

NEPHROLOGY

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Pathophysiology of Acute Kidney Injury

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The term “acute renal failure” (ARF) has traditionally been used to describe a syndrome with a rapid decline in glomerular filtration rate (GFR) occurring over a period of hours to weeks as the key feature. Recently, a consortium of nephrologists and intensivists, the Acute Kidney Injury Network (AKIN), representing many of the professional societies involved in the care of critically ill patients, recommended that the term “acute kidney injury” (AKI) replace ARF. This term includes the entire spectrum of ARF and recognizes that minor changes in kidney function (reflected by a change in serum creatinine [SCr] of 0.3 mg/dL) can portend worse patient outcome,¹ whereas the term “failure” is reserved for those patients whose renal functional impairment is so severe that replacement therapy is indicated, or at least considered. The previous issue of *Nephrology Rounds* reviewed the epidemiology, diagnosis, and treatment of AKI in various settings. This issue of *Nephrology Rounds* examines the pathophysiological underpinnings of AKI.

In addition to the prognostic indications, a number of other reasons contributed to the change in terminology from ARF to AKI. Telling patients that they have acute kidney injury is much less ominous than describing their condition as acute renal failure. Furthermore, the population generally recognizes “kidney” more than “renal” in referring to this organ. The AKIN network proposed that AKI be defined as “an abrupt (within 48 hours) reduction in kidney function, currently defined as an absolute increase in SCr of >0.3 mg/dL (>25 μmol/L), a percentage increase of 50%, or a reduction in urine output (documented oliguria of < 0.5 mL/kg/hr for >6 hours).”²

There are numerous potential causes of AKI; many relate to a mismatch between oxygen and nutrient delivery to the nephrons, and energy demand of the nephrons. The causes of AKI have been traditionally divided into prerenal, intrinsic renal, and postrenal. In prerenal azotemia, there is a decrease in GFR with changes in SCr, but no tubular injury. Intrinsic renal causes can be associated with ischemia, toxins, or primary interstitial or glomerular disease. It is important to recognize that relative oxygen deprivation often is not generalized, but because of the complexity of vascular and tubular relationships in the kidney, functional consequences of localized tubular injury may be amplified. Other causes relate to direct toxic effects of substances on the vasculature or epithelium. The kidney is particularly susceptible to toxic effects from many environmental or therapeutic substances, since many of these compounds are concentrated by the tubule as the filtrate moves down the nephron. In humans, acute injury is often superimposed on chronic kidney disease (CKD); as a result, AKI is increasingly recognized as an important precipitant in the progression to end-stage renal disease (ESRD). AKI is frequently associated with multiple organ failure and sepsis. Despite advances in preventive strategies and support measures, this syndrome continues to be associated with significant morbidity and mortality.

The pathogenesis of AKI is complex and, to some extent, varies based on the particular cause; however, many convergent processes lead to tissue injury and organ dysfunction. Causes associated with toxins also have a final common pathway contributing to local or generalized ischemia. Figure 1 summarizes the complex interplay between vascular and tubular processes that ultimately lead to organ dysfunction. AKI is a state often characterized by enhanced intrarenal vasoconstriction; it is also associated with enhanced renal-nerve activity and increased tissue levels of vasoconstrictive agents, such as angiotensin II and endothelin. A decreased responsiveness in the resistance vessels to vasodilators, such as acetylcholine, bradykinin, and nitric oxide (NO), as well as lower production levels of some vasodilators can enhance the impact of these vasoconstrictive agents. These effects on the resistance vessels are complemented by endothelial damage, enhanced leukocyte-endothelial adhesion (particularly in the postcapillary venules), and activation of coagulation pathways; together, these processes result in small-vessel occlusion and further activation of the leukocytes causing increases in inflammation and providing a positive-feedback network. The inflammation produces increased levels of mediators expanding the interactions between leukocytes and endothelial cells, and activating the coagulation pathways. The resultant effects on oxygen and nutrient delivery to the epithelial cells result in damage to those cells; furthermore, damaged tubular cells also generate proinflammatory mediators. Repair involves the replacement of lost cells in the tubule by mechanisms that are not completely understood.³

