized by a balance between tubule cell death and restoration (which occurs largely as a result of dedifferentiation of viable tubule cells, although stem cells and progenitor cells also may play a role). Measures to accelerate the endogenous regenerative process may hasten recovery. Illustration by Josh Gramling—Gramling Medical Illustration.

(46). Activation of ADF/cofilin also can induce apoptosis by triggering cytochrome c release, which may contribute further to its deleterious effects (47). Therefore, inactivation of ADF/cofilin, perhaps *via* transient inhibition of Slingshot, may represent a promising but unexplored direction in AKI.

Disruption of the apical cytoskeleton by ATP depletion also results in loss of tight junctions and adherens junctions. Reduced expression, redistribution, and abnormal aggregation of a number of key proteins that constitute the tight and adherens junctions have been documented after ischemic injury in cell culture, animal models, and human studies (48). The consequent loss of tight junction barrier function potentially can magnify the transtubular backleak of glomerular filtrate that is induced by obstruction (49).

Alterations in the Basolateral Cytoskeleton

Ischemia results in the early disruption of at least two basolaterally polarized proteins, namely Na,K-ATPase and integrins. The Na,K-ATPase is normally tethered to the spectrin-based cytoskeleton at the basolateral domain *via* the adapter protein ankyrin. In cell culture, animal models, and human studies, ischemia leads to a reversible cytoplasmic accumulation of Na,K-ATPase, ankyrin, and spectrin in viable cells (50). The mislocated Na,K-ATPase remains bound to ankyrin but is devoid of spectrin. Postulated mechanisms that lead to loss of Na,K-ATPase polarity include hyperphosphorylation of ankyrin with consequent loss of spectrin binding and cleavage of spectrin by ischemia-induced activation of proteases such as calpain (2,50). A physiologic consequence of the loss of basolateral Na,K-ATPase is an impairment in proximal tubular sodium reabsorption and a consequent increase in fractional excretion of sodium, which are diagnostic signatures of intrinsic ARF.

The β1 integrins are normally polarized to the basal domain, where they mediate cell-substratum adhesions. Ischemic injury leads to a redistribution of integrins to the apical membrane, with consequential detachment of viable cells from the basement membrane. There is good evidence for abnormal adhesion between these exfoliated cells within the tubular lumen, mediated by an interaction between apical integrin and the Arg-Gly-Asp (RGD) motif of integrin receptors. Administration of synthetic RGD compounds attenuates tubular obstruction and renal impairment in animal models, and the recent development of orally active integrin antagonists holds promise for human AKI (51). A recent animal study has shown that the state of β1 integrin activation also is critical for maintenance of tubule epithelial integrity (52). Preischemic intravenous administration of anti-activated β1 integrin therapy (*via* mAb named HUTS-21 that selectively recognize the active form) resulted in preservation of renal histopathology and function, maintenance of cell-substratum interactions, and amelioration of the inflammatory response (52). The multifaceted protective effect renders HUTS-21 a potentially attractive therapeutic candidate for human AKI, but the need for pretreatment is an obvious disadvantage.

Alterations in Cell Viability

Both experimental and human studies indicate that tubule epithelial cells can suffer one of three distinct fates after ischemic AKI. The majority of cells remain viable, suggesting that they either entirely escape injury or are only sublethally injured and undergo recovery. A subset of tubule cells display patchy cell death that results from at least two pathophysiologic mechanisms. Necrosis is an explosive, chaotic process that is characterized by loss of membrane integrity, cytoplasmic swelling, and cellular fragmentation. Apoptosis is a quiet, orderly demise that is typified by cytoplasmic and nuclear shrinkage, DNA fragmentation, and breakdown of the cell into membrane-bound apoptotic bodies that are rapidly cleared by phagocytosis. These two forms of cell death can coexist and are considered two extremes of a spectrum. After ischemic renal injury, the mode of cell death depends primarily on the severity of the insult and the resistance of the cell type. Necrosis usually occurs after more severe injury and in the more susceptible nephron segments, whereas apoptosis predominates after less severe injury and especially in the ischemia-resistant distal nephron segments. Apoptosis can be followed by "secondary necrosis," especially if the apoptotic cells are not rapidly removed. The commonly used assays for apoptosis (terminal deoxynucleotidyltransferase-mediated dUTP nick-end labeling assay and DNA laddering) do not adequately distinguish between apoptosis and necrosis. Strict morphologic criteria are desirable for the detection and quantification of apoptosis, including nuclear (condensation and fragmentation) and cytoplasmic (cell shrinkage and blebbing) changes.

