CHAPTER 32

# Localization of Injury and Repair Pathways

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**OBJECTIVES**

This chapter will:

1. Describe the principal targets of acute kidney injury and the renal stress response after injury.
2. Summarize what is known about the role of tubular epithelial cells in renal recovery.
3. Describe the existence of renal tubular progenitor cells and their role in renal regeneration.

## LOCALIZATION OF INJURY

Acute kidney injury (AKI) can be defined as an acute decrease of glomerular filtration rate, in many cases resulting from transient ischemia or exposure to nephrotoxins.[1,2] The hallmarks of AKI after either ischemic or toxic insults are tubular damage, characterized by loss of proximal tubular cell brush border, loss of epithelial cell apical-basal polarity, cell detachment from tubular basement membrane, cellular cast formation in the lumen of renal tubules, apoptosis, and necrosis.[3–6] The principal targets of injury are the S3 segment of the proximal tubule and the medullary thick ascending limb of the loop of Henle, because these tubular segments in the outer stripe of outer medulla are characterized by high metabolic activity and exist physiologically in relatively lower oxygen conditions.[7,8] In fact, the renal parenchyma is characterized by a nonhomogenous distribution of oxygenation, with $pO_2$ declining at the corticomedullary junction around 25 mm Hg under normal conditions. The medulla receives only 10% of total renal blood flow originating from the efferent arterioles of the juxtamedullary glomeruli. The low oxygen delivery in this area results from a limited blood supply and oxygen diffusion from descending to ascending vasa recta. In addition, the S3 segment is particularly susceptible to ischemia because it relies predominantly on aerobic ATP production and it is unable to produce energy through glycolysis under anaerobic conditions.[8] Furthermore, the proximal tubule reabsorbs most of the filtered substances including toxins.

During renal ischemia, the rapid depletion of ATP leads to collapse of the actin cytoskeleton and disruption of the adherent junction integrity, which result in the loss of cell polarity and cell matrix adhesion, facilitating cell exfoliation into the luminal space. This process culminates in tubular obstruction and may severely increase tubular pressure and impair fluid flow.[1,2] In addition to these structural changes of tubular epithelial cells, ATP depletion during renal ischemia also induces the expression of adhesion molecules and chemokines that attract mononuclear and polymorphic cells, producing a positive feedback pathway of inflammation and cellular damage not only to the epithelial cells but also to the vascular endothelial cells.[1,9]

If the damage initially localized in the outer stripe of outer medulla is extensive, it could give rise to a secondary

damage in the renal cortex as a consequence of hemodynamic injury mechanisms triggered by significantly reduced renal mass. Cortical damage would be particularly severe if medullary tubules undergo atresia and become obstructed. The cortical consequences of medullary tubular damage also are highlighted by clinical observations. For example, human papillary necrosis, such as that caused by acetaminophen toxicity, determines injury to the papilla, but it is followed by cortical atrophy.[10]

## ADAPTIVE REPAIR AFTER ACUTE KIDNEY INJURY: THE RENAL STRESS RESPONSE

After AKI, the kidney often recovers its structure and function via adaptive repair and regeneration. This process can be considered as an innate wound-healing response, consisting of injury, repair, and recovery phases. The cellular response to injury is heterogeneous with some cells undergoing death via apoptosis or necrosis,[11] whereas others are damaged sublethally. Cell death, combined with the detachment and loss of viable epithelial cells, leads to denudation of S3 segment areas. The severity of AKI may be related to the number of sublethally injured cells that are able to maintain viability and contribute to a repair process restoring kidney function. Indeed, the kidney has a remarkable capacity for repair, which is evidenced by apparently complete recovery of function occurring after AKI.[12–14]

In response to injury, surviving renal tubular cells activate the so-called "renal stress response," an intrinsic cytoprotective response (Fig. 32.1). The cellular stress response produces a "switch" of the cellular machinery from housekeeping activities toward reaction against stress[15] that increases the cell's chance of survival. In addition, a significant amount of data suggest that intrinsic protective mechanisms activated by kidney when exposed to a toxic or ischemic insult protect it against a subsequent injury.[16] This concept that prior injury protects against a second insult is termed *ischemic preconditioning.*

The protective renal stress response mainly includes at least three pathways:

1. heme oxygenase and antioxidant genes,
2. heat shock proteins, and
3. stress-activated protein kinases.