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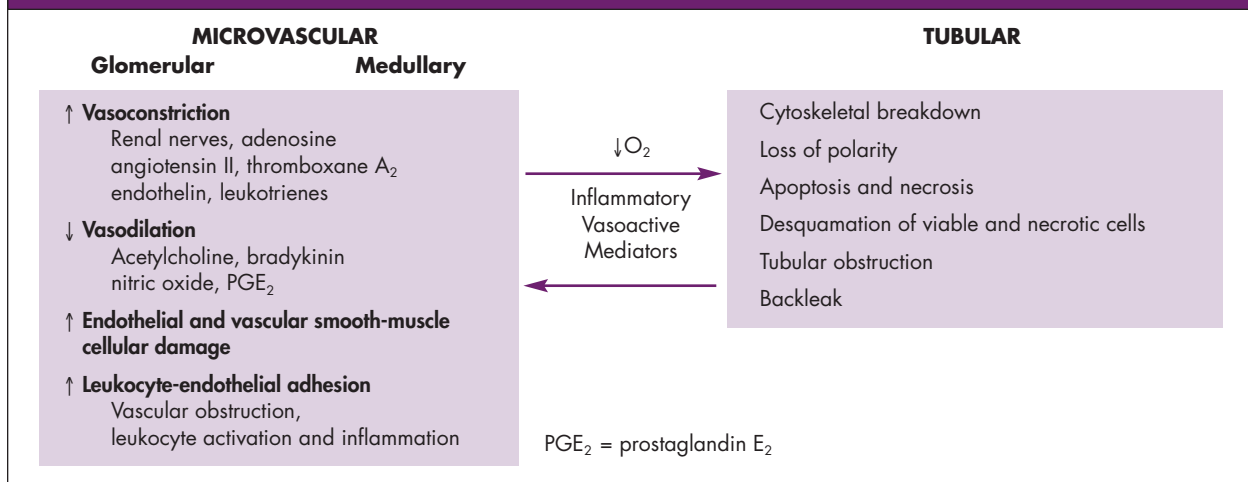
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Figure 1: The pathophysiology of acute kidney injury (AKI).



The pathophysiology of AKI may be divided into microvascular and tubular components; the former can be further divided into preglomerular and outer medullary vessel components. With AKI, there is enhanced vasoconstriction and decreased vasodilatation in response to agents that are present in the postschemic kidney. With increased endothelial and vascular smooth muscle cellular damage, there is enhanced leukocyte-endothelial adhesion leading to activation of the coagulation system and vascular obstruction with leukocyte activation and potentiation of inflammation. At the level of the tubule (described in Figure 2), there is cytoskeletal breakdown and loss of polarity followed by apoptosis and necrosis, intratubular obstruction, and backleak of glomerular filtrate through a denuded basement membrane. In addition, the tubule cells generate inflammatory vasoactive mediators that, in turn, can affect the vasculature to enhance vascular compromise. A positive feedback mechanism ensues whereby the vascular compromise results in decreased oxygen delivery to the tubules that, in turn, generate vasoactive inflammatory mediators to enhance the vasoconstriction and the endothelial-leukocyte interactions. Modified from Bonventre (2008)⁴¹

Whether the injury is related to oxygen deprivation, toxins, or, as is often the case, a combination of factors, there are many common features in the epithelial cell response. Figure 2 schematically depicts the processes of injury and repair to the kidney epithelium. Injury results in rapid loss of cell polarity and cytoskeletal integrity; the proximal tubule brush border sheds and there is a loss of polarity with the mislocalization of adhesion molecules and other membrane proteins (eg, sodium-potassium, adenosine triphosphatase [Na⁺K⁺ATPase] and β-integrins),⁴ apoptosis and necrosis ensues.⁵ With severe injury, viable and nonviable cells are desquamated, leaving regions where the basement membrane remains the only barrier between the filtrate and the peritubular interstitium. These cells and their debris combine with proteins present in the tubular lumen (eg, Tamm-Horsfall protein and fibronectin) and they enter the lumen,⁶ forming casts that can obstruct the tubule, increase intratubular pressure, and appear in the urine of humans as a hallmark of AKI. This increased intratubular pressure results in a reduction in the glomerular transcapillary hydrostatic pressure gradient with resulting reductions in the GFR and, combined with the loss of normal epithelial barrier function, allows for backleak of the filtrate. The activation and injury to the epithelium result in the generation of inflammatory and vasoactive mediators that may have autocrine and paracrine effects on adjacent tubular epithelial cells and can act on the vasculature to worsen the vasoconstriction and inflammation. Thus, inflammation contributes in a critical way to the pathophysiology of AKI.⁷