Mounting evidence now indicates that apoptosis is the major mechanism of early tubule cell death in contemporary clinical ARF (53–55). During recent years, several animal models of ischemic AKI consistently and unequivocally demonstrated the presence of apoptotic tubule cells using a variety of sensitive assays (56–79). Importantly, this now has been confirmed by several investigators in human models of AKI (10,80–85). Nevertheless, controversies still exist regarding the contribution of apoptosis to the syndrome of ARF. First, most estimates place the peak incidence of apoptosis at only approximately 3 to 5% of tubule cells after ischemic injury, which arguably is insufficient to explain the profound renal dysfunction. In response to this skepticism is that the degree of apoptosis is vastly underestimated because it is a rapidly occurring heterogeneously distributed event that is notoriously difficult to identify and quantify in tissues. Second, apoptosis is more commonly encountered in the distal tubule, whereas loss of viable cells occurs predominantly in proximal segments. Reconciliation of this argument is provided by the demonstration of both necrosis and apoptosis in the proximal tubule, where these processes may represent a continuum. Third, apoptosis generally is regarded as a physiologic process that removes damaged cells and therefore may be beneficial to the organ and the organism. The counterpoint to this supposition is that apoptosis after ischemic AKI is a double-edged sword that occurs in two waves, at least in animal models. The first wave is detectable within 6 to 12 h of the insult, peaks at approximately 3 d, and rapidly diminishes. This phase deletes previously healthy tu-

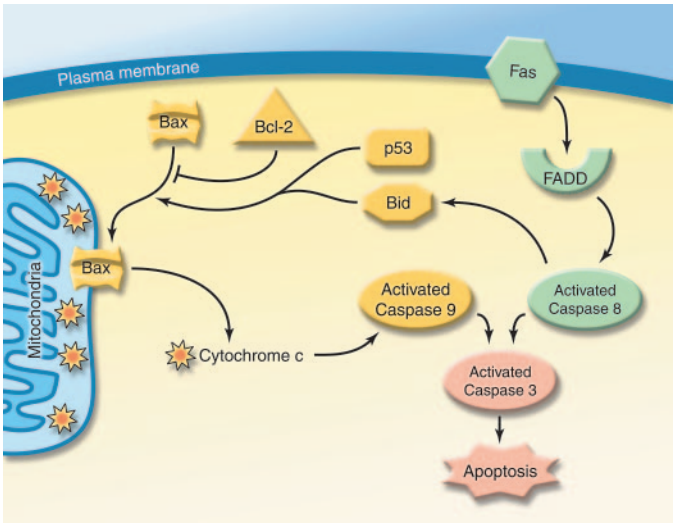

Figure 3. Major apoptotic pathways in human ischemic AKI. The extrinsic pathway requires activation of plasma membrane Fas receptor, with signal transduction *via* FADD resulting in activation of caspase 8. The intrinsic pathway requires translocation of Bax to the mitochondria, thereby forming pores for the release of cytochrome c and activation of caspase 9. Cross-talk between these pathways is provided by Bid activation. Bax also is activated by p53-dependent pathways. Bax activation is prevented in normal cells by Bcl2 and Bcl-xL. Both caspases 8 and 9 activate caspase 3, which initiates the final morphologic cascades of apoptosis. Inhibition of these pathways holds significant therapeutic promise in human acute renal failure. Many additional molecules that have been implicated in animal models (but not in human studies) are not shown. Illustration by Josh Gramling—Gramling Medical Illustration.

bule cells, thereby contributing to the ensuing dysfunction. The second wave becomes apparent approximately 1 wk later, removes hyperplastic and unwanted cells, and therefore may play a role in the remodeling of injured tubules.

Because the evidence is overwhelmingly in favor of apoptosis as a pathogenetic mechanism, considerable attention has been directed toward dissecting out the molecular pathways involved. A multitude of pathways, including the intrinsic (Bcl-2 family, cytochrome c, and caspase 9), extrinsic (Fas, FADD, and caspase 8), and regulatory (p53 and NF-κB) factors, seem to be activated by ischemic AKI, as illustrated in Figure 3. A leading contender for many years, the role of the Fas-FADD pathway in animal models, was reaffirmed recently by demonstration of upregulation of these proteins in apoptotic tubule cells after ischemia (58) and the functional protection that is afforded by small interfering RNA duplexes that target the *Fas* gene (61). However, convincing human data are lacking, because the induction of the *Fas* gene that was shown in one study of human cadaveric kidney transplants (83) was not reproduced in two subsequent publications (10,85). However, there is growing evidence implicating an imbalance between the proapoptotic (Bax and Bid) and antiapoptotic (Bcl-2 and Bcl-xL) members of the Bcl-2 family in both animal (63,79) and human (10,82–84) situations. Of the regulatory factors, the proapoptotic transcription factor p53 has been shown to be induced at the mRNA (56) and protein (55) levels, and inhibition of p53 by pifithrin-α suppresses ischemia-induced apoptosis by inhibiting transcriptional activation of Bax and mitochondrial translocation of p53 (57). However, pifithrin-α is an unlikely candidate for therapeutic consideration in humans because generalized inhibition of p53-dependent apoptosis likely will promote survival of damaged or mutation-bearing cells in other organ systems.

