Acute Renal Failure: Cellular Features of Injury and Repair

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Although ischemic acute renal failure (ARF) is likely the result of many different factors, much tubule injury can be traced back to a number of specific lesions that occur at the cellular level in ischemic polarized epithelial cells. At the onset of an ischemic insult, rapid and dramatic biochemical changes in the cellular environment occur, most notably perturbation of the intracellular levels of ATP and free calcium and increases in the levels of free radicals, which lead to alterations in structural and functional cellular components characteristic of renal epithelial cells [1–7]. These alterations include a loss of tight junction integrity, disruption of actin-based microfilaments, and loss of the apical basolateral polarity of epithelial cells. The result is loss of normal renal cell function [7–12].

After acute renal ischemia, the recovery of renal tubule function is critically dependent on reestablishment of the permeability barrier, which is crucial to proper functioning of epithelial tissues such as renal tubules. After ischemic injury the formation of a functional permeability barrier, and thus of functional renal tubules, is critically dependent on the establishment of functional tight junctions. The tight junction is an apically oriented structure that functions as both the "fence" that separates apical and basolateral plasma membrane domains and the major paracellular permeability barrier (gate). It is not yet clear how the kidney restores tight junction structure and function after ischemic injury. In fact, tight junction assembly under normal physiological conditions remains ill-understood; however, utilization of the

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"calcium switch" model with cultured renal epithelial cells has helped to elucidate some of the critical features of tight junction bioassembly. In this model for tight junction reassembly, signaling events involving G proteins, protein kinase C, and calcium appear necessary for the reestablishment of tight junctions [13–19]. Tight junction injury and recovery, like that which occurs after ischemia and reperfusion, has similarly been modeled by subjecting cultured renal epithelial cells to ATP depletion ("chemical anoxia") followed by repletion. While there are many similarities to the calcium switch, biochemical studies have recently revealed major differences, for example, in the way tight junction proteins interact with the cytoskeleton [12]. Thus, important insights into the basic and applied biology of tight junctions are likely to be forthcoming from further analysis of the ATP depletion-repletion model. Nevertheless, it is likely that, as in the calcium switch model, tight junction reassembly is regulated by classical signaling pathways that might potentially be pharmacologically modulated to enhance recovery after ischemic insults.

More prolonged insults can lead to greater, but still sublethal, injury. Key cellular proteins begin to break down. Many of these (*eg*, the tight junction protein, occludin, and the adherens junction protein, E-cadherin) are membrane proteins. Matrix proteins and their integrin receptors may need to be resynthesized, along with growth factors and cytokines, all of which pass through the endoplasmic reticulum (ER). The rate-limiting events in the biosynthesis and assembly of these proteins occur in the ER and are catalyzed by a set of ER-specific molecular chaperones, some of which are homologs of the cytosolic heat-shock proteins [20]. The levels of mRNAs for these proteins may increase 10-fold or more in the ischemic kidney, to keep up with the cellular need to synthesize and transport these new membrane proteins, as well as secreted ones.

If the ischemic insult is sufficiently severe, cell death and/or detachment leads to loss of cells from the epithelium lining the kidney tubules. To recover from such a severe insult, cell regeneration, differentiation, and possibly morphogenesis, are necessary. To a limited extent, the recovery of kidney tubule function after such a severe ischemic insult can be viewed as a recapitulation of various steps in renal development. Cells must proliferate and differentiate, and, in fact, activation of growth factor–mediated signaling pathways (some of the same ones involved in kidney development) appears necessary to ameliorate renal recovery after acute ischemic injury [21–30].

The Ischemic Epithelial Cell

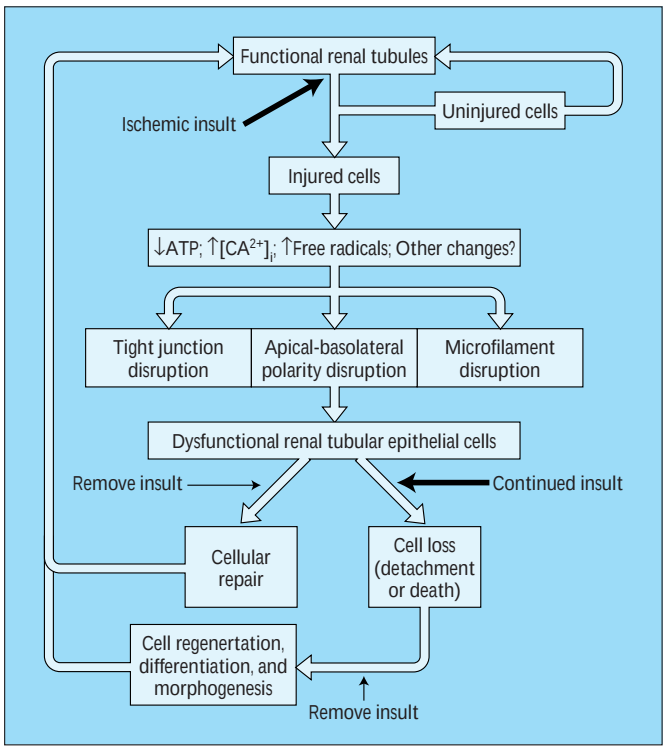

FIGURE 16-1

Ischemic acute renal failure (ARF). Flow chart illustrates the cellular basis of ischemic ARF. As described above, renal tubule epithelial cells undergo a variety of biochemical and structural changes in response to ischemic insult. If the duration of the insult is sufficiently short, these alterations are readily reversible, but if the insult continues it ultimately leads to cell detachment and/or cell death. Interestingly, unlike other organs in which ischemic injury often leads to permanent cell loss, a kidney severely damaged by ischemia can regenerate and replace lost epithelial cells to restore renal tubular function virtually completely, although it remains unclear how this happens.

