Available online at www.sciencedirect.com
SCIENCE DIRECT®
Biochemical Pharmacology 66 (2003) 1589–1594
Biochemical Pharmacology
www.elsevier.com/locate/biochempharm

Targeting apoptosis in acute tubular injury

Alberto Ortiz*, Pilar Justo, Ana Sanz, Corina Lorz, Jesús Egido

Nefrología, Fundación Jiménez Díaz, IRSIN y Universidad Autónoma de Madrid, Av Reyes Católicos 2, Madrid 28040, Spain

Received 17 March 2003; accepted 23 April 2003

Abstract

Recent research has shown that apoptosis and its regulatory mechanisms contribute to cell number regulation in acute renal failure. Acute tubular necrosis is the most frequent form of parenchymal acute renal failure. The main causes are ischemia–reperfusion, sepsis and nephrotoxic drugs. Exogenous factors such as nephrotoxic drugs and bacterial products, and endogenous factors such as lethal cytokines promote tubular cell apoptosis. Such diverse stimuli engage intracellular death pathways that in some cases are stimulus-specific. We now review the role of apoptosis in acute renal failure, the potential molecular targets of therapeutic intervention, the therapeutic weapons to modulate the activity of these targets and the few examples of therapeutic intervention on apoptosis.

Keywords: Apoptosis; Kidney; Acute renal failure; Bcl2; Death receptor; Caspase

1. Acute tubular injury

ARF is a syndrome characterized by an acute loss of renal function. ARF has an incidence of 208 per million population in Europe [1]. Acute tubular necrosis is the most common form of ARF of renal origin. The treatment of acute tubular necrosis is symptomatic and consists in substitution of renal function by dialysis if renal failure is severe. There is no established therapy to accelerate the recovery and attempts at preventing ARF are not universally effective. Despite the reversibility of the loss of renal function in most patients that survive, the mortality of ARF remains high (over 50%) [1]. Acute tubular necrosis, is characterized by tubular cell death [2,3]. In human studies tubular cell death was the best histopathological correlate of renal dysfunction [2,3]. The important role of tubular cell death in the genesis of ARF is supported by the fact that several nephrotoxins that induce ARF also promote tubular cell death in culture [4,5]. In addition, proximal tubular cell-specific nephrotoxins, such as cidofovir [6], can evoke full-blown ARF that may be irreversible [7], further supporting a central role for tubular cell death in this syndrome. Tubular cell death in the early stages of acute tubular injury of different etiologies (ischemic, toxic, septic) can proceed through apoptosis or necrosis [5,8]. However, it is often difficult to determine the mode of cell death, because only the absence of the tubular cell is noted. The relative contribution of the two mechanisms to the initial tubular cell loss is uncertain, and may depend on the severity of the insult [9,10]. The term acute tubular necrosis was already in use in the medical literature before the appearance of the term apoptosis. Furthermore, it is derived from studies of human necropsy specimens. Thus, the term acute tubular necrosis does not indicate a role for a specific form of cell death in the syndrome. Hence, we have used the term acute tubular injury in the manuscript.

2. Apoptosis

Apoptosis is an active mode of cell death (cell suicide) under molecular control [11–14]. Indeed, apoptosis is defined by the requirement of energy for cell death to proceed. However, the distinction between different forms of cell death is not always clear-cut. Hence, from a therapeutic point of view, we are interested in any form of cell death that can be manipulated by maneuvers designed to interfere with the molecular pathways that regulate apoptosis.

Apoptosis is tightly regulated by extracellular and intracellular molecules that provide multiple regulatory and

* Corresponding author. Tel.: +34-915504940; fax: +34-915494764.
E-mail address: aortiz@fjd.es (A. Ortiz).

Abbreviations: ARF, acute renal failure; ER, endoplasmic reticulum; FasL, Fas ligand; IAP, inhibitors of apoptosis proteins; zVAD, benzyloxycarbonyl-Val-Ala-DL-Asp-fluoromethylketone.

0006-2952/$ – see front matter © 2003 Elsevier Inc. All rights reserved.
doi:10.1016/S0006-2952(03)00515-X

contrarregulatory pathways. These molecules are potential targets for therapeutic intervention. However, the design of appropriate therapeutic strategies requires a correct understanding of the role of apoptosis in ARF and of the molecular regulation of renal tubular cell apoptosis.