Inhibition of apoptosis does hold promise in ischemic AKI (86). Caspase activation is by and large the final common "execution" step in apoptosis (although caspase-independent apoptosis also has been described), and cell-permeant caspase inhibitors have provided particularly attractive targets for study (73). Currently available inhibitors largely have been investigated only in animals, provide only partial protection, and are most effective when administered before the injury. However, these characteristics render caspase inhibition as a potentially attractive approach to reducing apoptotic damage during cold storage of deceased-donor kidneys before transplantation, as has been demonstrated in animal models (87). In this regard, an orally active pan-caspase inhibitor (IDN-6556) was developed recently (88) and shown to be effective in preventing injury after lung and liver transplantation in animals (88,89). IDN-6556 is currently undergoing evaluation in Phase II clinical trials for injury prevention in human liver transplantation.

Several other modalities ameliorate apoptosis and AKI in experimental situations. Pretreatment with erythropoietin conferred structural and functional protection, inhibition of apoptosis, and upregulation of the antiapoptotic transcription factor NF-κB (65,77). However, inhibition of NF-κB by intrarenal transfection of decoy oligonucleotides resulted in a paradoxic attenuation of ischemic AKI, perhaps by inhibiting transcription of proinflammatory factors (90). α-1-Acid glycoprotein (an acute-phase protein of unknown function [59]), minocycline (62), A1 adenosine receptor agonists (64), peroxisome proliferator–activated receptor β ligands (66), geranylgeranylacetone (an inducer of heat-shock proteins [HSP] [67]), and poly(ADP-ribose) polymerase inhibitors (91) all have provided encouraging functional protection from ischemic AKI with inhibition of apoptosis and inflammation, but the underlying mechanisms have not been fully elucidated. Some of these agents are already widely available and safely used in other human conditions, and results of their use in AKI should be forthcoming. Challenges for the future clinical use of apoptosis inhibition in AKI include determining the best timing of therapy, optimizing the specificity of inhibitor, minimizing the extrarenal adverse effects, and tubule-specific targeting of the apoptosis modulatory maneuvers.

The mechanisms whereby the majority of tubule cells escape cell death and either emerge unscathed or recover completely after ischemic AKI remain under active investigation. HSP have surfaced as prime arbitrators of this cytoprotection (92–94). Induction of HSP is part of a highly conserved innate cellular response that is activated swiftly and robustly after ischemic AKI. HSP promote cell survival by inhibiting apoptosis (95),

and liposomal delivery of HSP-72 into cultured renal tubule cells blocks ischemia-induced apoptosis (96). HSP also facilitate the restoration of normal cellular function by acting as molecular chaperones that assist in the refolding of denatured proteins as well as proper folding of nascent polypeptides. For instance, there now is broad evidence for the role of HSP in the restoration of cytoskeletal integrity and Na,K-ATPase polarity after ischemic AKI in animal models (92–94). In cultured tubule cells, inhibition of the HSP response by gene-silencing techniques produced profound impairment of cellular integrity and Na,K-ATPase polarity (97), and overexpression of HSP-70 mitigated the loss of Na,K-ATPase polarity after ATP depletion (98). Collectively, these findings suggest that maneuvers that enhance the innate HSP response have potential benefit in human AKI but that transition of therapy from bench to bedside has not been achieved yet. However, that this also may activate undesirable cellular processes such as increased immunogenicity (99) serves to caution us against leaping from the frying pan into the fire when contemplating HSP therapies.

Mechanisms of Repair

Surviving renal tubule cells possess a remarkable ability to regenerate and proliferate after ischemic AKI (100). Morphologically, repair is heralded by the appearance of dedifferentiated epithelial cells that express vimentin, a marker for multipotent mesenchymal cells (101). The origin of these cells remains contentious (and is addressed next), but they most likely represent surviving tubule cells that have dedifferentiated. In the next phase, the cells upregulate genes that encode for a variety of growth factors, such as IGF-1, hepatocyte growth factor (HGF), and fibroblast growth factor, and undergo marked proliferation. In the final phase, cells express differentiation factors such as neural cell adhesion molecule (NCAM) and osteopontin and undergo re-differentiation until the normal fully polarized epithelium is restored. Therefore, during recovery from ischemia, renal tubule cells recapitulate phases and processes that are very similar to those during normal kidney development (100–102). Recently identified examples of genes that lend support to the concept of "recapitulation of phylogeny by ontogeny" include NGAL (38–41), leukemia inhibitory factor (103), transcription factor Ets-1 (104), and Wnt-4 (105). All of these transcripts not only are critical to early kidney development but also are markedly induced in the mature kidney after ischemic injury, where they seem to play a crucial role in the regeneration and repair processes.