### *Heme Oxygenase and Antioxidant Genes*

Heme oxygenase (HO) is the rate-limiting enzyme in the degradation of heme, converting heme to biliverdin, during which iron is released and carbon monoxide is emitted. Three isoforms of HO exist: an inducible isoform HO-1 and two constitutive isoforms, HO-2 and HO-3.[17] In healthy kidneys, HO-1 is weakly expressed in the proximal and distal tubules, in the loop of Henle, and in the medullary collecting tubules, whereas HO-2 is expressed in the preglomerular vasculature, the thick ascending limb, distal convoluted and connecting tubules, and the collecting duct. A lot of stimuli involved in the pathogenesis of renal injury, such as heme, nitric oxide, cytokines, ischemia, LPS, irradiation, and nephrotoxins, induce an overexpression of HO-1.[17] Induction of HO-1 occurs as an adaptive and beneficial response to these stimuli, as demonstrated by different studies, thanks to its vasorelaxant, antiinflammatory, and antiapoptotic actions. It has been hypothesized that HO-1 exerts a protective antioxidant response because it degrades heme, a pro-oxidant factor, and replaces it with bilirubin, a potent antioxidant.[18] In animal models, HO-1 is induced rapidly after ischemia/reperfusion (IRI),[19] glycerol-rhabdomyolysis,[20] and nephrotoxic injury.[21] The beneficial role of HO-1 in AKI derives from multiple studies in which HO activity is impaired. In a model of IRI, the inhibition of HO activity by tin mesoporphyrin resulted in an increased of heme concentration. Consequently, the latter significantly exacerbated renal function, as demonstrated by a sustained increase in serum creatinine concentration and extensive tubular epithelial cell injury.[22] Similarly, pretreatment with tin protoporphyrin, in a model of cisplatin-induced nephrotoxic injury, led to higher serum creatinine and reduced glomerular filtration rate.[21] Mice with a null mutation in HO-1 showed greater loss of kidney function and increased mortality in response to ischemia reperfusion,[23] glycerol,[20] and LPS.[24] Conversely, the prior induction of HO-1 by small, non toxic doses of hemoglobin strikingly protected against acute renal failure.[18]

### Heat Shock Proteins

Heat shock proteins (HSPs) are abundant intracellular proteins constitutively expressed. They are molecular chaperones, and their main functions are regulation of protein complex formation, protein trafficking, refolding of denatured proteins, mitochondrial protein folding and assembly, targeting of misfolded proteins for proteasome degradation, preventing unfolded protein aggregation, and inhibiting apoptosis. It is believed that HSPs have a protective effect in AKI.[25] One of the first reports supporting this role was from Emami et al.,[26] who described an increase in HSP72 after a transient ischemia of 15 min. Now it is well known that, in addition to HSP72, other HSP family members are induced significantly in various models of renal injury.[27–30] It is suggested that the cytoprotective role of HSPs in kidney injury is related to a combination of effects:

- Correction of protein conformation:
  After cellular injury, HSPs refold and stabilize damage proteins, target irreparable damaged proteins for degradation, prevent aggregation of unfolded proteins, and assist the correct folding, assembly, and transport of new proteins.[31]
- Cytoskeleton stabilization:
  After AKI, tubular cells lose their polarity and cytoskeleton is destroyed rapidly. There is broad experimental evidence that HSPs have an important role in repairing essential proteins involved in stabilizing cytoskeletal structure.[15]
- Antiinflammatory effects:
  HSPs also may provide protection in the setting of injury by attenuating inflammation. Indeed, HSP70 can limit proinflammatory nuclear factor-κB (NF-κB) signaling in kidney after IR by stabilizing IKB or marking proinflammatory HSP90 client proteins for degradation.[32]
- Apoptosis inhibition:
  HSP activity may confer cytoprotection by interacting with or inhibiting important proteins involved in apoptotic pathways.[33] For instance, HSP72 associates with AIF (apoptosis-inducing factor) and prevents DNA fragmentation in ATP depletion.[34] Furthermore, in renal IRI, HSP70 limits apoptosis by controlling the activity of the protein kinase B (also known as Akt) and glycogen synthase kinase 3β, which regulate the activity of the proapoptotic protein Bax.[35] As a result, the selective overexpression of HSP72 has been shown to decrease apoptosis in vitro.[36]