In contrast to the heart or brain, the kidney can recover from an ischemic or toxic insult resulting in cell death, although it is becoming increasingly recognized that there are longer-term detrimental effects from even brief periods of ischemia.⁸ The surviving cells that remain adherent can undergo repair and potentially can recover normal renal func-

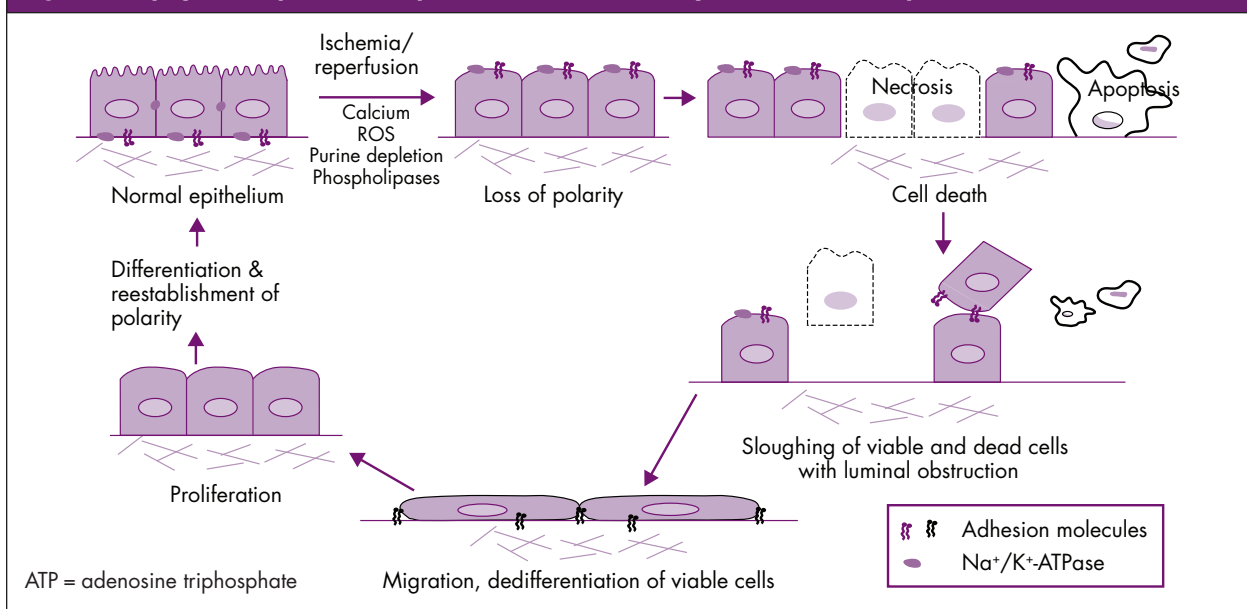
tion. Whether there is a subpopulation of stem or progenitor cells in the kidney interstitium or in the tubule itself is a matter of active study.⁹ Our research indicates that bone marrow does not contribute directly to the replacement of cells, but bone-marrow-derived cells may have paracrine effects potentially facilitating repair by reducing inflammation.⁹ During recovery, there is epithelial cell spreading and migration to cover the exposed areas of the basement membrane. Proteins are expressed on the cells that are normally expressed only during kidney development, suggesting cell dedifferentiation; further, a marked proliferation restores cell number and is followed by differentiation that restores the functional integrity of the nephron.¹⁰

Vasculature reactivity

The vasculature plays a critical role in the pathophysiology of AKI. While systemic or localized disturbance of renal blood flow is a major factor in the etiology of AKI, intrinsic renal factors contribute to the pathogenesis of the disease. Two foci of persistent vasoconstriction following kidney injury have been identified. The first proposes that persistence of preglomerular vasoconstriction is facilitated by a high salt load arriving in the distal tubule, as a result of inadequate sodium reabsorption in the injured, more proximal parts of the tubule. Further, studies of regional renal blood flow reveal reductions in local blood flow to the outer medulla that persist for many hours after renal injury in both experimental models of injury in rodents and in human biopsy specimens. Three factors may contribute to a reduction in perfusion in the outer medulla:

- the medullary blood flow is postcapillary, and hence low pressure
- injured endothelial cells swell and, in combination with leukocyte adhesion to the injured endothelium, will impede low-pressure blood flow
- coagulation cascades may become activated.

