SECTION 7

Mechanisms of Repair or Progression

CHAPTER 28

Renal Repair and Recovery

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OBJECTIVES

This chapter will:

1. Review the pathogenesis of AKI, including mechanisms of cell death and the cell types that restore renal tubular function after an episode of AKI.
2. Briefly review the role of other cell types (endothelium, inflammatory cells) and of growth factors in the pathogenesis of AKI and recovery from AKI.
3. Determine the impact of renal replacement therapy on renal recovery.

For many years it was accepted that acute kidney injury (AKI) was a reversible process that was followed by renal recovery in survivors. However, with the recognition that even mild AKI is associated with an increased risk of subsequent chronic kidney disease (CKD), this concept has become more controversial. Recovery from AKI is as of yet a poorly understood process that involves a variety of complex mechanisms, and despite a significant interest in therapeutics, it is not clear which factors determine whether functional recovery or progressive kidney fibrosis occurs after AKI.

This chapter reviews common elements of the pathophysiology of different types of AKI and the effects on normal renal architecture. This is followed by a discussion of what is known about the mechanisms of repair and recovery, including updates on progenitor cells, cellular stress responses, growth factors, and the interaction with adjacent cells, extracellular matrix, and endothelium. Most of our understanding of renal injury and recovery is based on experimental animal models, which have had significant limitations when translated to human studies. Many explanations have been proposed, including differences in the nature of the injury (human AKI is often multifactorial, whereas most animal models of AKI focus on either ischemic or septic AKI; furthermore, in general, rodent models are relatively resistant to sepsis) and differences in the timing of therapy (in animal models, therapy can be administered before or at the time of the injury, which is usually not practical in humans). Nonetheless, animal and cell-based models give us the best opportunity to understand in detail specific mechanisms that may play a role in renal repair and recovery. Finally, we will summarize what is known about renal recovery from AKI in human studies.

NORMAL RENAL ARCHITECTURE

Under normal conditions, renal tubule cells are highly polarized epithelial cells.[1] The apical side is characterized by microvilli that contain bundled F-actin filaments. The actin cytoskeleton is a dynamic structure characterized by a highly regulated, steady-state equilibrium between F-actin filaments and G-actin monomers. Cells are connected one to another near the apical surface by a junctional complex that is made up of tight junctions and adherens junctions. The tight junction forms the border between the apical and basolateral surfaces of the cell and segregates proteins and phospholipids to the appropriate cell surface (gate function) as well as blocks paracellular permeability (fence function).

The basolateral surface of the cell also is characterized by distinct proteins and phospholipids. For example, the Na+/K+ ATPase is localized to the basolateral side of the cell and is critical for Na+ transport to the interstitium. Transmembrane integrins bind to extracellular matrix (ECM) proteins. Epithelial cells also have specialized protein complexes at ECM binding sites called focal adhesion complexes. Together, these interactions cause the renal tubular epithelial cell to firmly adhere to the basement membrane.

ACUTE KIDNEY INJURY: COMMON PATHOPHYSIOLOGIC MECHANISMS OF INJURY

Cellular damage in AKI involves two forms of injury: sublethal damage resulting in depolarization of cells (and therefore loss of appropriate cellular functions), as well as

lethal damage resulting in cell death.[2–4] Although there has been controversy regarding which segment of the tubule is the most affected, it is clear that the proximal tubule, and in particular the S3 segment, undergoes significant morphologic changes and therefore has been the subject of much study.[5]

Sublethal cellular injury has been described in animal models and in human studies. In animal models, short ischemic times lead to loss of and fusion of the apical microvilli, whereas longer ischemic times result in shedding of microvilli into the tubular lumen, loss of integrity of the actin cytoskeleton, and ultimately cell death.[6] Junctional complexes are disrupted after AKI, leading to increased paracellular permeability resulting from loss of the "gate" function as well as loss of cell polarity resulting from loss of the "fence" function. For example, the Na+/K+ ATPase that typically is localized exclusively on the basolateral surface can be found on the apical surface after ischemic injury. Mislocalization of these channels contributes to the inability of the proximal tubule to reabsorb Na+, as is commonly seen in AKI.[7] Thus the recovery process must result in reestablishment of polarity of sublethally injured cells, as well as establishment of polarity in the de novo epithelial cells. Reestablishment of polarity appears to require signaling cues from adjacent cells as well as from the extracellular matrix.