Tubular cell death through apoptosis is thought to play a prominent role in the development of renal injury during ARF. Apoptotic tubular cell death has been documented in the course of ARF both in animal models and in clinical kidney diseases [3,8,15,16]. In addition, changes in the expression or activity of apoptosis regulatory factors have been observed in cultured renal cells and *in vivo* kidney disease (reviewed in [14]). Apoptosis also contributes to tissue remodeling and recovery of normal tissue structure. Apoptosis may represent a physiologic balance to clear redundant cells and resolve an exaggerated compensatory proliferative response that leads to tubular hyperplasia in the recovery phase of acute tubular injury [8]. Apoptosis also regulates inflammation and the immune response.

From this brief glimpse at the diverse potential roles of apoptosis in renal injury, we can infer that both the cellular target and the timing of the intervention on apoptosis may have a remarkable influence on the ultimate therapeutic consequences.

3. Overview of the molecular regulation of apoptosis

Cell death is usually a response to the cell microenvironment. The absence of certain factors (survival factors) or the presence of lethal factors promotes apoptosis. Surrounding cells, soluble mediators and the extracellular matrix regulate cell death and survival. Surrounding cells can synthesize survival or lethal factors or compete for such factors. A lethal cell microenvironment activates intracellular factors that promote apoptosis.

3.1. The cell microenvironment

3.1.1. Survival factors

Most cells need survival signals from their surroundings to remain alive. However, the survival factors vary depending on cell type and functional status. IGF-1, EGF, HB-EGF, HGF are survival factors for tubular epithelial cells [12]. Many survival factors have additional functions. Cell proliferation is one of the most common. Thus, regulation of apoptosis may collaborate to the therapeutic effect of survival factors, but it will be difficult to dissect this from other biological actions.

3.1.2. Lethal factors

Lethal factors that cause receptor-independent cell stress usually kill by a mechanism involving mitochondria. Lethal cytokines belonging to the TNF superfamily bind to and activate cell membrane death receptors [18]. TNF and FasL have been extensively investigated in renal cells. In the kidney both cytokines may be synthesized by infiltrating leukocytes and intrinsic renal cells, the main source of intrinsic FasL being the tubular epithelial cell [19].

3.1.3. Interaction of survival and lethal factors

The cell microenvironment usually contains multiple survival and lethal factors. The potential for interaction between survival and lethal factors varies in a stimulus- and cell-specific manner. For example, the absence of survival factors predisposes renal tubular epithelial cells to death induced by lethal cytokines and nephrotoxic drugs [15]. Other lethal stimuli, such as HMGCoA inhibitors, induce apoptosis in actively proliferating tubular cells [20].

3.2. Intracellular regulation of apoptosis

3.2.1. Proapoptotic Bcl2-like proteins

The Bcl2-family includes proapoptotic and anti-apoptotic proteins. Bcl2-like proteins containing only the BH3 domain (BH3-only proteins) are considered sensors that facilitate the onset of the apoptosis process in response to injury [21]. Some of them have been reported to be activated in an stimulus-specific fashion, such as Bid in the course of death receptor-induced apoptosis and noxa upon serum deprivation [21]. A two-class model for BH3 domains has been proposed: Bid-like domains that ‘‘activate’’ Bax and Bak, and Bad-like domains that ‘‘sensitize’’ by occupying the pocket of anti-apoptotic members of the family [21]. Multidomain proapoptotic Bcl2-like proteins, such as Bax or Bak, can induce caspase-independent cell death [22]. Bax shuttles from its cytoplasmic location to the mitochondria upon induction of apoptosis. Mechanisms for their proapoptotic activity include: (1) binding and inhibition of Bcl2 or BclxL, and (2) inducing the opening of mitochondrial membrane channels, thus promoting the release of mitochondrial apoptogenic factors into the cytoplasm.