Figure 2: Injury and repair to the epithelial cell of the kidney with ischemia/reperfusion.



With injury to the kidney, an early response is loss of the brush border and the polarity of the epithelial cell with mislocation of adhesion molecules and Na⁺/K⁺-ATPase and other proteins. With increasing injury, there is cell death by either necrosis or apoptosis. Some of the necrotic debris is then released into the lumen, where it interacts with luminal proteins and can ultimately result in obstruction. In addition, with the mislocation of adhesion molecules, viable epithelial cells lift off the basement membrane and are found in the urine. The kidney can respond to the injury by initiating a repair process, if there are sufficient nutrients and sufficient oxygen delivery, and the basement membrane integrity has not been altered irreparably. Viable epithelial cells migrate and cover denuded areas of the basement membrane. The source of these cells appears to be from the kidney itself and not from the bone marrow. Bone-marrow cells may contribute to the interstitial cellular infiltrate and may produce factors to modulate inflammation and facilitate repair. Cells replacing the epithelium may derive from differentiated epithelial cells or from a subpopulation of progenitor cells in the tubule; the cells undergo division and replace lost cells. Ultimately, the cells go on to differentiate and reestablish the normal polarity of the epithelium. Modified from Bonventre (2008)⁴¹

The inflammatory aspects of this response are discussed in the next section of this review. Reduced blood flow to the outer medulla can have particularly detrimental effects on the tubular cells in that region of the kidney, since the outer medulla is normally hypoxic due to the countercurrent exchange properties of the vasa recta.¹¹

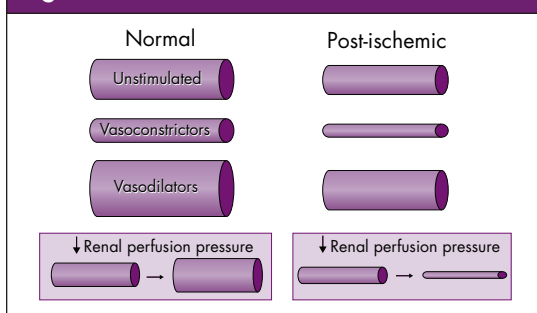
Measurement of renal blood flow in rats 1-week following ischemic injury points to persistent dysregulation of vascular tone at rest and in response to vasodilators and constrictors. The renal vasculature is tonically more constricted, hyper-responsive to vasoconstrictors, hyporesponsive to vasodilators, and responds inappropriately to a fall in perfusion pressure by vasoconstriction (Figure 3).¹² This vasoconstrictive response to a lowering of perfusion pressure has served to motivate, in part, the use of continuous renal replacement therapy in humans. It can be argued that, since this approach is associated with less hypotension in patients than intermittent hemodialysis, then recovery from AKI would be facilitated by continuous therapy. The data, however, do not substantiate this conclusion, since most large, randomized, controlled trials do not show a benefit of continuous therapy over intermittent dialytic therapy.¹³

Many potent vasoconstrictors have been identified in the ischemic kidney, including endothelin-1, angiotensin II, thromboxane A₂, prostaglandin H₂, leukotrienes C₄ and D₄, adenosine, and sympathetic nerve stimulation.¹⁴ This increased vascular reactivity to vasoconstrictors may not be limited to the acute ischemic phase, since a recent study revealed that 5-8 weeks after acute ischemia in the rat there was increased responsiveness to angiotensin II in microvessels

