

Molecular Responses and Growth Factors

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The kidney possesses a remarkable capacity for restoring its structure and functional ability following an ischemic or toxic insult. It is unique as a solid organ in its ability to suffer an injury of such magnitude that the organ can fail for weeks and yet recover full function. Studying the natural regenerative process after an acute renal insult has provided new insights into the pathogenesis of acute renal failure (ARF) and possible new therapies. These therapies may limit the extent of injury or even accelerate the regenerative process and improve outcomes for patients suffering with ARF. In this chapter we illustrate some of the molecular responses of the kidney to an acute insult and demonstrate the effects of therapy with growth factors in the setting of experimental models of ARF. We conclude by demonstrating strategies that will provide future insights into the molecular response of the kidney to injury.

The regions of the nephron most susceptible to ischemic injury are the distal segment (S_3) of the proximal tubule and the medullary thick ascending limb of the loop of Henle. Following injury, there is loss of the epithelial lining as epithelial cells lose their integrin-mediated attachment to basement membranes and are sloughed into the lumen. An intense regenerative process follows. Normally quiescent renal tubule cells increase their nucleic acid synthesis and undergo mitosis. It is theorized that surviving cells situated close to or within the denuded area dedifferentiate and enter mitotic cycles. These cells then redifferentiate until nephron segment integrity is restored. The molecular basis that regulates this process is poorly-understood. After an injury, there is a spectrum of cell damage that is dependent on the type and severity of the insult. If the intensity of the insult is limited, cells become dysfunctional but survive. More severe injury results in detachment of cells from the tubule basement membranes, resulting in necrosis. Still other cells have no apparent damage and may proliferate to repithelialize the damaged nephron segments. Thus, several

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different processes are required to achieve structural and functional integrity of the kidney after a toxic or ischemic insult: 1) uninjured cells must proliferate and reepithelialize damaged nephron segments; 2) nonlethally damaged cells must recover;

and 3) some damaged cells may actually die—not as a result of the initial insult but through a process of programmed cell death known as apoptosis. Figure 17-1 provides a schematic representation of the renal response to an ischemic or toxic injury.

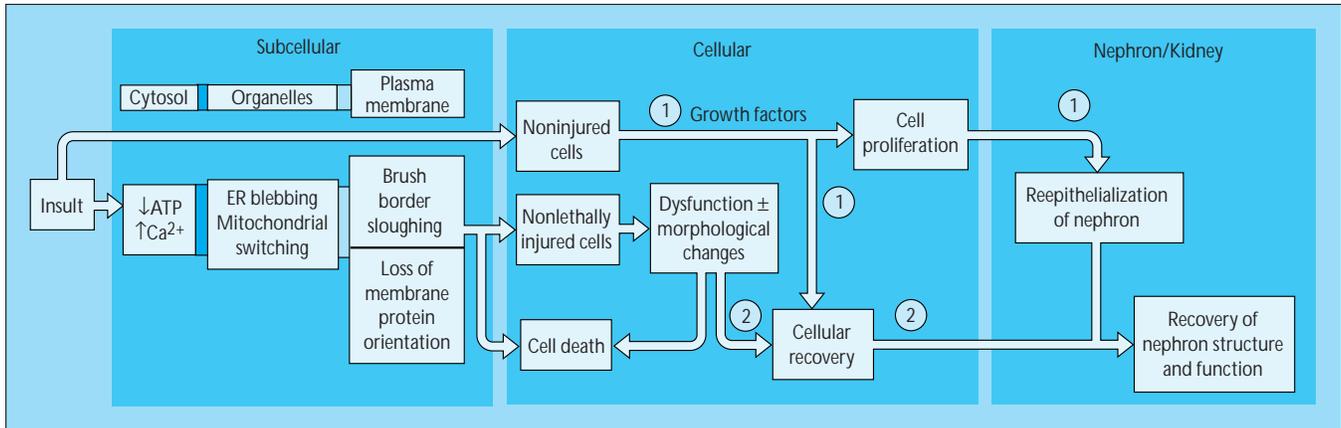


FIGURE 17-1

Schematic representation of some of the events pursuant to a renal insult and epithelial cell repair. **Subcellular;** Initial events include a decrease in cellular ATP and an increase in intracellular free calcium. There is blebbing of the endoplasmic reticulum with mitochondrial swelling and dysfunction. The brush border of the proximal tubules is sloughed into the tubule lumen, and there is redistribution of membrane proteins with the loss of cellular polarity. **Cellular;** At a cellular level this results in three populations of tubule cells, depending on the severity of the insult. Some cells are intact and are poised to participate in the proliferative process (*Pathway 1*). Growth factors participate by

stimulating cells to undergo mitosis. Nonlethally injured cells have the potential to follow one of two pathways. In the appropriate setting, perhaps stimulated by growth factors, these cells may recover with restoration of cellular integrity and function (*Pathway 2*); however, if the injury is significant the cell may still die, but through a process of programmed cell death or apoptosis. The third population of cells are those with severe injury that undergo necrotic cell death. **Nephron/Kidney;** With the reepithelialization of damaged nephron segments and cellular recovery of structural and functional integrity, renal function is restored. (*Modified from Toback [1]; with permission.*)

