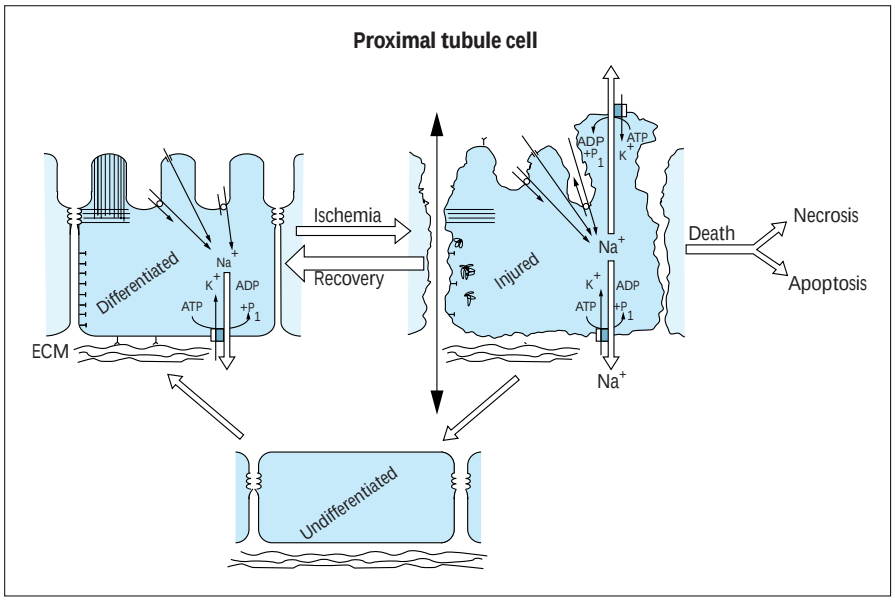


FIGURE 13-3
Fate of an injured proximal tubule cell. The fate of a proximal tubule cell after an ischemic episode depends on the extent and duration of the ischemia. Cell death can occur immediately via necrosis or in a more programmed fashion (apoptosis) hours to days after the injury. Fortunately, most cells recover either in a direct fashion or via an intermediate undifferentiated cellular pathway. Again, the severity of the injury determines the route taken by a particular cell. Adjacent cells are often injured to varying degrees, especially during mild to moderate ischemia. It is believed that the rate of organ functional recovery relates directly to the severity of cell injury during the initiation phase. ECM—extracellular membrane; Na^+—sodium ion; K^+—potassium ion; P_1—phosphate.

ISCHEMIA INDUCED PROXIMAL TUBULE CELL ALTERATIONS

Alterations	References
Surface Membrane Alterations	
1. Microvilli fusion, internalization, fragmentation and luminal shedding resulting in loss of surface membrane area and tubular obstruction	[21]
2. Loss of surface membrane polarity for lipids and proteins	[2,22,23]
3. Junctional complex dissociation with unregulated paracellular permeability (backleak)	[6,24–27]
4. Reduced PTC vectorial transport	[28]
Actin Cytoskeletal Alterations	
1. Polymerization of actin throughout the cell cytosol	[6,16,29]
2. Disruption and delocalization of F-actin structures including stress fibers, cortical actin and the junctional ring	[2,7,16]
3. Accumulation of intracellular F-actin aggregates containing surface membrane proteins—myosin I, the tight junction proteins ZO-1, ZO-2, cingulin	[20,30]
4. Disruption and dissociation of the spectrin cytoskeleton	[31,32]
5. Disruption of microtubules during early reflow in vivo	[33]
6. The cytoskeleton of proximal tubule cells, as compared to distal tubule cells, is more sensitive to ischemia in vivo and ATP depletion in vitro	[6,16,34]

FIGURE 13-4
Ischemia induced proximal tubule cell alterations.