and resistance vessels of the skeletal vascular beds.¹⁵ Numerous studies indicate that blockade of endothelin receptors prior to an ischemic insult protects the rat kidney from injury. There are two vascular smooth-muscle cell receptors for endothelin, ER-A and ER-B; ER-A appears to function primarily in vasoconstriction, and selective blockade in rats has proven beneficial to recovery. Angiotensin receptor blockade, however, is widely implicated in the induction of ischemic injury through paralysis of postglomerular arterioles. To date, successful diminution of postinjury vasoconstriction in animal models with improved functional response has not translated into practical therapies for humans. As an example, low-dose dopamine has been used extensively in human AKI; however, many studies have demonstrated that it is ineffective. In a recent meta-analysis of 61 clinical trials, no effect of low-dose dopamine was found on mortality or the need for renal replacement therapy.¹⁶ Nevertheless, therapies directed toward the vasculature in AKI will continue to be evaluated. It is very possible that initiating therapy earlier in the course of the disease will prove to be more effective, and therapeutic approaches that spare the systemic vasculature while acting on the renal vasculature may be helpful. It is possible that the appropriate receptor important for vasoconstriction has yet to be adequately targeted.

Sepsis is present in a large number of patients with AKI. Early in the sepsis-associated AKI found in animals, a predominant response is vasoconstriction with the relative preservation of tubular function.¹⁷ Over time, however, endotoxemia induces enhanced production of peripheral vasodilatory agents, including inflammatory cytokines, such as tumor

Figure 3: Effects of AKI on arteriolar tone



John Conger and colleagues (University of Colorado) found that the postischemic arteriole is more sensitive to vasoconstrictive agents and less sensitive to vasodilatory agents. In addition, whereas a normal arteriole has a vasodilatory autoregulatory response to a decrease in perfusion pressure, the postischemic arteriole vasoconstricts. Modified from Bonventre (2008)⁴¹

necrosis factor alpha (TNF- α) and interleukin-1 (IL-1), as well as NO, resulting in systemic vasodilation. To counterregulate this vasodilation, there are increased systemic levels of catecholamines and activation of the renin-angiotensin system. Furthermore, the renal nerves are believed to participate in the intrarenal vasoconstriction, since denervation markedly protects the kidney against the decrease in GFR seen with endotoxemia.¹⁷ Endotoxins can also result in endothelial cell damage with a loss of plasma volume, increased interstitial edema in the kidney, and a decreased ability of the renal vasculature to respond to vasoconstrictive influences with counterregulatory NO generation.

Site of tubular injury

In the rodent model of ischemia produced by clamping the renal artery, the proximal tubule in the outer medulla is the most affected following ischemic injury. Even when total perfusion to the kidney is normalized, the outer medulla fails to promptly recover normal blood flow. In the outer medulla, the S3 portion of proximal tubules and the medullary thick ascending limb (MTAL) of Henle dominate. These nephron segments require metabolic substrates for high levels of ATP production; both segments have a vigorous response to ischemia and both generate a large number of cytokines. In most animal models, cell injury is more apparent in the S3 segment of the proximal tubule. There is some controversy as to the relative extent of proximal- versus distal-tubule injury in humans with AKI.⁴ When the urine of patients with AKI from a multitude of causes was examined, a markedly increased amount of kidney injury molecule-1 (KIM-1) ectodomain in the urine was found.¹⁸ Since the proximal tubule cell only produces KIM-1 under conditions of injury, there is clearly a great deal of proximal-tubule injury in human AKI. It is often stated that the degree of histologic injury on biopsy is less than could possibly be predicted by clinical observations of the functional deficit. Unfortunately, there are limited clinicopathological correlations in AKI, since biopsies are not performed on most patients. Furthermore, if tissue is available, it is usually a sample from the cortex and not from the outer medulla where there may be considerable injury. Nevertheless, the appearance of casts and tubular cells in

the urine confirms that there is tubular cell damage with apoptosis and/or necrosis in most cases of human AKI.

Inflammation

Inflammation is an important component of human AKI. Plasma proinflammatory cytokine levels are significantly higher in critically ill patients and patients with AKI than in healthy subjects. Plasma protein oxidation is also more pronounced in patients with AKI compared with healthy subjects, ESRD patients, and critically ill patients.¹⁹ Increased oxidative stress may be an important target for nutritional and pharmacologic therapy in AKI patients. Inflammation contributes in an important way to the reduction of local blood flow to the outer medulla with adverse consequences on tubule function and viability. Furthermore, inflammation likely contributes in a direct way to tubular injury; however, the contributions of inflammation to vascular and tubular pathophysiology remain incompletely understood.