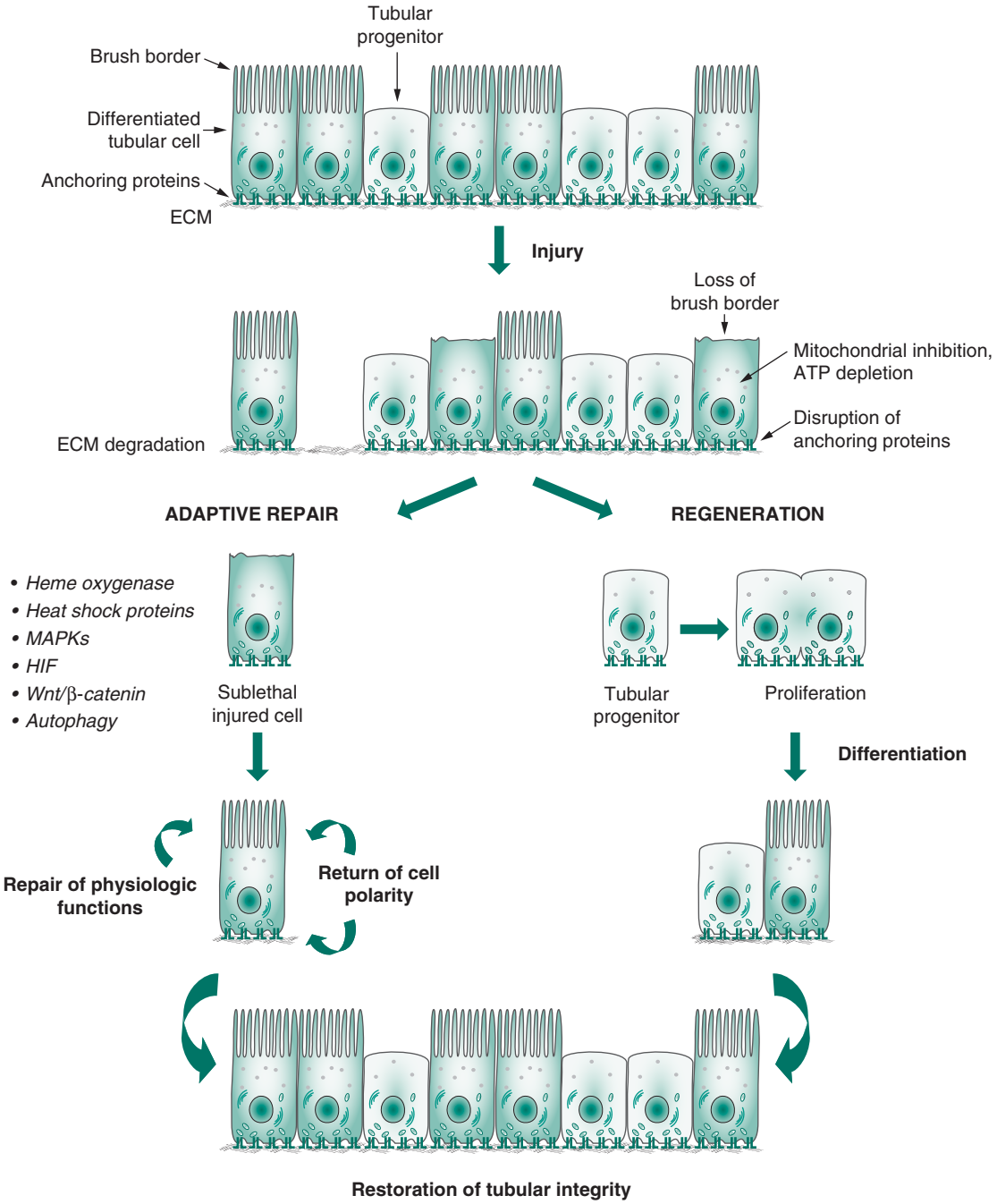


**FIGURE 32.1** Adaptive repair and regeneration of tubular cells after acute kidney injury (AKI). After AKI some tubular cells die via apoptosis or necrosis and detach from the extracellular membrane (ECM), other cells are sublethally injured. They lose their brush border and anchoring protein integrity, and they undergo mitochondrial inhibition and ATP depletion. In response to these insults, sublethally injured cells activate cytoprotective adaptive repair processes, stress response and other adaptive mechanisms, that mitigates the insult and allows them to restore normal physiologic functions and reacquire correct cell polarity. On the other side, tubular progenitor cells, which are more resistant to death, survive, proliferate, and differentiate to replace lost tubular cells. These two processes, adaptive repair of survived differentiated cells and regeneration of progenitor cells, contribute to the restoration of renal function and reepithelialization of damaged nephrons. *ATP,* Adenosine Triphosphate; *HIF,* hypoxia-inducible factor; *MAPKs,* mitogen-activated protein kinase.

## Stress-Activated Protein Kinases

The responses of renal cells to hypoxia encompass a series of signaling pathways that enables them to adapt to hypoxic conditions. Among them, mitogen-activated protein kinase (MAPK) pathways have been studied recently. MAPKs are a group of serine/threonine kinases that regulate cell proliferation, differentiation, and survival. There are four different MAPKs: extracellular signal-regulated kinase-1 and -2 (ERK1/2), c-Jun N-terminal kinase (JNK), p38 MAPK, and extracellular signal-regulated kinase-5 (ERK5/BMK1). These systems are activated in response to kidney injury and/or renal tubular cell stress in vitro.[37–40] Several studies showed that, although ERKs are prosurvival factors, p38 and JNK

are proapoptotic, under hypoxic/ischemic conditions.[37,41] However, understanding of the role of MAPKs is not so simple; a lot of conflicting results in recent studies require clarification. ERK1/2 activation determines renal epithelial cell survival during oxidative injury, and this effect can be prevented by ERK1/2 inhibition in the kidney.[37] Moreover, inhibition of monoamine oxidase in a model of ischemia/reperfusion promoted ERK1/2 activation, increased tubular cell proliferation, and decreased necrosis of renal tubular cells.[41] The phosphorylation of ERK1/2, induced by heme oxygenase-1, ameliorated kidney ischemia/reperfusion injury, enhanced tubular recovery and subsequently prevented further renal injury in mouse kidneys.[42] In addition, a recent study demonstrated that activation of ERK after IRI is required for restoration of damaged tubular cells and the inhibition of fibrosis progression after injury.[43]

In contrast, however, a significant body of literature demonstrates a role for ERK activation in the induction of apoptosis. For example, Ka et al.[44] showed that 4,5,6,7-tetrabromobenzotriazole, an ATP/GTP inhibitor of casein kinase-2, induced the suppression of NF-κB activation through the inhibition of the ERK1/2 pathway and significantly improved renal function and architecture after IRI. In another study, inhibition of ERK activation using U0126 pretreatment protected against F-actin reorganization and disruption of focal adhesions in a model of IRI. In addition, U0126 significantly attenuated injury to the kidney.[45] These conflicting results may depend on different experimental model, stress type, and many other factors, so the role of ERK1/2 requires further clarifications.