At the other end of the spectrum, AKI can cause lethal damage of renal cells, resulting in loss of tubular integrity. Different forms of tubule cell death have been identified, depending on the nature and severity of the injury. Apoptosis is a form of programmed cell death that is characterized by cell shrinkage, nuclear condensation and fragmentation, and rapid clearance by phagocytosis. Most normal cells constitutively express the machinery necessary for apoptosis but are prevented from undergoing apoptosis by the presence of survival factors. Loss of these survival, or growth, factors leads to triggering of apoptosis via a "default" pathway.[4] Apoptotic cell death can occur from extrinsic and intrinsic pathways as well as endoplasmic reticulum (ER) stress.[8] It has been shown that cellular contact with adjacent cells and with the ECM appear to protect cells from apoptosis. After injury, major structural components of the basement membrane including laminin and fibronectin III as well as the cell surface receptors for these basement membrane proteins (e.g., integrins) are upregulated.[9,10] Integrins also are mislocalized after renal injury; this may allow epithelial cells to migrate as part of the recovery process.[11] Normal cell-cell contact via cadherins also provides an antiapoptotic signal in proximal tubular cells.[12]

Depending on the nature and duration of injury, cells also may undergo necrosis, where the release of unprocessed cellular contents into the extracellular space can cause inflammation and creates further damage. A future therapeutic target could be the transformation of cell death by necrosis into apoptosis, which may decrease AKI severity or accelerate recovery. More recently, the process of necroptosis, a form of regulated necrosis,[13] has been described. Necroptosis can be inhibited by RIP1-targeting chemical necrostatin-1 (Nec-1), and treatment with Nec-1 has been shown to partially protect from ischemic AKI.[14]

In addition, AKI frequently is characterized by damage to other cellular compartments. Microvascular injury plays a critical role in septic and ischemic AKI.[15,16] Given the enormous oxygen tension gradient within the normal kidney, small changes in oxygen delivery may greatly exacerbate tissue hypoxia. Furthermore, endothelial cell damage may lead to leukocyte activation and sludging within the capillaries and to release of inflammatory mediators. In ischemic AKI, neutrophils and T cells are recruited to the injured tissue and modulate injury.[17]

In renal biopsies from patients with ischemic kidney injury (e.g., after cadaveric kidney transplantation), the majority of tubules may appear fairly normal, with limited overt cellular shedding or death. However, in animal models of either toxin or ischemia-mediated kidney injury, cellular shedding and death are typically widespread, leading to denuded areas, where the tubular epithelium is no longer intact. These differences may be due to the fact that in animal models, severe ischemia is induced by exposure to high doses of a nephrotoxin or by cross-clamping of the renal artery. In animal models of septic AKI, cellular morphology often appears relatively normal.[18] These differences highlight important distinctions between the clinical entity of AKI and animal models[19–21] and may explain partially why many of the successful interventions for AKI in animal models have not been efficacious in clinical trials.

RECOVERY FROM ACUTE KIDNEY INJURY: MECHANISMS OF MALADAPTIVE REPAIR

The mechanisms involved in regenerating normal renal architecture after AKI are complex and involve recruitment of inflammatory cells, as well as proliferation and differentiation of surviving cells to form polarized epithelial tubules.[22] In some cases the recovery process becomes maladaptive, and not much is known about the molecular switch that differentiates adaptive tissue repair from an impaired repair process that results in fibrosis. Clinical factors associated with maladaptive repair include increasing age, baseline renal function, and the duration and type of kidney injury.[23]

Normally tubular epithelial cells divide at a very slow rate. After mild tubular injury, the rate increases, leaving surviving epithelial cells to enter cell cycle and proliferate and thereby restore the injured areas. A study in three different mouse models of ischemic, toxic, and obstructive AKI showed that the proximal tubular cells arrested in the G2/M stage of the cell cycle after AKI; this G2/M stage cell cycle arrest was associated with activation of a profibrotic phenotype with high levels of secreted cytokines, including transforming growth factor-β1 (TGF-β1).[24] Thus an injury of sufficient severity to cause arrest cells in the G2/M phenotype may contribute to maladaptive repair; modulation of this pathway may prevent progression to CKD.