The innate immune response

Both the innate and adaptive immune responses are important contributors to the pathobiology of ischemic injury. The innate component is responsible for the early response to infection or injury and is foreign-antigen independent. Toll-like receptors (TLRs), which are important for the detection of exogenous microbial products and the development of antigen-dependent adaptive immunity,²⁰ also recognize host material released during injury.²¹ The role of TLRs was evaluated using an ischemia/reperfusion model in chimeric mice deficient or not in TLR2 (ie, TLR2^{-/-} and TLR2^{+/+}).²² The absence of TLR2 clearly had an anti-inflammatory effect on the response to ischemia/reperfusion, and this effect was associated with functional protection.

Leukocyte-endothelial interactions

With ischemia/reperfusion, endothelial cells upregulate integrins, selectins, and members of the immunoglobulin superfamily, including intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule (VCAM). A number of vasoactive compounds may also affect leukocyte-endothelial interactions. Vasodilators (eg, NO) may have anti-inflammatory effects; NO inhibits adhesion of neutrophils to TNF- α -exposed endothelial cells.²³ Enhanced leukocyte-endothelial interactions can result in cell-cell adhesion that can physically impede blood flow.²⁴ Furthermore, these interactions will additionally activate both leukocytes and endothelial cells, and contribute to the generation of local factors that promote vasoconstriction, especially in the presence of other vasoactive mediators; this results in compromised local blood flow and impaired tubule cell metabolism.²⁵ Due to the anatomical relationships of vessels and tubules in the outer medulla, these leukocyte-endothelial interactions likely impact the outer medulla to a greater extent than the cortex.

In an early study to evaluate the significance of endothelial-leukocyte interactions and inflammation to the pathobiology of ischemic injury, our research revealed that anti-ICAM-1 antibodies or genetic deletion of ICAM-1 resulted in protection of the kidney from injury.^{26,27} We proposed that this upregulation of ICAM-1 was related to the upregulation of proinflam-

matory cytokines, TNF- α and IL-1. Later phases of AKI are characterized by infiltration of macrophages and T lymphocytes that predominate over neutrophils. Reactive oxygen species (ROS) are generated both during reperfusion and as a result of the inflammatory response, and they play a major role in cell injury. ROS are generated by activated infiltrating leukocytes and by epithelial cells; they are directly toxic to tubular epithelial cells, with ROS-generating systems mimicking the effects of ischemic injury.²⁸

There also may be anti-inflammatory influences that act to decrease the injury associated with ischemia/reperfusion or toxins. Resolvins (Rv) and protectins (PD) are two newly identified families of naturally occurring omega-3 fatty acid docosahexaenoic acid metabolites. In collaboration with the Serhan laboratory that discovered these compounds, our recent research revealed that, in response to bilateral ischemia/reperfusion (I/R) injury, mouse kidneys produce D-series resolvins (RvDs) and PDI;²⁹ these compounds, when administered to animals, can reduce the severity of AKI due to ischemia/reperfusion.

Tubule contribution to inflammatory injury

Both the S3 segment of the proximal tubule and MTAL generate proinflammatory and chemotactic cytokines such as TNF- α , monocyte chemoattractant protein-1 (MCP-1), interleukin (IL)-8, IL-6, IL-1 β , and transforming growth factor-beta (TGF- β), the chemokine-regulated on activation normal T cell expressed and secreted (RANTES or CCL5), and epithelial neutrophil-activating peptide-78 (ENA-78).³⁰ Proximal tubular epithelia may respond to T-lymphocyte activity through activation of receptors for T-cell ligands.³¹ When CD40 is ligated in response to interaction with CD154, there is MCP-1 and IL-8 production, TNF-receptor activating factor-6 (TRAF-6) recruitment, and mitogen-activated protein kinase (MAPK) activation.³¹ CD40 also induces RANTES production by human renal tubular epithelia, an effect that is amplified by production of IL-4 and IL-13 by Th2 cells, a subpopulation of T cells.³² B7-1 (CD80) and B7-2 (CD86) can be induced on proximal tubule epithelial cells *in vivo* and *in vitro*; after their induction, proximal tubule epithelial cells costimulate CD28 on T lymphocytes, resulting in cytokine production.³³