## OTHER ADAPTIVE AND REPARATIVE MECHANISMS

In addition to the classic stress response described earlier, renal cells are able to activate other adaptive response pathways that may mitigate the insult transforming potentially lethal cellular insults into sublethal forms of cell injury (see Fig. 32.1).

### Hypoxia and Oxidative Stress Mediators

Hypoxia plays a central role in ischemic, toxic, and sepsis-induced AKI. One of the self-preserving mechanisms that the kidney can activate in response to low oxygen levels is hypoxia-inducible factor (HIF) stabilization with the induction of protective HIF-dependent genes. HIF1 and -2 are key mediators in cellular oxygen homeostasis and regulate the expression of gene products involved in cellular energy metabolism, glucose transport, angiogenesis, erythropoiesis, pH regulation, apoptosis, and cell proliferation as well as cell-cell and cell-matrix interactions.[46] HIF1 and -2 are heterodimeric helix-loop-helix transcription factors constituted by two subunits: an oxygen-sensitive α subunit and a constitutively expressed β subunit. Under normoxic conditions, HIFα binds to von Hippel-Lindau tumor suppressor protein and prolyl hydroxylase domain and is degraded.[46] By contrast, during hypoxia, prolyl hydroxylases are inactivated; for this reason HIFα is not degraded and translocates to the nucleus, where it dimerizes with HIFβ to regulate the transcription of target genes.[46]

HIF1α/HIFβ dimerization and nuclear translocation has been reported in kidneys after ischemic injury.[47] A recent study demonstrated that HIF1α (+/-) and HIF2α (+/-) mice subjected to IRI underwent substantially more severe injury despite controls.[48] In addition, treatment with l-mimosine and dimethyloxalylglycine, two small molecules that, inhibiting HIF hydroxylases, activate HIF to protect mouse kidneys from IRI.[48] These observations are consistent with a protective role for HIF.

In another study, Morg1 (MAPK organizer1), an enzyme that interacts with prolyl hydroxylase, regulating the expression of HIF1α and HIF2α, was evaluated in transgenic mice.[49] It was observed that renal ischemia in Morg1 (+/-) mice resulted in less renal inflammation, reduction of proinflammatory cytokines, and less apoptosis and tubular damage compared with control mice.[49]

### Wnt/β-Catenin Pathway

Evidence is emerging that several key developmental pathways, including Wnt signaling, have an essential role in promoting kidney repair and regeneration after injury, demonstrating that the renal response to injury is able to recapitulate its own development.[50,51]

Both gain-of-function and loss-of-function studies indicate that Wnt/β-catenin pathway has an essential role in minimizing initial kidney damages and promoting adaptive repair and regeneration after AKI.[52–54] Indeed, Wnt/β-catenin has been shown to be a potent survival factor, protecting tubular epithelial cells against apoptosis both in vitro and in vivo during the injury phase,[52] a potent inducer of cell-cycle progression of renal tubular cells[55,56] during the regeneration phase, and an inducer of apoptosis of fibroblasts during the recovery phase. β-catenin signaling promotes survival by inhibiting Bax activation, oligomerization, and translocation to mitochondria.[57] In addition, recent studies illustrated that activation of β-catenin by Wnt1 protected tubular epithelial cells from apoptosis, activated Akt, induced survival, and repressed p53 and Bax expression, demonstrating that early and appropriate activation of Wnt/β-catenin signaling was required for minimizing the initial renal damages after AKI. Accordingly, in conditional knockout mice with tubule-specific ablation of β-catenin, ischemic or toxic AKI caused higher mortality, elevated serum creatinine, and more severe morphologic injury compared with control mice.[52] Regarding the proliferation of tubular cells after AKI, recent studies show that Wnt/β-catenin signaling participates also in this process. The best characterized targets of Wnt/β-catenin are cyclin D1 and c-myc, two of the most crucial proteins in regulating cell proliferation and cell-cycle progression, suggesting that Wnt4 and β-catenin could induce proliferation of renal tubular cells, enabling these cells to restore denuded epithelium after AKI.[55,56] A complete recovery after AKI requires not only full tubular repair and regeneration but also the subsequent resolution of renal infiltrated cells and activated fibroblasts. Indeed, renal fibroblast activation is transient in the cortex and in the outer stripe of outer medulla and then gradually disappears when renal function restores.[58] The mechanism underlying such resolution of activated fibroblasts is related partially to the Wnt/β-catenin–mediated induction of matrix metalloproteinase 7 (MMP7) that in turn induces Fas ligand (FasL) expression in fibroblasts, potentiating their apoptosis in renal interstitium.[59] However, a prolonged activation of Wnt/β-catenin in vivo accelerates AKI-to-CKD progression through the activation of interstitial fibroblasts.[60] Collectively, these findings support the notion that an early and transient activation of Wnt/β-catenin after AKI is renoprotective by facilitating tubular repair and regeneration, whereas sustained