Understanding the molecular mechanisms of repair may provide clues toward accelerating recovery from ARF. For example, HGF has been documented extensively to be renoprotective and renotrophic in animal models of AKI, mediated by its proliferative, antiapoptotic, and anti-inflammatory actions (68). However, the use of HGF in humans has been hampered at least in part by the widespread expression of its receptor, raising the possibility of serious extrarenal adverse effects (106). Indeed, transgenic mice with generalized overexpression of HGF display diverse tumors, polycystic kidney disease, and inflammatory bowel disease (106). Encouraging, selective overexpression of the HGF transgene in the proximal tubule *via* the γ-glutamyl transpeptidase-1 promoter bestowed remarkable functional protection from ischemic AKI, with enhanced tubule cell proliferation and decreased apoptosis (107). Selected delivery of HGF to the human proximal tubule, however, remains a challenge. In the case of IGF-1, enthusiasm for its renoprotective effects has been dampened by its exacerbation of inflammation and neutrophilic infiltration in the kidney after ischemia in animals (108), and clinical trials with recombinant human IGF-1 have not proved to be beneficial (109). Interest in IGF-1 therapy has been rekindled by the recent discovery of ghrelin, a naturally occurring growth hormone secretagogue that markedly increases serum IGF-1 levels and protects the kidney from ischemic injury by improving endothelial function and vasodilation in animals (78).

Identification of the source of multipotent mesenchymal cells that are involved in the regeneration and repair processes may have important therapeutic implications and has been a matter of intense contemporary research. Evidence for an extrarenal progenitor, namely bone marrow–derived mesenchymal stem cells (MSC), stems from detection of tagged MSC in the recipient kidney after cross-gender transplantation or systemic infusion (111–115). Administered MSC clearly enhance recovery from ischemic AKI in animals, but several controversies exist. First, the number of bone marrow–derived MSC that finally appear in the postischemic kidney is very small, and their detection has been fraught with technical false-positive results (116,117). Second, the majority of these bone marrow–derived cells were detected in the interstitial compartment and not in nephron segments, raising concerns for accentuation of renal fibrosis after AKI (118,119). Third, the overall balance of evidence now is in favor of the notion that restoration of the tubule epithelium after ischemic AKI occurs predominantly *via* proliferation of endogenous renal cells (116–120). Although resident stem cells with tubulogenic capacity have been described in the kidney (121–123), their contribution to the repair process is unclear, and the native tubule epithelial cells seem to represent the primary healing source. Fourth, the mode of protection by exogenously administered MSC may be related not to transdifferentiation processes but rather to powerful anti-inflammatory and antiapoptotic mechanisms that are being uncovered (117,124,125). Because bone marrow–derived MSC are easily accessible, this therapeutic approach certainly holds promise in human AKI.

Alterations in the Microvasculature

In recent years, the concept of the vascular endothelium as an organ that is both a source of and a target for inflammatory injury has become widely appreciated, and the role of endothelial alterations in the initiation and extension of AKI has received increasing attention (13–17). Morphologically, disruption of the actin cytoskeleton and junctional complexes, similar to those previously described in tubule epithelial cells, now has been documented in endothelial cells in experimental AKI (126,127). Consequent endothelial cell swelling, blebbing, death, and detachment of viable cells occur, and circulating endothelial cells have been demonstrated in humans with septic shock (128). Sites of endothelial denudation may be prone to

prolonged vasoconstriction, and minimally invasive intravital microscopy has revealed sporadic cessation and even reversal of blood flow in peritubular capillaries during reperfusion (129,130). Systemic or intrarenal administration of fully differentiated endothelial cells into postischemic rat kidneys resulted in a significant functional protection (130). A similar, albeit less impressive, amelioration was achieved using surrogate cells that expressed endothelial NO synthase. Furthermore, ischemic injury leads to a marked upregulation of angiostatin, a widely known antiangiogenic factor that induces apoptosis of endothelial cells (131). Collectively, these findings provide a rationale for the use of proangiogenic agents that can increase the pool or mobilization of endothelial progenitor cells, such as erythropoietin, bone morphogenic protein, vascular endothelial growth factor, and statins (17).