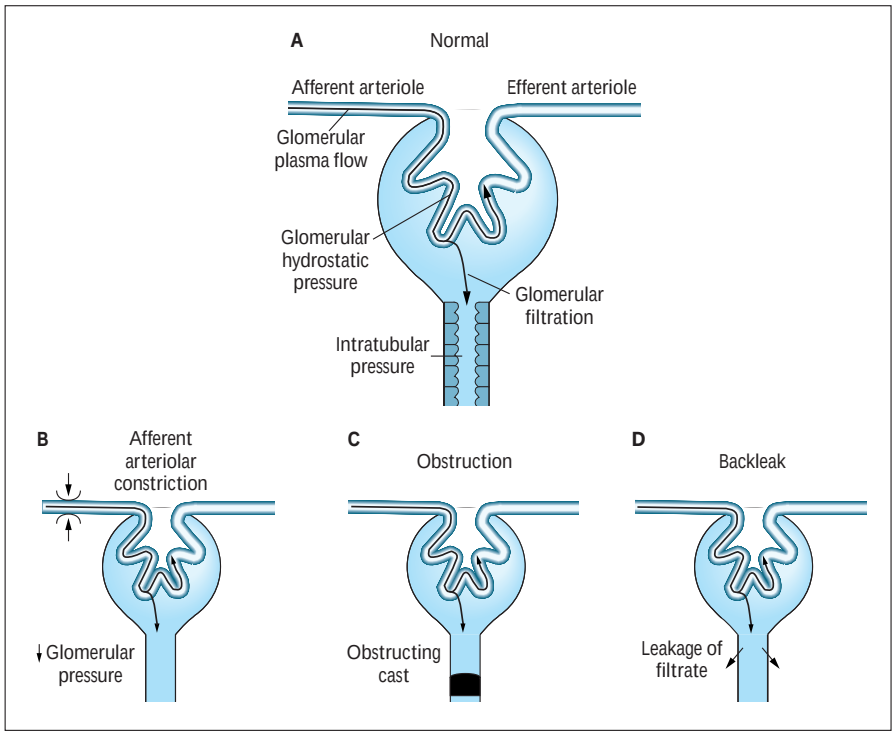
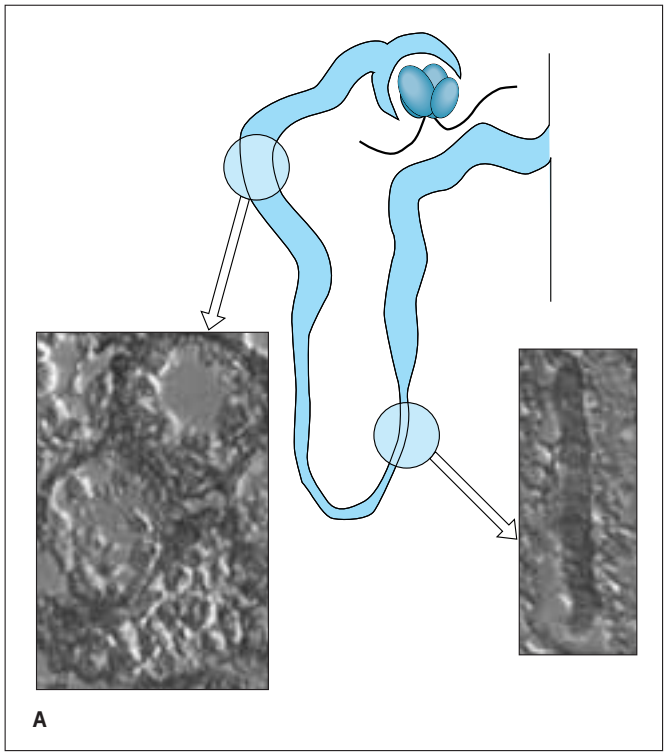


FIGURE 13-5

Mechanisms of proximal tubule cell—mediated reductions in glomerular filtration rate (GFR) following ischemic injury. **A**, GFR depends on four factors: 1) adequate blood flow to the glomerulus; 2) an adequate glomerular capillary pressure as determined by afferent and efferent arteriolar resistance; 3) glomerular permeability; and 4) low intratubular pressure. **B**, Afferent arteriolar constriction diminishes GFR by reducing blood flow—and, therefore, glomerular capillary pressure. This occurs in response to a high distal sodium delivery and is mediated by tubular glomerular feedback. **C**, Obstruction of the tubular lumen by cast formation increases tubular pressure and, when it exceeds glomerular capillary pressure, a marked decrease or no filtration occurs. **D**, Back-leak occurs when the paracellular space between cells is open for the flux of glomerular filtrate to leak back into the extracellular space and into the blood stream. This is believed to occur through open tight junctions.