Macrophages appear to play an important role in determining kidney outcomes after injury, and the balance of macrophage response may contribute to maladaptive repair.[25] Macrophages are recruited the kidney in response to injury. The M1 macrophage is believed to have proinflammatory effects, and if this signal persists, the M1 macrophages amplify the injury and may contribute to fibrosis development.[26] In contrast, M2 macrophages are believed to have beneficial effects and promote proliferation and kidney repair through secretion of growth factors.[27] The M2 macrophages can be recruited from the circulation or by M1 macrophages to adopt an M2 phenotype.

Another vital part of restoring normal architecture is removal of dead tubular epithelial cells after injury. If not removed, these cells can result in renal tubular obstruction, induce inflammation, and impair tissue repair. The clearance of cellular debris is carried out by phagocytosis by a variety of cell types, including macrophages, dendritic cells, and dedifferentiated epithelial cells. Kidney injury molecule-1 (KIM-1) is a marker of kidney injury and is known to promote

phagocytic removal of debris by dedifferentiated epithelial cells. The balance of KIM-1 expression is complex because chronic expression of KIM-1 is thought to be maladaptive and to induce kidney fibrosis, whereas acute upregulation of KIM-1 is believed to be beneficial because of its phagocytic properties.[28,29] Apoptosis inhibitor of macrophage (AIM) has been identified as a ligand to KIM-1 and is expressed on cellular debris. By binding to KIM-1, it promotes the clearance of intraluminal debris and promotes resolution of AKI. Mice with a deficiency of AIM have renal dysfunction and impaired recovery, whereas administration of recombinant AIM was shown to have a beneficial effect on debris clearance and could be a future therapeutic target.[30]

RECOVERY FROM ACUTE KIDNEY INJURY: THE PROGENITOR CELL

One of the first steps in renal recovery is the dedifferentiation of surviving epithelial cells as well as migration of appropriate epithelial cell precursors to the damaged tubules. In various model systems, multiple different types of cells have been implicated in this process: renal tubular epithelial cells, renal-specific progenitor cells, and bone marrow–derived mesenchymal stem cells.

After ischemic injury, surviving renal tubular epithelial cells dedifferentiate.[11] These cells express vimentin, an intermediate filament protein that is found in undifferentiated mesenchymal cells but not differentiated kidney cells, and proliferating cell nuclear antigen (PCNA), a marker of mitogenic activity.[31] In contrast, injured cells do not express either vimentin or PCNA. The molecular drivers of the intrinsic repair process have not been identified, but the transcription factor Sox9 has been suggested to be an important part of the cellular pathway of renal repair in surviving tubular epithelial cells.[32]

Renal-specific stem cells have been described by several independent groups. These cells can be identified using bromodeoxyuridine (BrdU) to label cells that are going through the cell cycle. These cells have been identified in the renal tubules as well as the papilla[33,34] and are capable of expressing epithelial markers in vitro when subjected to appropriate extracellular cues.[33,34] After ischemic renal injury, these cells proliferate and appear to contribute to repopulation of the tubule in animal models. However, study of the role of these cells in renal repair has been limited by the lack of markers that specifically identify this population.

A number of recent studies have examined the potential role of organ-specific stem cells as well as mesenchymal stem cells in renal repair (Fig. 28.1).[35] Renal-specific or bone marrow–derived mesenchymal stem cells may accelerate the repopulation of tubules by direct proliferation or through paracrine effects. Although transplantation studies originally suggested that recipient-derived cells may directly repopulate injured tubules,[36,37] additional studies have suggested that mesenchymal stem cells may predominantly exert their beneficial effects via paracrine mechanisms.[38–41] In addition to the direct release of cytokines, mesenchymal stem cells may release microvesicles, which can allow cell-to-cell communication and protect against renal injury.[42] For example, modulated expression of miRNA in renal proximal tubular epithelial cells may lead to increased protection from apoptosis.[43] Unfortunately, the beneficial effects of mesenchymal stem cells in animal models have not been confirmed in human studies. In a phase 2, double-blinded, placebo-controlled clinical trial in patients undergoing cardiac surgery, there were no significant differences in time to renal recovery.[43a] Currently there is an ongoing phase 1 trial to test the efficacy and safety of mesenchymal stem cells in cisplatin-induced AKI.[43b]