Ischemic AKI also leads to increased endothelial expression of a variety of adhesion molecules that promote endothelial–leukocyte interactions. These include intercellular adhesion molecule-1 (ICAM-1), P-selectin, and E-selectin (14,132). Although ablation of the ICAM-1 gene and pretreatment with ICAM-1 antibody rendered mice resistant to ischemic AKI, human trials with anti–ICAM-1 mAb administered after ischemia did not prevent AKI in cadaveric transplant recipients (14). Similarly, gene knockouts, mAb, and pharmacologic inhibitor studies have suggested a role for E- and P-selectins (132–134). However, subsequent studies have shown that it is platelet P-selectin, not endothelial P-selectin, that is the key component leading to AKI (135). Possible mechanisms include (*1*) adhesion of platelets to the endothelium, with subsequent leukocyte adhesion, and (2) adhesion of platelets to neutrophils, with consequent aggregate formation and trapping in narrow peritubular capillaries (132). These abnormalities, combined with other derangements in the coagulation cascade such as alterations in tissue-type plasminogen activator and plasminogen activator inhibitor-1 in the kidney (136), may account for the fibrin deposits that characteristically are found in the renal microvasculature after ischemic injury.

Alterations in the Inflammatory Response

A growing body of evidence indicates that the inflammatory response plays a major role in ischemic AKI. Inflammatory cascades that are initiated by endothelial dysfunction can be augmented dramatically by the generation of a number of potent mediators by the ischemic proximal tubule, which is thought to represent a "maladaptive response" (13,14,137–139). These include proinflammatory cytokines (*e.g.*, TNF-α, IL-6, IL-1β, TGF-β) and chemotactic cytokines (*e.g.*, monocyte chemoattractant protein-1 [MCP-1], IL-8, RANTES). Elegant human studies demonstrated recently that the levels of the proinflammatory cytokines IL-6 and IL-8 in the plasma predict mortality in patients with AKI (139), and the levels of CXCR3-binding chemokines in the urine predict AKI after kidney transplantation (140), attesting to the clinical significance of these mechanisms. Toll-like receptor 2 (TLR2) may represent a major component of this proinflammatory response (70). Renal tubular expression of TLR2 is enhanced upon ischemic AKI, and TLR2 gene silencing by knockout and antisense treatment prevents ischemia-induced renal dysfunction; neutrophil influx; tubule apoptosis; and induction of MCP-1, TNF-α, IL-6, and IL-1β. Bone morphogenic protein-7 also is induced in postischemic tubules (75) and protects against ischemic AKI by decreasing the levels of MCP-1, IL-8, IL-6, and IL-1β in cultured proximal tubule cells (141).

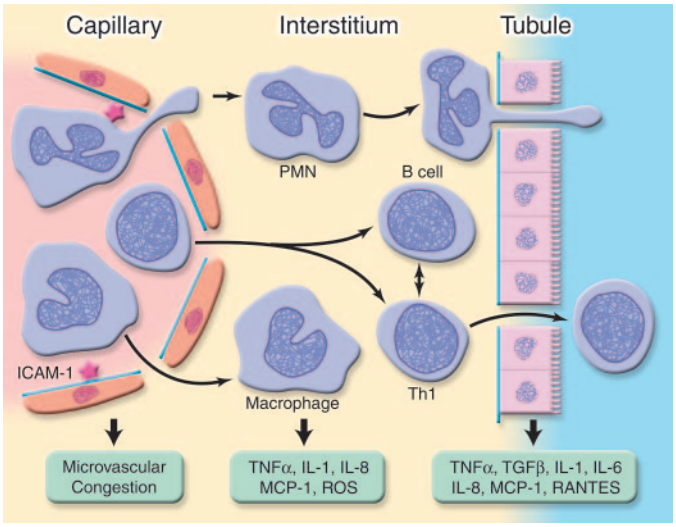

Figure 4. Alterations in the microvasculature and inflammation in ischemic AKI. During the extension phase, endothelial injury leads to intense vasoconstriction, microvascular sludging, and microvascular congestion with leukocytes. Activated leukocytes produce a number of inflammatory mediators and reactive oxygen species that potentiate tubule cell damage. In addition, tubule cells exhibit a maladaptive response by generating cytokines and chemokines that further amplify the inflammation. PMN, polymorphonuclear leukocyte; Th1, T-helper 1 cell. Strategies that modulate the inflammatory response may provide significant beneficial effects in ischemic AKI. Illustration by Josh Gramling—Gramling Medical Illustration.

Morphologically, several leukocyte subtypes have been shown to aggregate in peritubular capillaries, interstitial space, and even within tubules after ischemic AKI (Figure 4), and their relative roles remain under investigation (14). Neutrophils are the earliest leukocytes to accumulate in the postischemic kidney. However, neutrophil depletion or blockade of neutrophil function provides partial functional protection in some but not all animal models. Furthermore, neutrophils are not a prominent feature of ischemic AKI in humans, casting doubts about the clinical significance of neutrophil infiltration. Macrophages are the next to accumulate in animal models (90), in response to upregulation of MCP-1 in tubule cells (142) and induction of its cognate receptor CCR2 on macrophages (143). Selective macrophage depletion ameliorates ischemic AKI, but the induction of tissue injury by macrophages seems additionally to require the coordinated action of T cells and neutrophils (144). However, T cells have been identified in animal as well as human models of ischemic AKI (14), and T cell depletion is protective in experimental AKI (145–147). Double CD4/CD8 knockout mice are protected from ischemic AKI (148), and adoptive transfer of wild-type T cells into the null mice abrogates this protective