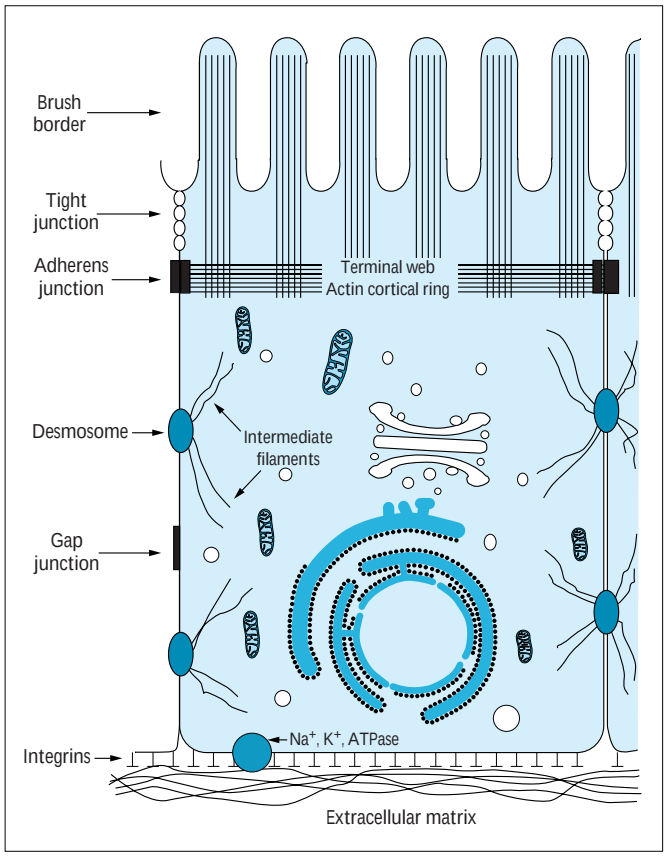

FIGURE 16-2

Typical renal epithelial cell. Diagram of a typical renal epithelial cell. Sublethal injury to polarized epithelial cells leads to multiple lesions, including loss of the permeability barrier and apical-basolateral polarity [7–12]. To recover, cells must reestablish intercellular junctions and repolarize to form distinct apical and basolateral domains characteristic of functional renal epithelial cells. These junctions include those necessary for maintaining the permeability barrier (*ie*, tight junctions), maintaining cell-cell contact (*ie*, adherens junctions and desmosomes), and those involved in cell-cell communication (*ie*, gap junctions). In addition, the cell must establish and maintain contact with the basement membrane through its integrin receptors. Thus, to understand how kidney cells recover from sublethal ischemic injury it is necessary to understand how renal epithelial cells form these junctions. Furthermore, after lethal injury to tubule cells new cells may have to replace those lost during the ischemic insult, and these new cells must differentiate into epithelial cells to restore proper function to the tubules.

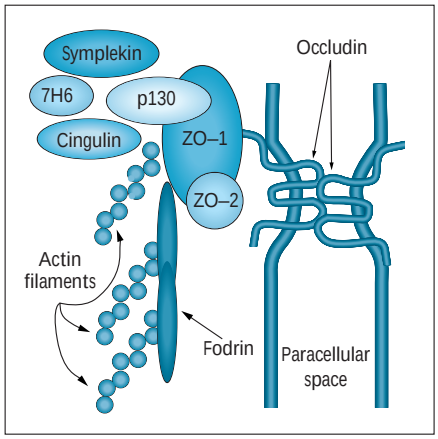

FIGURE 16-3

The tight junction. The tight junction, the most apical component of the junctional complex of epithelial cells, serves two main functions in epithelial cells: 1) It separates the apical and basolateral plasma membrane domains of the cells, allowing for vectorial transport of ions and molecules; 2) it provides the major framework for the paracellular permeability barrier, allowing for generation of chemical and electrical gradients [31]. These functions are critically important to the proper functioning of renal tubules. The tight junction is comprised of a number of proteins (cytoplasmic and transmembrane) that interact with a similar group of proteins between adjacent cells to form the permeability barrier [16, 32–37]. These proteins include the transmembrane protein occludin [35, 38] and the cytosolic proteins zonula occludens 1 (ZO-1), ZO-2 [36], p130, [39], cingulin [33, 40], 7H6 antigen [34] and symplekin [41], although other as yet unidentified components likely exist. The tight junction also appears to interact with the actin-based cytoskeleton, probably in part through ZO-1–fodrin interactions.