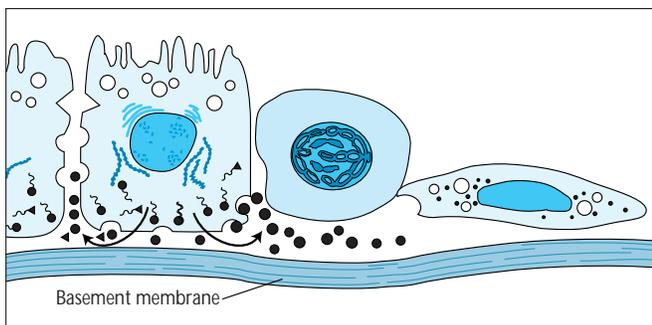


FIGURE 17-2

Growth regulation after an acute insult in regenerating renal tubule epithelial cells. Under the influence of growth-stimulating factors the damaged renal tubule epithelium is capable of regenerating with restoration of tubule integrity and function. The growth factors may be 1) produced by the tubule epithelium itself and act locally in an autocrine, juxtacrine or paracrine manner; 2) produced by surrounding cells to work in a paracrine manner; or 3) presented to the regenerating area via the circulation mediated by an endocrine mechanism. Cells at the edge of an injured nephron segment are illustrated on the left. These cells proliferate in response to the growth-stimulating factors. The middle cell is in the process of dividing and the cell on the right is migrating into the area of injury. (*Adapted from Toback [1]; with permission.*)

Growth Factors in Acute Renal Failure

GROWTH FACTORS IN ACUTE RENAL FAILURE

EGF	HGF
Ischemic and toxic	Ischemic and toxic
IGF-I	Established ARF
Ischemic and toxic	
Pretreatment and established ARF	

ARF—acute renal failure; EGF—epidermal growth factor; HGF—hepatocyte growth factor; IGF-I—insulin-like growth factor.

FIGURE 17-3

At least three growth factors have now been demonstrated to be useful as therapeutic agents in animal models of acute renal failure (ARF). These include epidermal growth factor (EGF), insulin-like growth factor I (IGF-I) and hepatocyte growth factor (HGF). All have efficacy in ischemia models and in a variety of toxic models of ARF. In addition, both IGF-I and HGF are beneficial when therapy is delayed and ARF is “established” after an ischemic insult. IGF-I has the additional advantage in that it also ameliorates the course of renal failure when given prophylactically before an acute ischemic insult.

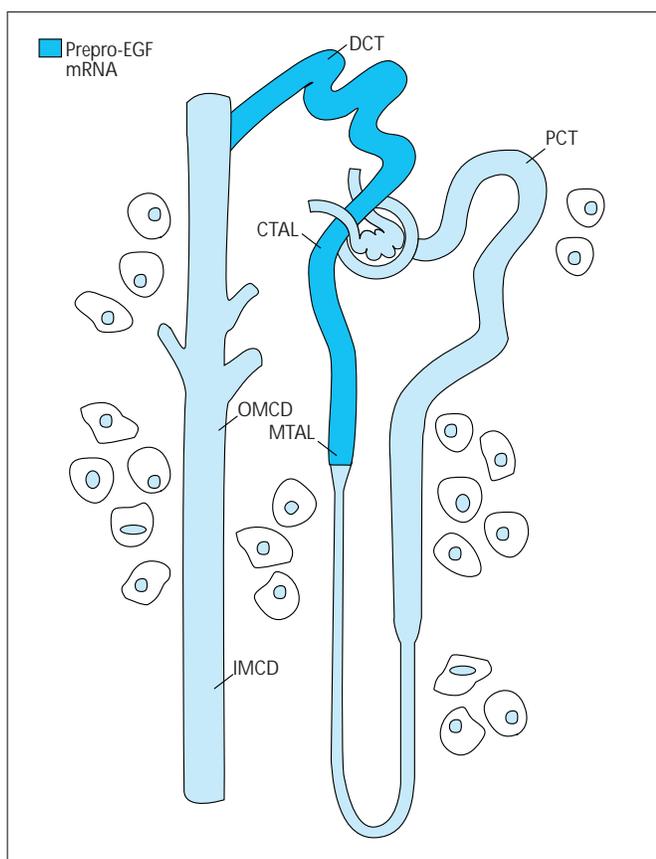


FIGURE 17-4

Expression of messenger RNA (mRNA) for prepro-epidermal growth factor (EGF) in kidney. This schematic depicts the localization of mRNA for prepro-EGF under basal states in kidney. Prepro-EGF mRNA is localized to the medullary thick ascending limbs (MTAL) and distal convoluted tubules (DCT). Immunohistochemical studies demonstrate that under basal conditions the peptide is located on the luminal membrane with the active peptide actually residing within the tubule lumen. It is speculated that, during pathologic states, preformed EGF is either transported or routed to the basolateral membrane or can enter the interstitium via backleak. After a toxic or ischemic insult, expression of EGF is rapidly suppressed and can remain low for a long time. Likewise, total renal content and renal excretion of EGF decreases. CTAL—cortical thick ascending limb; IMCD—inner medullary collecting duct; OMCD—outer medullary collecting duct; and PCT—proximal convoluted tubule.