effect (149). However, inconsistencies exist, and recent data suggest that the role of T cells in ischemic AKI may be complex, with the identification of both protective (Th2 phenotype) and deleterious (Th1 phenotype) subtypes of T cells (150). Moreover, animals that are deficient in both T and B cells are not protected from ischemic AKI (151), and depletion of peripheral CD4 T cells failed to bestow protection from ischemic AKI (152). The potential role of B cells in ischemic AKI is intriguing. Compared with wild-type animals, B cell–deficient mice are partially protected from structural and functional ischemic renal injury, despite comparable neutrophil and T cell infiltrations (153). Wild-type serum transfer but not B cell transfer into B cell–deficient mice restored susceptibility to ischemic AKI, implicating a soluble serum factor as a mechanism by which B cell deficiency confers renal protection (153).

Activation of the complement system in ischemic AKI, with a resultant amplification of the inflammatory response in the kidney, has received widespread attention in recent years (154–157). Whereas ischemia-reperfusion injury in most organs activates the complement cascade *via* classical pathways, studies in animals (158) and humans (159) have implicated a predominant role for the alternative pathway in ischemic AKI (160). However, this remains debatable, because other reports have identified a role for the mannose-binding lectin pathway as well in complement activation after animal and human ischemic AKI (161,162). Equally controversial is the identification of the final active complement component. Whereas earlier studies pointed to the C5b-directed formation of a membrane attack complex (163,164), several recent observations have challenged this view and have identified a predominant role for C5a in ischemic AKI (154–157). C5a is a powerful chemoattractant that recruits inflammatory cells such as neutrophils, monocytes, and T cells. The kidney is one of the few organs in which the C5a receptor is normally expressed, in proximal tubule epithelial cells as well as interstitial macrophages (165). C5a receptor expression in tubule epithelial cells is markedly upregulated after ischemia-reperfusion injury (166) and sepsis (167). Inhibition of C5a generation using mAb protected against renal dysfunction that was induced by ischemia and inhibited neutrophil and macrophage influx in experimental models (168). Importantly, pretreatment with orally active small-molecule C5a receptor antagonists substantially reduced the histologic and functional impairment that was induced by ischemic AKI in animal models (166,169). Small-molecule antagonists for C5a receptor are currently undergoing a Phase II clinical trial in rheumatoid arthritis and represent promising agents for the treatment or prevention of ischemic AKI.

Other strategies that modulate the inflammatory response also may provide significant beneficial effects in human AKI, and several have already been tried in experimental situations. For example, IL-10 is a potent anti-inflammatory cytokine that has been shown to provide functional protection against ischemic AKI by inhibiting maladaptive cytokine production by Th1 cells (170). Administration of a mAb against the proinflammatory cytokine IL-6 ameliorated structural and functional consequences of ischemic AKI, decreased neutrophil infiltration, and reduced proinflammatory cytokine production (171). Bimosiamose, a novel pan-selectin inhibitor, protected from ischemic AKI in a kidney transplant model by reducing infiltration of macrophages and T cells and inhibiting intragraft expression of chemokines and cytokines (172). In addition to cholesterol lowering in humans, widely used statins possess several properties that may be beneficial in ischemic AKI, including profound anti-inflammatory effects, inhibition of reactive oxygen species, and stimulation of endothelial NO production (173–175). Not surprising, several investigators have reported impressive structural and functional protection from ischemic AKI by short-term pretreatment with statins (176–179). Similarly, erythropoietin, used extensively in humans for stimulating erythropoiesis, also has prominent antiapoptotic and anti-inflammatory actions (179) and has been used successfully for functional amelioration of ischemic AKI in animals (65,77,180). Finally, α-melanocyte stimulating hormone, an anti-inflammatory cytokine, protects against ischemic AKI by inhibiting the maladaptive activation of genes that cause inflammatory and cytotoxic renal injury (180,181). Of interest, α-melanocyte stimulating hormone potentiates the beneficial effect of erythropoietin (180), remains effective even when administered after the renal ischemia (180), and also protects against the distant lung injury that occurs after ischemic AKI (181). The widespread clinical experience with some of these interventions and their overall safety record render them highly promising candidates for the prevention and treatment of ischemic AKI.