activation of the same signaling promotes AKI-to-CKD progression.

## Selective Autophagy

Autophagy is an intracellular degradation process used by eukaryotic cells as a basal quality-control mechanism to degrade and turnover aged or damaged cellular components to maintain homeostasis. The final step of autophagy involves reactivation of mTOR (mammalian target of rapamycin), a pivotal modulator of cell growth, survival, and metabolism. Accumulating autophagy research corroborates the critical role of this cellular homeostasis pathway in regulating cell viability during tissue injury and repair.[61] Several genetically modified animal models, with either tubule epithelial cell-specific or systemic deficiency of genes involved in the autophagic pathway, provide evidence that supports a cytoprotective role of autophagy in various kidney diseases and AKI.[62] Indeed, autophagy has been shown to be rapidly induced in ischemic AKI model, and autophagic flux was increased during the reperfusion phase after ischemic injury, which occurred well ahead of tissue damage.[63] In these stressed situations, selective autophagy occurs to remove toxic materials within cells. Under pathologic conditions, mitochondrial dysfunction such as the uncoupling of oxidative phosphorylation and loss of mitochondrial membrane integrity involve excessive production of Reactive oxygen species, ROS, (superoxide, $O_2^-$; peroxynitrite, $ONOO^-$; nitric oxide, NO). Oxidative damage leads to mitochondrial disruption, mitochondrial permeability transition, and the release of proapoptotic proteins.[64] Mitochondrial fragmentations and the subsequent severe oxidative stress (ROS) are the upstream signals that induce the activation of a selective autophagy (mitophagy) that occurs to remove damaged or fragmented mitochondria. Such mitophagy is important to our understanding of the pathophysiology of AKI and the mechanisms linking AKI to the progression of chronic kidney disease. Alteration of mitophagic state significantly exacerbated AKI in a cisplatin-induced AKI model in mice. Indeed, inhibition of autophagy obtained through knockout of a mitophagy-related molecule, autophagy gene-related 7 (Atg7), in proximal tubules exacerbated renal dysfunction, acting through tissue damage and apoptosis. In contrast, rapamycin treatment, which activates the mitophagic pathway, attenuated tubular damage in cisplatin-induced AKI.[65] Molecular mechanisms of mitophagy in the kidney are not well understood, but activation of p53 has been reported in several models of AKI, and p53-mediated inhibition of mitophagy contributes to AKI pathophysiology.[66] Antimycin A or myxothiazol has been investigated as pharmacologic inducers of mitophagy. Treatment with this molecule can ameliorate cisplatin-induced p53 activation and exert cytoprotective effects in vitro.[67] However, drugs that induce mitophagy also induce mitochondrial depolarization, suggesting that these drugs exhibit a dual function. For this reason, drugs that remove specifically dysfunctional mitochondria are desirable.