RECOVERY FROM ACUTE INJURY: THE CELLULAR STRESS RESPONSE

In response to injury, cells have an adaptive response to restore normal function. However, if the injury is very severe or prolonged, the cells may tip toward a maladaptive response that can lead to impaired repair.[44,45] Thus targeting the unfolded protein response (UPR), improving protein-folding capacity, and reducing ER stress may be novel mechanisms to prevent impaired recovery.

Autophagy is a cellular stress response that is activated in injured cells to maintain intracellular homeostasis and that at its extreme can lead to cell death. It is characterized by vacuolization of damaged organelles that then are eliminated.[46] Autophagy can be induced in tubular cells in response to injury from AKI. For example, when renal tubular epithelial cells are injured, mitochondrial swelling and fragmentation can occur. The injured mitochondria release reactive oxygen species, cytochrome C, and mitochondrial DNA that can amplify cell injury and promote cell death.[47] Recovery after injury requires the safe removal of fragmented mitochondria (mitophagy) along with mitochondrial biogenesis. Peroxisome proliferator-activated receptor-γ coactivator 1-α (PGC1-α) is a major mediator of mitochondrial biogenesis and has been suggested to play a key role in accelerating renal recovery in mouse models.[48–50] Autophagy may have renoprotective effects by preventing cell death, but the processes are poorly understood.

RECOVERY FROM ACUTE INJURY: ROLE OF ENDOTHELIUM

At present, specific mechanisms of endothelial repair and recovery remain unclear. However, it is clear that endothelial injury plays a critical role in the pathogenesis of AKI.[15] Furthermore, the endothelium regulates leukocyte recruitment to areas of injury and T-helper cell stimulation through upregulation of adhesion molecules, including E-selectin, P-selectin, and ICAM-1.[11] However, immune cell recruitment to the injured tissue may lead to chronic inflammation and maladaptive repair processes after AKI. Multiple strategies to block ICAM-1 have shown that ICAM-1 blockade is protective in the setting of AKI. Interestingly, in a study in which statins ameliorated ischemic renal damage in an animal model, upregulation of ICAM-1, inflammatory cell infiltration, and increased iNOS production were attenuated.[51]

Along the same lines, modulation of the coagulation cascade by activated protein C (APC) may reduce renal injury; APC has been shown to downregulate iNOS and to ameliorate lipopolysaccharide (LPS)-induced AKI[52] as well as ischemic AKI through the ubiquitin-proteasome system, providing evidence that APC also has potent antiinflammatory effects that may limit the extent of tubular damage.[53]

Sphingosine-1-phosphate (S1P) is a bioactive phospholipid that serves as a key regulator in vascular development