Paracrine effects of bone-marrow-derived stem cells

There is a potential role for interstitial bone-marrow-derived cells in the production of protective paracrine factors that may facilitate repair of the epithelium.⁹ Our research revealed that injection of mesenchymal stem (stromal) cells (MSCs) is protective against renal injury, as assessed by SCr measured 24 hours after ischemia.³⁴ Other groups have found that MSCs protect against ischemic renal injury by a differentiation-independent mechanism.³⁵ In the adriamycin-nephropathy model, injection of the side-population cells (thought to represent a progenitor population) is also protective in the absence of tubular integration.³⁶ The mechanism of such protection may be through intrarenal paracrine effects to decrease inflammation or by systemic immune modulation, since immune cells in the spleen, liver, and lungs may rapidly ingest injected cells. It is

increasingly recognized that MSCs can modulate innate immunity by generating a large number of agents that modify this response.³⁷

Preconditioning

An important finding in animal models of ischemic renal injury is that previous injury protects against future injury and this “preconditioning” effect lasts for several weeks.⁸ These studies indicate that the kidney can activate endogenous protective mechanisms; these mechanisms appear to protect vessels as well as tubules from injury.³ Exploiting these mechanisms will likely lead to new therapies. Although the deliberate induction of sublethal renal ischemia has little practical application to patients, studies of preconditioning in the myocardium have revealed that several pharmacological agents can mediate the same protection as ischemic preconditioning. Cardiac studies have highlighted signaling pathways involving protein kinase A, protein kinase D, and MAPK in preconditioning. Our research findings indicate that NO, a pluripotential molecule derived from inducible NO synthase (iNOS), is a key mediator of protection associated with preconditioning in the kidney.⁸ A recent report from a controlled trial found that 10 minutes of sequential crossclamping in the common iliac arteries resulted in reduced myocardial and renal injury after elective abdominal aortic aneurysm repair.³⁸

Where do we stand with therapy for AKI in humans?

Despite the extensive effort that has gone into studying the pathophysiology of AKI, there are few interventions that have demonstrated effectiveness in humans. Many potential reasons exist to explain why this clinical syndrome has been recalcitrant to effective therapeutics:

- the disease is multifaceted and a single therapy may not be effective
- patients are quite varied with many comorbidities, making the design of clinical trials difficult
- the diagnosis of AKI has depended upon the use of a very insensitive biomarker, SCr, which is delayed in elevation and is affected by a number of factors other than the GFR it is used to measure. This has resulted in a delay in the initiation of therapies in clinical trials.
- the paucity of clinical trials and the absence of an effective clinical trial network
- remaining uncertainties about the critical features in the pathophysiology that are amenable to intervention
- the lack of good surrogate markers for the effectiveness of an intervention.

Despite these disappointments there are a number of reasons to be optimistic. New biomarkers have been identified that will ultimately make the early diagnosis of AKI more tractable.³⁹ The AKIN has been formed to bring the kidney and critical-care communities together to work toward a better understanding and improved treatment of AKI. There is greater recognition of the importance of AKI in the progression to chronic renal failure, and more resources are being allocated to this entity from federal and private funding agencies. Many potential therapeutics are ready to be tested.⁴⁰

Conclusions

Renal injury is a dynamic process that often exists in the context of multiple organ failure; it involves hemodynamic alterations, inflammation, and direct injury to the tubular epithelium, followed by a repair process that restores epithelial differentiation and function. Inflammation plays a considerable role in the pathophysiology of AKI. While the emphasis has been placed on understanding mechanisms of inflammation that contribute to this pathophysiology, it is becoming increasingly recognized that the organism has endogenous mechanisms that are used to control the inflammation. Understanding the regulation of these anti-inflammatory processes may provide insight into possible interventions to facilitate and enhance these mechanisms, and the devastating consequences of AKI may be prevented or mitigated.

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