# RENAL REPAIR AFTER ACUTE KIDNEY INJURY: EVIDENCE FOR THE EXISTENCE OF A TUBULAR PROGENITOR RESPONSE

For many years it was accepted that AKI was fully reversible, in particular after mild tubular injury episodes, as kidney function was restored within a few days in survivors of AKI.[2,68] The kidney's capacity for regeneration was attributed to an efficient mechanism for the production of new tubular cells to replace those lost through apoptosis and necrosis or shed in the urine. This efficient mechanism traditionally is assigned to a diffuse proliferative response of surviving tubular cells that dedifferentiate, proliferate, migrate to denuded areas, and redifferentiate to reconstruct functional tubules.[2,68] However, despite the supposed efficient regenerative capacity of the kidney, the mortality rate associated with acute renal failure remains high, and an increasing number of epidemiologic studies reveal that survivors of AKI, even after a mild AKI episode, exhibit a persistently increased risk of progressive CKD, proteinuria, and an excess risk of cardiovascular mortality.[69] These observations are incompatible with the assumption that all tubular cells are able to divide and replace lost cells, and suggest that, probably, the renal tubule is unable to repair itself in a complete and efficient manner.

For this reason, in recent years, more attention has been paid to understanding the mechanisms that regulate kidney repair and whether tubular regeneration after injury arises from proliferation of surviving mature cells or from renal stem cells.

In 2011 a novel subpopulation of proximal tubular cells was described.[70] Because these cells showed a distinct morphology and were scattered throughout the entire proximal tubule, they were termed *scattered tubular cells,* STCs.[70] When STCs first were discovered, it was proposed that they were the most likely candidate cell population to mediate cellular regeneration after AKI.[70,71] Despite the surrounding tubular cells, these scattered progenitor cells showed ultrastructurally distinct features: they contained less cytoplasm, fewer mitochondria, no brush border, and higher levels of the anchoring protein collagen-7A1 (COL7A1) and the tight junction protein claudin-1 (CLDN1).[72,73] The lower mitochondrial content indeed may increase their resilience to hypoxia, in addition to the increased expression of antiapoptotic BCL-2.[70] Another trait of robustness is likely represented by the expression of COL7A1 and CLDN1, which confer an increased adherence to the basement membrane and therefore a higher resistance to mechanical stress (see Fig. 32.1).[73]

Accordingly, in a subsequent study, Angelotti et al. described the existence of a population of tubular-committed progenitors, which are scattered within the proximal tubule, the thick ascending limb, the distal convoluted tubule, and the connecting segment and are characterized by expression of CD133 and CD24 (markers of renal progenitor cells localized in the Bowman's capsule) in the presence of low levels of differentiation tubular markers.[74] These cells in vivo displayed the capacity to regenerate tubular structures. Indeed, once injected in Severe Combined Immunodeficiency (SCID) mice affected by AKI, they engrafted within the kidney, generated novel tubular cells, and significantly reduced the morphologic and functional kidney damage, a property that was not shared by other tubular cell types in the adult kidney. Interestingly, these renal progenitors localized prevalently in the S3 segment, the tubular segment most susceptible to ischemic and toxic insults. Even if they represent only 2% to 6% of proximal tubular cells, when terminally differentiated tubular cells are damaged and die, these progenitors become a large proportion of the surviving epithelium.[74] Consistently, in renal biopsy of patients affected by acute or chronic kidney disease, regenerating tubules show long stretches of proliferating CD133+CD24+ progenitor cells.[74] This observation suggests that tubular progenitor cells are more resistant to death than

differentiated epithelium, so in presence of an injury, differentiated cells preferentially die and progenitor cells become the prevalent population. This enrichment could explain why, for so a long period, it was believed that the presence of an undifferentiated population after kidney injury was the result of a dedifferentiation process of tubular mature cells. The higher resistance to apoptotic stimuli also was confirmed in vitro after treatment with an injurious agent, such as the nephrotoxic hemoglobin.[74]

In agreement with these observations in humans, Langworthy et al., using a novel NFATc1 (nuclear factor of activated T cells cytoplasmic 1) transgenic mouse line, demonstrated the existence of a tubular subpopulation that displayed a high resistance to apoptosis and that proliferated after injury with mercuric chloride.[75] This study demonstrates that also in mice, as well as in humans, tubular regeneration is due to scattered progenitor cells that, by virtue of their resistance to death, survive to renal damages, proliferate, and replace lost tubular cells (Fig. 32.1).

