Renal cell loss through cell suicide

Kidneys from most patients with end-stage renal disease (ESRD) are small. Indeed, a striking decrease in parenchymal cell number, associated with an increased amount of extracellular matrix, are features of chronic renal injury. However, only recently have researchers addressed the mechanisms responsible for renal cell loss. As parenchymal renal cells do not migrate to other organs, cell death is considered to be the main process of renal cell demise. Apoptosis is an active form of cell death (cell suicide) that accounts for the clearance of most of the 100,000 cells that die physiologically each second in a human. Apoptosis has drawn the interest of nephrologists because it is regulated by extracellular and intracellular proteins that are potential targets for a therapeutic intervention [1].

In this issue of *Kidney International*, Ying, Wang, and Sanders describe an increased rate of glomerular and tubular cell apoptosis in an experimental model of one of the most common causes of ESRD, that is, hypertensive nephrosclerosis [2]. Increased rates of apoptosis are also found in human and experimental renal diseases characterized by parenchymal renal cell loss, such as acute renal failure and chronic progressive nephropathies. An abnormally high rate of parenchymal cell apoptosis in renal injury may have different, even contradictory consequences. First, apoptosis can be a compensatory response to increased cell proliferation, as exemplified by the regression of glomerular hypercellularity in experimental mesangial glomerulonephritis [3]. Indeed, Ying, Wang, and Sanders also noted an increased rate of cell proliferation [2]. However, the overall decrement in cell number as evidenced by tubular atrophy and glomerular sclerosis argues against this possibility in their model. Second, apoptosis could be contributing to the progression of chronic renal injury through cell loss and, third, apoptosis could be an epiphenomenon that is not contributing to the progression of injury and leads to the loss of otherwise damaged cells. To discriminate between these two latter possibilities, functional studies aimed at specifically inhibiting apoptosis are needed.

The susceptibility of a given cell to apoptosis is regulated both by the extracellular microenvironment and by the expression and activity of intracellular apoptosis regulatory proteins [1]. Representative families of apoptosis regulatory proteins include the cell death receptor (sensors for lethal stimuli), Bcl2 (comprising pro-apoptotic and anti-apoptotic members) and caspase (intracellular effectors of apoptosis) families. Each of these families comprises multiple, apparently redundant members. However, in some cases these proteins regulate cell death in a cell- and stimulus-specific manner. In this regard it is necessary to characterize the apoptosis regulatory proteins that determine renal cell fate during acute and chronic renal injury. In vitro studies suggest that some of these proteins, such as Fas and BclxL, do indeed modulate renal cell survival. Increased Fas expression sensitizes tubular and mesangial cells to the lethality of FasL [4], while high levels of BclxL protect tubular epithelial cells from a lethal environment [5]. The study by Ying, Wang, and Sanders is one of a flurry of papers describing changes in the expression of apoptotic regulatory proteins during the course of renal injury [2, 4–7]. These data identify potential targets for a therapeutic intervention and provide a framework for the design of functional studies that directly address the role of specific apoptosis regulatory proteins in the progression of renal failure.

In Dahl/Rapp salt-sensitive rats fed a high NaCl diet for 21 days the renal expression of the pro-apoptotic proteins Fas, Bax and BclxS was increased [2], although the cells expressing these proteins were not identified. This pattern of high expression of pro-apoptotic proteins is reminiscent of that described in other renal and extrarenal pathologies characterized by an increased rate of apoptosis. Increased tubular expression of Bax was observed in nephrotoxic acute renal failure, although in this murine model BclxS was not detected in the kidney [5]. Increased tubular Fas was noted in two models of murine chronic renal failure [6]. These data suggest that some molecular mechanisms for apoptosis are common to renal injury of different origins. One striking result is that a high NaCl dietary intake modulates the expression of the anti-apoptotic protein BclxL in both Dahl/Rapp salt-sensitive rats and control rats [2]. This finding merits further exploration, as dietary salt content is known to modulate susceptibility to nephrotoxic injury [8]. As cells expressing BclxL were not identified, we cannot draw conclusions about the ability of BclxL to prevent cell death in this model. It should be emphasized, however, that a high expression of pro-apoptotic Bcl2-family members, such as Bax and BclxS, negates the protective effect of BclxL.

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It remains to be determined whether interference with apoptosis is an effective therapeutic target in chronic renal injury. Inhibition of tubular epithelial cell apoptosis by either the administration of survival factors or inhibitors of caspases prevents the acute decrease in renal function following renal ischemia-reperfusion [9]. Such studies are more difficult to perform in the chronic setting. In this regard, the contribution of certain apoptotic regulatory proteins to the progression of renal injury can now be addressed by the use of knockout mice. One feature of Bax knockout mice is an increased ovarian lifespan due to the lack of apoptotic demise of oocytes [10]. As increased tubular Bax has been reported in several nephropathies characterized by tubular cell apoptosis [5, 7], the sensitivity of these mice to renal injury should be tested. The widespread occurrence of apoptosis in normal tissue homeostasis and its tight regulation suggests that interference with apoptosis, especially when chronic, may result in dangerous side effects, including tumorigenesis. For this reason apoptosis modulatory therapies should target only specific cell populations during a limited period of time.

Although incomplete, the available in vitro and in vivo data suggest that apoptosis and its regulatory molecules contribute to a variety of renal diseases. Future research should focus on the definition of the cellular and molecular targets as well as the optimal time frame for therapeutic intervention in each renal pathology in experimental models before such therapies can be considered in human disease.

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REFERENCES