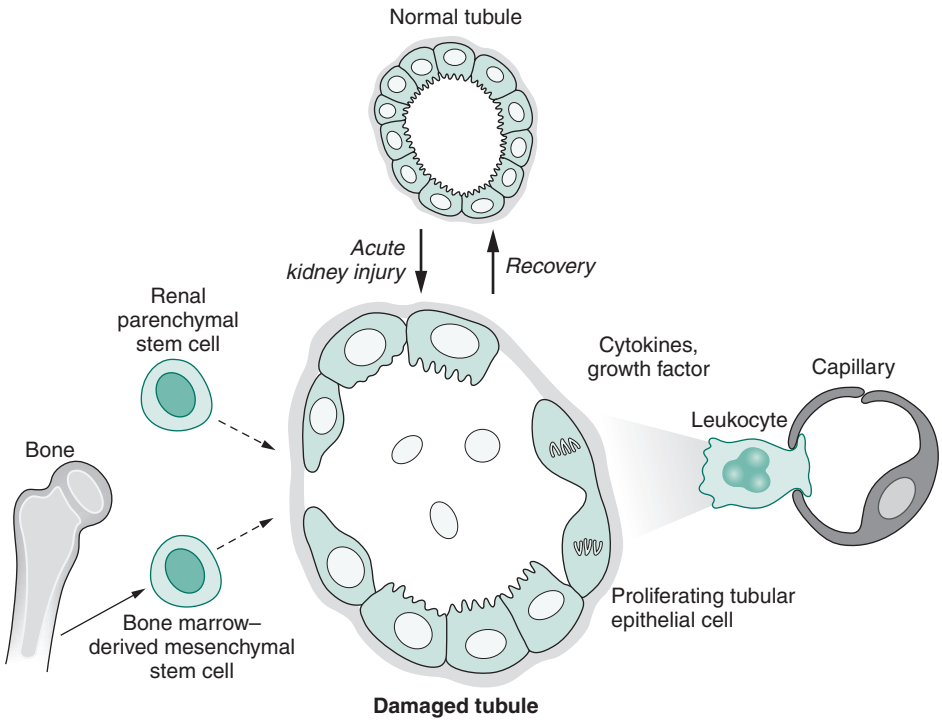

FIGURE 28.1 Critical mediators of renal recovery and repair. After renal injury, multiple cell types participate in the reconstitution and repolarization of the tubular epithelium.

and endothelial barrier integrity. S1P acts through binding to five different G protein coupled receptors (S1P1-5). Deletion of endothelial S1P1-receptor in a mouse model led to exacerbated kidney injury and inflammation and an overall increase in fibrosis. Thus S1P may be involved in renal recovery after AKI and mediate its beneficial effects through activation of endothelial S1P1.[54]

RECOVERY FROM ACUTE INJURY: ROLE OF GROWTH FACTORS

Growth factors may exert important antiapoptotic and proliferative effects on damaged cells. Thus the recovery process may recapitulate many aspects of renal development.[11] A number of growth factors enhance proliferation of tubular epithelial cells in animal models as well as cell culture systems.[21,55] In animal models, administration of exogenous growth factors has been shown to accelerate renal recovery from injury. Although some of these polypeptide growth factors have been studied in clinical trials and not shown to have any significant benefit, these studies highlight important components of the process of renal recovery.

Epidermal Growth Factor

Epidermal growth factor (EGF) is a ubiquitous polypeptide growth factor capable of stimulating proliferation of many types of epithelial cells. EGF activates cellular signaling by engaging the EGF receptor (EGFR), a receptor tyrosine kinase. EGFR is expressed in the adult kidney, and administration of EGF to animals with ischemic or toxin-mediated AKI shortens recovery time.[56] This likely is due to downstream activation of cell survival pathways, including phosphoinositide 3-kinase (PI3K)/Akt and extracellular signal-regulated kinase. Renal epithelial cells and progenitor cells have been shown to proliferate in response to EGF.[34,57] Mice with a targeted mutation in the EGFR have delayed recovery from nephrotoxic AKI,[58] suggesting that this pathway may play an important role in renal repair.

Insulin-like Growth Factor-1

Although insulin-like growth factor-1 (IGF-1) is minimally expressed in the adult human kidney, its receptor is expressed abundantly on proximal tubule cells. After renal injury, expression of IGF-1 is upregulated in surviving proximal tubule cells. In addition, recruited inflammatory cells such as macrophages produce IGF-1.[59] Not only is IGF-1 mitogenic but also it induces expression of EGFR[60] and may enhance proliferation of remaining tubular cells through EGFR signalling. IGF-1 promotes renal blood flow and leads to an increase in glomerular filtration rate, likely via production of prostaglandins and nitric oxide. Finally, IGF-1 promotes anabolism and protein synthesis,[61,62] which may aid in recovery from acute illness. Unfortunately, despite the promise of IGF-1 in animal models, clinical trials in humans failed to demonstrate a benefit of IGF-1.[63]