The introduction of significantly advanced technology has opened new possibilities to understand kidney repair capacity and to finally dissect the contribution to regeneration of tubular progenitor versus differentiated cells. Recently Rinkevich et al. performed a clonal analysis of tubular cells at a single level, using an inducible transgenic mouse model, in which the expression of Confetti reporter is driven by the ubiquitous actin promoter.[76] With this system, all renal epithelial cells are marked with one of four fluorescent proteins expressed stochastically (red, yellow, green, and blue) regardless of their location, and a clonal expansion of a cell appears as a long line of cells with the same color. In this mouse model, after IRI, Rinkevich described the appearance of single-color clones in the damaged kidney, suggesting that the kidney can undergo tubulogenesis through clonal proliferation of fate-restricted progenitors.

Unfortunately, a marker that specifically identifies tubular progenitors in the mouse adult kidney remains unknown. The identification of a specific marker for tubular progenitors in mice and the use of genetic tagging experiments will allow tracing of the progenitor population in the mouse kidney, finally establishing the real contribution of tubular progenitors to regeneration.

## CONCLUSION

Several studies suggest that there is a delicate and dynamic relationship between tissue repair and progression or regression of renal injury. The factors that govern this delicate balance must be analyzed extensively for future therapies, in the attempt to stop AKI progression into end-stage renal failure.

Indeed, AKI is a global public health problem associated with high morbidity and about 1.7 million deaths per year.[69,77] The majority of research in the field has focused on the determination of events that cause renal tubular cell injury and death. However, despite the advent of dialysis and increasing knowledge regarding the causes of AKI, nearly half of those who develop the disease do not survive. This suggests that it is necessary to approach the problem from a different point of view to develop more efficacious therapeutic strategies. It is now well known that the kidney is able to activate intrinsic pathways that are cytoprotective and increase the cell's chance of survival. Selective modulations of these pathways may represent potential therapeutic targets to reduce the severity of AKI and obtain a shift toward regeneration rather than progression.

The regenerative capacity of the kidney is well documented, and the role of stem cells is a very active topic of research. In addition, new genetic technologies are emerging that may have future benefits for lineage tracing studies in the kidney, allowing to perform tracking of specific cell subpopulations in mice. These novel genomic manipulation techniques could help to solve many of the ongoing questions and debates regarding kidney regeneration.

Understanding pathways that govern regeneration is a critically important question, because modulation of these pathways could have a significant impact on injury repair, reducing the risk of progression to chronic kidney disease.

### Key Points

1. The principal targets of acute kidney injury (AKI) are the S3 segment of the proximal tubule and the medullary thick ascending limb of the loop of Henle, because these tubular segments exist physiologically in relatively lower oxygen conditions and are unable to produce energy through glycolysis under anaerobic conditions.
2. The cellular response to AKI is heterogeneous with some cells undergoing death via apoptosis or necrosis, whereas others are sublethally damaged.
3. Surviving renal tubular cells that are sublethally injured activate adaptive and cytoprotective response pathways that allow them to repair physiologic functions and restore normal architecture.
4. Recent studies demonstrated that tubular progenitor cells exist throughout the tubules, they are more resistant to death, survive after injuries, proliferate, and differentiate to replace lost tubular cells.
5. These two processes, adaptive repair of survived differentiated cells and regeneration of progenitor cells, contribute to the restoration of renal function and reepithelialization of damaged nephrons.

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A complete reference list can be found online at ExpertConsult.com.

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