Alterations in Global Gene Expression

Attempts at unraveling the molecular basis of the myriad pathways that are activated by complex nephrologic processes such as ischemic AKI have been facilitated by recent advances in functional genomics and cDNA microarray-based technologies (100,182–185). Several investigators have used these techniques in human and animal models of ischemic AKI to obtain expression profiles of thousands of genes. When combined with bioinformatic tools, these studies have identified novel genes with altered expression, new signal transduction pathways that are activated, and even new drug targets and biomarkers in AKI. One of the first induced molecules to be identified in the postischemic kidney using genomic approaches was kidney injury molecule 1 (KIM-1) (186). KIM-1 protein subsequently was demonstrated to be upregulated in postischemic animal and human kidney tubules, predominantly on the apical membranes of proximal tubule epithelial cells, where it may play a role in renal regeneration (187,188). An ectodomain is shed into the urine, making KIM-1 a promising noninvasive urinary biomarker of ischemic human AKI (187–189).

Another recent example is NGAL, one of the most highly induced genes in the early postischemic kidney (56,100). NGAL protein is markedly upregulated in kidney tubules very early after ischemic AKI in animals (38) and humans (190) and is rapidly excreted in the urine, where it represents a novel, sensitive, early biomarker of ischemic AKI (38,191). In the postischemic kidney tubules, NGAL protein accumulates in a punctate cytoplasmic distribution that co-localizes with endosomal markers (38). Importantly, NGAL is highly expressed in tubule cells that are undergoing proliferation, suggesting a protective

or regenerative role after AKI. Further support for this notion derives from the critical role played by NGAL in kidney development, during conversion of kidney progenitors into epithelia and tubules (192). Indeed, administration of NGAL in experimental models before, during, or even shortly after ischemic injury provides remarkable protection at the functional and structural levels, with an induction of proliferation and striking inhibition of apoptosis of tubule epithelial cells (40,41). In this context, NGAL mitigates iron-mediated toxicity by providing a reservoir for excess iron and may provide a regulated source of intracellular iron to promote regeneration and repair. Exogenously administered NGAL also markedly upregulates heme oxygenase-1, a proven multifunctional protective agent in experimental AKI that works by limiting iron uptake, promoting intracellular iron release, enhancing production of antioxidants such as biliverdin and carbon monoxide, and inducing the cell cycle regulatory protein p21 (193–195). Because of its multifaceted protective action, NGAL has emerged as a prime therapeutic target in ischemic AKI.

Another maximally induced gene that is identified very early after ischemic injury is Zf9, a Kruppel-like transcription factor that is involved in the regulation of a number of downstream targets (196). Zf9 protein is strongly expressed during kidney development and is markedly upregulated in the postischemic tubule cells, along with its major transactivating factor, TGF-β1. Gene silencing of Zf9 abrogated TGF-β1 overexpression and mitigated the apoptotic response to ATP depletion *in vitro* (196). These studies thus have identified a hitherto unrecognized pathway that may play a critical role in the early tubule cell death that accompanies ischemic renal injury.

Transcriptome profiling in rat models recently has identified thrombospondin 1 (TSP-1), a previously known p53-dependent proapoptotic and antiangiogenic molecule in malignant cells (197), as another maximally induced gene early after ischemic AKI (74). The TSP-1 protein product is upregulated in the postischemic proximal tubule cells, where it co-localizes with activated caspase-3. TSP-1 null mice were partially protected from ischemic injury, with striking structural preservation of kidney tissue (74). These results thus have identified yet another previously unknown apoptotic pathway that is activated in proximal tubule cells early after ischemic AKI.

It is an underappreciated fact that after an initial "recovery" from an episode of clinical ARF, a significant proportion of patients exhibit persistent or progressive deterioration in renal function. It now is clear that the postischemic kidney is not fully restored to its immaculate preinjury state, and animal models display a reduction in renal microvasculature, interstitial fibrosis, tubular hypercellularity and atrophy, and persistent inflammation when closely examined in the recovery period (195,198–202). Microarray analysis has been used to identify persistently altered gene expression in the kidney during an intermediate stage, after functional "recovery" from ischemic AKI but before the onset of chronic fibrotic or sclerotic changes (203). Markedly induced transcripts that were novel to the ARF field included C4 complement (inflammation associated), calcium-binding protein S100A4 (fibrosis inducer), and matrix Gla protein (calcification related). Future downstream studies should shed light on the role of these and other gene products in the long-term consequences of ischemic AKI.