Alpha-Melanocyte Stimulating Hormone

Alpha-melanocyte stimulating hormone (α-MSH) is an antiinflammatory cytokine derived from pro-opiomelanocortin.[64] Endogenous α-MSH production is upregulated in inflammatory states, and α-MSH downregulates leukocyte activation. α-MSH also appears to have direct

effects on renal tubules, including downregulation of inducible nitric oxide synthase (iNOS), which may attenuate the extent of injury. However, recent clinical trials testing the benefit of exogenous α-MSH for AKI after high-risk surgical procedures were stopped because of lack of apparent benefit.[64a,b]

Erythropoietin

Erythropoietin (EPO) has been shown to accelerate recovery from ischemic AKI.[65] It has been proposed that this is due to improved endothelial cell survival and function, as well as direct effects on tubular epithelial cell proliferation of tubular epithelial cells. However, the positive effect of EPO was not confirmed in a clinical trial from 2010, in which patients were randomized to receive either high-dose EPO or placebo.[66]

Hepatocyte Growth Factor

Hepatocyte growth factor (HGF) has been shown to have mitogenic, morphogenic, motogenic, and differentiating effects via c-met, a receptor tyrosine kinase.[67,68] Injury leads to rapid activation of HGF and c-met within the kidney. In animal models of AKI, HGF therapy at the time of injury markedly accelerated functional and histologic recovery.[69,70] Not only does HGF have important effects on cellular proliferation, it may prevent tubule damage by promoting adhesion of tubular cells to the basement membrane[71] and by activating antiapoptotic signaling pathways.[72] In the late phases of recovery, HGF has antifibrotic effects that may have an important role in the prevention of long-term fibrosis and scarring.[68] However, there have been no trials of HGF in human subjects, in part because of complexities of manufacturing and in part because of the potential for pleiotropic effects.

Bone Morphogenetic Protein-7

Bone morphogenetic protein-7 (BMP-7), also known as osteogenic protein-1, is a member of the TGF-β superfamily,[73] whose expression persists in the adult kidney, in particular in the collecting tubule, the glomeruli, and the renal arteries. Renal ischemia leads to decreased levels of BMP-7 mRNA, likely because of local tissue damage.[74] Administration of exogenous BMP-7 at the time of ischemic injury attenuates the severity of the injury,[75] perhaps via reduced ICAM-1 expression and decreased inflammatory cell–mediated injury. In cell culture models, BMP-7 also appears to downregulate proinflammatory cytokines, including interleukin-6 and monocyte chemotactic protein-1, as well as endothelin-2, a potent vasoconstrictor.[76] Like HGF, BMP-7 appears to have important antifibrotic effects in the recovering kidney.[77]

Transforming Growth Factor-β

TGF-β is a profibrotic growth factor that is a critical mediator of the epithelial to mesenchymal cell transition (EMT).[77] Although TGF-β receptor expression is upregulated after injury, TGF-β does not appear to play a critical role in early renal recovery because immediate treatment with TGF-β neutralizing antibodies does not slow renal recovery.[78] However, treatment with neutralizing antibodies results in reduced capillary dropout and interstitial inflammation, suggesting that TGF-β may play a critical role in the long-term effects of AKI. Indeed, TGF-β appears to be an important mediator of renal fibrosis in many different contexts.

EMERGING RESEARCH AREAS: ROLE OF EPIGENETICS IN ACUTE KIDNEY INJURY

In epigenetic regulation, DNA methylation and histone modification modulate gene expression without changes in the DNA sequence. Epigenetic regulation may provide a novel way to enhance renal recovery through alternate expression of relevant genes. A recent study explored the epigenetics of important AKI-associated genes in ischemia/reperfusion and endotoxin-induced AKI models and found significant heterogeneity in the transcriptional and epigenetic responses of important genes (including tumor necrosis factor [TNF], neutrophil gelatinase-associated lipocalin [NGAL], kidney injury molecule-1 [KIM-1], and intercellular adhesion molecule-1 [ICAM-1]) depending on the type of injury.[79] This diversity, which was determined predominantly by the type of kidney injury, supports the theory that AKI is a multifactorial disease. There is still a long way before epigenetic regulation in AKI will be the therapeutic target, but research in this area could provide useful insight into transcriptional changes that are associated with impaired response signals and subsequent fibrosis.[27]