3.2.2. Mitochondria

Mitochondria are key participants in apoptosis [23]. More recently the involvement of other organelles, such as the ER and lysosomes, in the initial phase of apoptosis has been emphasized [24]. Mitochondrial changes during apoptosis include: (1) release of proteins, such as cytochrome *c*, AIF, HtrA2, Smac/Diablo and caspases, from the mitochondrial intermembrane space to the cytosol, where they participate in the effector phase of apoptosis; (2) dissipation of the mitochondrial transmembrane potential (MMP) gradient ($\Delta\Psi_m$). Both events can occur independently of each other. In many cells, release of mitochondrial proteins is a caspase-independent, bax-dependent phenomenon, while loss of MMP is caspase-dependent.

Mitochondrial injury activates several cell death pathways. The release of cytochrome *c* facilitates caspase activation, while Smac/Diablo prevents inactivation of active caspases. The consequence is classic apoptosis. On the other hand, AIF is a caspase-independent death effector which

translocates to the nucleus, where it causes chromatin condensation and large scale DNA fragmentation.

3.2.3. Endoplasmic reticulum

ER stress can also result in apoptosis [25]. Caspase-12 is localized to the ER and activated by ER stress, but not by mitochondrial-targeted apoptotic signals [26]. Mice that are deficient in caspase-12 are resistant to ER stress-induced apoptosis [26]. However, an active form of caspase-12 may be absent in humans.

3.2.4. Proteolytic enzymes: caspases

Several families of proteolytic enzymes are activated in the course of apoptosis. Caspases are the most widely studied apoptotic proteases. Most caspases are constitutively expressed as inactive proenzymes (procaspases). Caspases are sequentially activated by proteolysis during apoptosis [27]. The main function of some caspases, such as caspase-1, appears to be regulation of inflammation. Caspase 1 participates in the activation of interleukins-1 and -18.

Procaspases possess considerably less activity than mature caspases. As a result, recruitment and oligomerization of initiator procaspases mediated by adaptor proteins, in the death receptor complex or the apoptosome, constitutes a basic mechanism of caspase activation by proteolysis. Caspase-9 is the initiator caspase of the mitochondrial pathway for apoptosis. It is activated after binding to the cytosolic adaptor protein Apaf-1. Apaf-1 itself must be activated through a conformational change that occurs in the presence of dATP when cytochrome *c* is released from the mitochondria. Activated Apaf-1 molecules oligomerize and, together with caspase-9, form a protein complex dubbed the apoptosome. Caspases-8 and -10 are the initiator caspases of death receptor-induced apoptosis. Additional pathways may exist, in which caspase-2 is the initiator caspase leading to mitochondrial injury [28]. The complex phenotypes of the caspase knockout mice further indicate that multiple mechanisms of caspase activation operate in parallel and that death signal transduction pathways are both cell-type- and stimulus-specific. Initiator caspases activate effector caspases (-3, -6, -7). Effector caspases can, in turn, activate initiator caspases, providing a positive feed-back loop. Over 40 substrates for caspases have been identified. Caspase targets include inactivation of protective proteins, such as BclxL and Bcl2, that may even yield proapoptotic fragments, dismantling of structural proteins and activation of DNAses.

Other proteolytic enzymes that become activated and participate in apoptosis include calpaine, cathepsins and the proteasome [29].

3.2.5. Anti-apoptotic Bcl2-like proteins

Survival Bcl2-like proteins, such as Bcl2 and BclxL, protect from cell death in which the mitochondrial pathway for apoptosis is activated [22]. They may fail to protect from receptor-induced apoptosis, one exception being type II cells, in which lethal signal needs to be amplified through the mitochondrial pathway. Proapoptotic and anti-apoptotic members of the Bcl2 family can interact, and the overall effect on cell survival may depend on the balance between the activity of proapoptotic and anti-apoptotic Bcl2 proteins [22]. The mechanisms of the protection afforded by Bcl2 family members are still been debated. Theories involving sequestering of proapoptotic molecules, closing the mitochondrial transition pore and preventing the release of mitochondrial apoptogenic factors and a role as transmembrane protein translocators have been proposed.

3.2.6. IAPs and others

IAPs were initially identified in baculoviruses. They are characterized by the presence of one to three domains known as baculoviral IAP repeats (BIR). Several BIR-containing proteins inhibit apoptosis [30]. Some of these proteins interact with and inhibit active caspases. Smac/Diablo, antagonizes IAPs by displacing caspases from their IAP binding site.