Temporal Patterns of Structural and Functional Alterations

The clinical course of ischemic AKI has been divided classically into three phases: Initiation, maintenance, and recovery (204). To this paradigm, the addition of an "extension" phase after the initiation phase has been proposed, primarily to reflect previously underestimated amplification processes (15,205). Recent advances in the pathogenesis of ischemic AKI allow us to postulate temporal relationships between the clinical phases and the cellular alterations detailed in this review. The initiation phase is the period during which initial exposure to the ischemic insult occurs, kidney function begins to fall, and parenchymal injury is sprouting but not fully entrenched. Intracellular ATP depletion is profound, sublethal injury to the tubule epithelial and endothelial cells predominates, generation of reactive oxygen molecules is initiated, and activation of inflammatory mechanisms commences. Intrarenal protective mechanisms, such as induction of HSP in tubule cells, also are brought to play during the initiation phase. If the injury is alleviated at this stage, then complete restitution and recovery is the rule. Prolongation of ischemia followed by reperfusion ushers in the extension phase. Blood flow returns to the cortex, and tubules undergo reperfusion-dependent cell death but also commence the regeneration process. In contrast, medullary blood flow remains severely reduced, resulting in more widespread tubule cell death, desquamation, and luminal obstruction. Injured endothelial and epithelial cells amplify the raging inflammatory cascades, and the endothelial denudation potentiates the intense vasoconstriction. The GFR continues to decline. This phase probably represents the most optimal window of opportunity for early diagnosis and active therapeutic intervention. During the maintenance phase, the parenchymal injury is established, and the GFR is maintained at its nadir even though renal blood flow begins to normalize. Both cell injury and regeneration occur simultaneously, and the duration and severity of this phase may be determined by the balance between cell survival and death. Repair of both epithelial and endothelial cells seems to be critical to overall recovery. Measures to accelerate the endogenous regeneration processes may be effective during this phase. The recovery phase is characterized functionally by improvement in GFR and structurally by reestablishment of tubule integrity, with fully differentiated and polarized epithelial cells. However, the repair process may be incomplete, and both microvascular and tubular dropout has been demonstrated in animal studies.

Conclusions and Future Perspectives

According to Greek mythology, the Hydra was a dreaded multitasking monster with several heads, a serpent body, and deadly breath. One of its heads was invincible to weapons, and if any of the other heads were severed, then another would burgeon in its place. Annihilating the Hydra required a diversified, multifunctional approach, including finding its hiding place, cutting off each head, cauterizing the stumps, burying

Table 1. Emerging therapies for AKI on the basis of recent mechanistic insights[a]

Agent	Mechanism	Reference
Endothelin receptor antagonist	Vasodilation	(18)
CO-releasing compounds	Vasodilation	(19,20)
Edaravone	Reactive oxygen molecule scavenger	(34)
Apotransferrin	Iron chelation	(36)
NGAL	Iron chelation, growth factor, antiapoptosis	(40,41)
β1-integrin antagonist	Anti-inflammatory	(52)
α1-acid glycoprotein	Anti-inflammatory, antiapoptosis	(59)
Adenosine receptor agonist	Anti-inflammatory, antiapoptosis	(64)
PPAR-β/δ agonist	Anti-inflammatory, antiapoptosis	(66)
Geranylgeranylacetone	Induction of cytoprotective HSP	(67)
Caspase inhibitor IDN-6556	Antiapoptosis	(88)
PARP inhibitor	Antiapoptosis	(91)
Hepatocyte growth factor	Growth factor, antiapoptosis	(107)
Mesenchymal stem cells	Anti-inflammatory, antiapoptosis	(124)
C5a receptor antagonist	Anti-inflammatory	(166,168)
IL-10	Anti-inflammatory	(170)
IL-6 antagonist	Anti-inflammatory	(171)
Statins	Anti-inflammatory	(176–178)
Erythropoietin	Anti-inflammatory, antiapoptosis	(180)
α-Melanocyte stimulating hormone	Anti-inflammatory, antiapoptosis	(180)

[a]AKI, acute kidney injury; CO, carbon monoxide; NGAL, neutrophil gelatinase–associated lipocalin; PPAR, peroxisome proliferator–activated receptor; HSP, heat-shock protein; PARP, poly(ADP-ribose)polymerase inhibitor.

the invincible head under a boulder, and systematically chopping up the serpentine body. A modern-day Hydra, ischemic AKI, is a potentially lethal condition with multiple pathophysiologic mechanisms that interplay with and amplify each other. Just like Heracles was summoned to vanquish the Hydra, a call to arms has been issued to the nephrology community to intervene in AKI (206,207). Conquering AKI also will require a comprehensive approach, including finding the beast (making an early diagnosis) and executing a multifaceted therapeutic approach that is based on a better understanding of the multiheaded pathophysiology. The remarkable progress in basic and translational AKI research that has been made since this topic last was reviewed in *JASN* less than 3 yr ago (208) is chronicled in this update. The cellular and molecular tools of modern science undeniably have provided critical new insights into the roles of apoptosis, oxidant and iron-mediated injury, endothelial changes, regeneration and repair, and the inflammatory response in the pathogenesis of ischemic AKI. Novel strategies that have emerged from these recent findings (Table 1) hold tremendous promise for the proactive treatment of human AKI and currently are under intense investigation.

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