STRATEGIES TO ACCELERATE RENAL RECOVERY: HUMAN STUDIES

A number of clinical treatments have been proposed to enhance renal recovery from acute injury[21] or are under active study,[80] but none have shown efficacy. Thus dialysis is the primary supportive therapy for patients with severe AKI. The impact of renal replacement therapy on renal recovery has been the subject of significant interest and has been reviewed recently.[81] The best established aspect of dialysis in the context of AKI is dose, where there appears to be a minimum accepted dose.[82,83] However, the impact of several aspects of the dialysis prescription remain controversial or unknown. A number of studies have focused on the effects of dialyzer membranes on mortality and renal recovery because the original cellulose-containing membranes activate complement and coagulation factors. Newer synthetic membranes including polysulfone as well as cellulose membranes containing synthetic sidegroups are more "biocompatible." Although these membranes initially were shown to have a positive impact on renal recovery and mortality, subsequent studies did not support these results. Several meta-analyses have been published, with varying conclusions; nonetheless, at present, biocompatible membranes are used routinely and may have a modest effect on renal recovery.[84]

With regard to the impact of timing of dialysis initiation on renal recovery, a recent large randomized multicenter clinical trial and a multicenter pilot study suggested that among patients who are randomized to receive early versus standard dialysis, a substantial proportion of patients in the standard dialysis arm had renal recovery before initiating dialysis.[85,86] In the larger AKIKI trial, there was no difference in the rate of dialysis dependence at day 28 or 60 between the two arms, but the rates of dialysis dependence were low.[85] Not surprisingly, patients who were randomized to receive standard dialysis had fewer days of RRT than those

randomized to accelerated initiation. The long-term effects of these therapies on kidney function remain unknown. Although a single-center clinical trial suggested that there was benefit to early initiation,[87] this study has been criticized because dialysis was initiated extremely early, and the magnitude of the effect was larger than could be reasonably expected.[88] Additional clinical trials to examine the impact of timing on renal recovery are ongoing.

Finally, there has been much interest in the impact of dialysis modality on renal recovery. Continuous renal replacement therapy has an a number of features that may enhance renal recovery compared with intermittent hemodialysis,[89] predominantly prevention of intradialytic hypotension. It also has been proposed that CRRT may lead to enhanced clearance of inflammatory mediators, but this benefit is purely theoretical and has not been substantiated with current membranes. There have been a number of randomized clinical trials of modality. In these studies, patients could be included only if the mean arterial pressure could be maintained at more than 65 mm Hg. Furthermore, in some of these studies, intermittent dialysis sessions were long and perhaps better described as prolonged intermittent renal replacement therapy (PIRRT). However, in aggregate, modality does not appear to have a significant impact on overall survival or renal recovery.[81]

CONCLUSION

AKI is a complex process, involving sublethal cell injury and cell death through a number of mechanisms, with a resultant need for repair, proliferation, and repolarization of remaining tubule cells. In addition, changes to the renal microvasculature contribute to tubular injury. Renal tubular epithelial cells as well as renal specific and mesenchymal stem cells appear to contribute to the recovery process, although it appears that most of the effect of mesenchymal stem cells is paracrine. A number of peptide growth factors have been studied in animal models and shown to play a role in the recovery process or to accelerate recovery, although new therapies for human disease based on this work have not yet been possible. Last, additional studies are needed to understand the effects, positive and negative, of renal replacement therapy on recovery from AKI.

Key Points

1. The pathogenesis of acute kidney injury (AKI) involves sublethal tubular cell injury and cell death (apoptosis, necrosis including necroptosis, and in extreme cases, autophagic cell death).
2. Tubular epithelial cells, renal specific progenitor cells, mesenchymal stem cells, and leukocytes appear to play a role in the recovery process.
3. Although the mechanisms of endothelial repair are not well understood, it is clear that endothelial injury is a critical mediator of AKI.
4. Growth factors appear to play a critical role in tubular repair/recovery.
5. The impact of renal replacement therapy on renal recovery is not well understood.

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