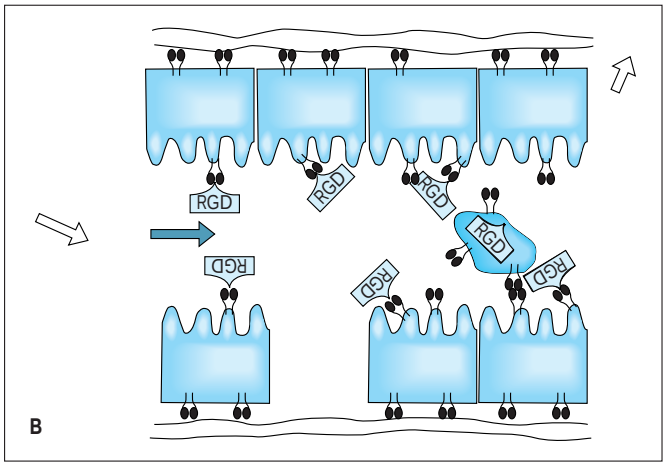


FIGURE 13-6

Overview of potential therapeutic effects of cyclic integrin-binding peptides. **A**, During ischemic injury, tubular obstruction occurs as a result of loss of apical membrane, cell contents, and detached cells released into the lumen. **B**, Also, basolateral integrins diffuse to the apical region of the cell. Biotinylated cyclic peptides containing the sequence cRGDDFV bind to desquamated cells in the ascending limb of the loop of Henle and in proximal tubule cells in ischemic rat kidneys. The desquamated cells can adhere to injured cells or aggregate, causing tubule obstruction.

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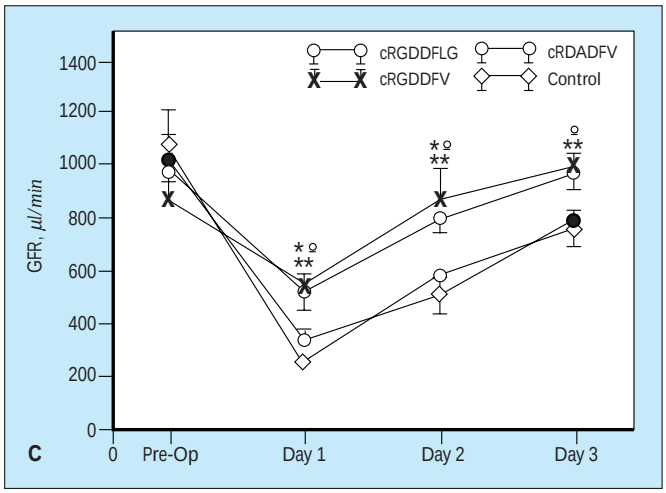
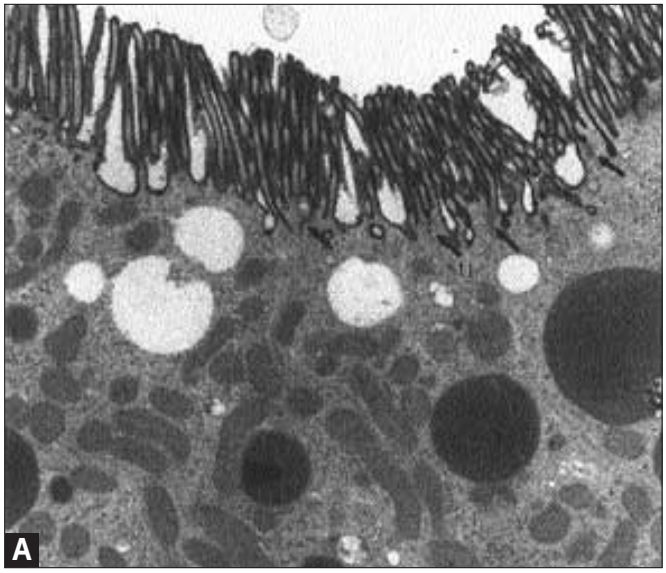
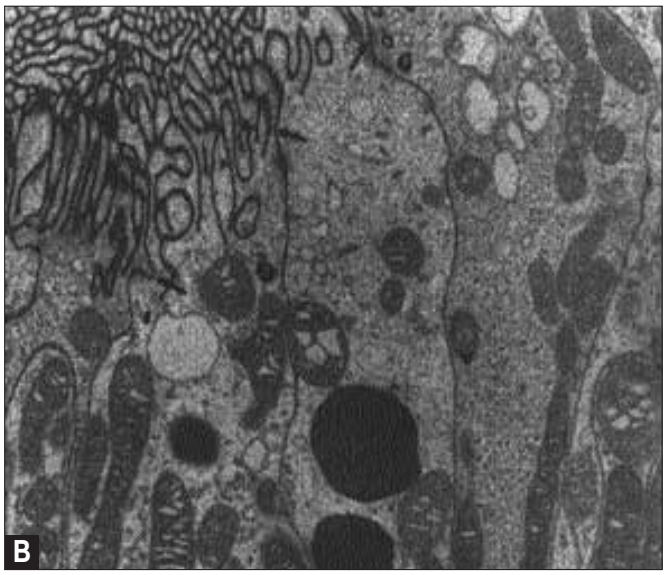


FIGURE 13-6 *(Continued)*

C, When cyclic peptides that contain the RGD canonical binding site of integrins are perfused intra-arterially, the peptides ameliorate the extent of acute renal failure, as demonstrated by a higher glomerular filtration rate (GFR) in rats receiving peptide containing the RGD sequence. **B**, Proposed mechanism of renal protection by cyclic RGD peptides. By adhering to the RGD binding sites of the integrins located on the apical plasma membrane or distributed randomly on desquamated cells, the cyclic peptide blocks cellular aggregation and tubular obstruction [12–15]. (*Courtesy of* MS Goligorski, MD.)





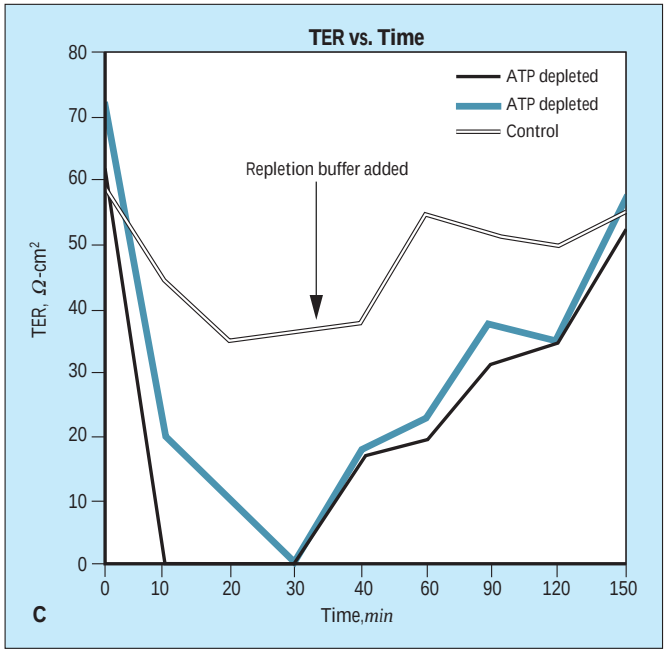


FIGURE 13-7

Functional and morphologic changes in tight junction integrity associated with ischemic injury or intracellular ATP depletion. **A** and **B**, Ruthenium red paracellular permeability in rat proximal tubules. **A**, In control kidneys, note the electron-dense staining of the brush border, which cuts off at the tight junctions (tj, *arrows*). **B**, Sections from a perfusion-fixed kidney after 20 minutes of renal artery cross-clamp [35]. The electron-dense staining can be seen at cell contact sites beyond the tight junction (*arrows*). The paracellular pathway is no longer sealed by the tight junction, permitting backleak of the electron-dense ruthenium red. **C**, Changes in the transepithelial resistance (TER) versus time during ATP depletion and ATP repletion [36]. Paracellular resistance to electron movement

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