4. Regulation of apoptosis in renal tubular epithelium

Both endogenous mediators and exogenous toxins regulate survival and death in tubular epithelium and can contribute to cell death in ARF. Understanding the pathways for cell death engaged by these mediators may have an application in the therapeutic approach both to ARF or the chronic loss of tubular epithelium that characterizes chronic renal disease.

4.1. Endogenous mediators

Endogenous mediators, such as survival factors and lethal cytokine regulate renal tubular epithelial cell survival. The origin of these mediators may be the intrinsic renal cell or infiltrating leukocytes that accumulate in the course of renal inflammation, such as that occurring during sepsis or renal ischemia–reperfusion.

Our group has explored the molecular mechanisms of tubular cell-induced apoptosis. Deprivation of survival factors results in tubular cell apoptosis [15]. Deprivation of survival factors leads to a coordinated regulation at the mRNA level of members of the Bcl2 family [15]. The end-result is the creation of a proapoptotic intracellular milieu characterized by high Bax and low BclxL levels. This milieu would be expected to favor cell death. Indeed, serum-deprived tubular epithelial cells are more sensitive to death induced by inflammatory mediators, such as TNF and FasL, under these conditions [15,19]. However, they remain resistant to TRAIL (unpublished observation). TNF also has independent effects on the expression of apoptosis-related molecules that could be the basis for its delayed cytotoxicity. TNF further decreases BclxL levels (Fig. 1).

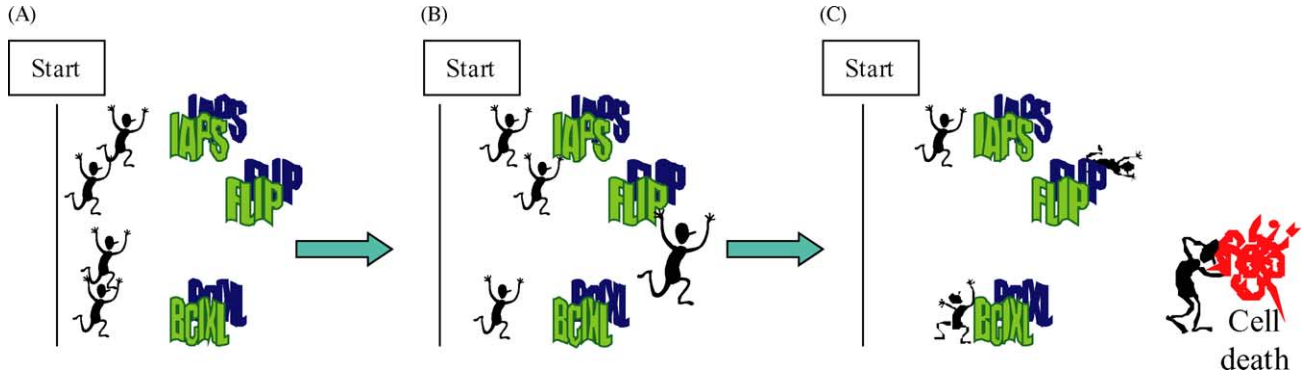

Fig. 1. A lethal stimulus may activate (start) several proapoptotic pathways (A). However, the cell may constitutively express anti-apoptotic factors that block the proapoptotic pathways (B). If the lethal stimulus fails to inactivate these anti-apoptotic factors or even activates them, some or all of the activated proapoptotic pathways may not proceed to completion. However, a single activated pathway, involving amplification by positive feed back loops, is able to kill the cells (C).

Under basal conditions tubular cells are quite resistant to FasL-induced apoptosis, as expected by their constitutive expression of the cytokine [19]. However, they become sensitized to FasL lethality upon exposure to inflammatory cytokines [19]. TNF, INF-γ and IL-1β are some of the cytokines that increase the expression of Fas in tubular cells and facilitate Fas-dependent cell death.

The self-defense of tubular epithelial cells against aggression implies the release of autocrine survival factors. Recent studies have elegantly demonstrated the need for autocrine secretion of VEGF to protect tubular epithelium firm cyclosporin A toxicity both in cell culture and in the whole animal [17].

4.2. *Exogenous toxins*

Both bacterial products, such as bacterial LPS and nephrotoxic drugs, such as cyclosporin A and acetaminophen, promote tubular epithelial cell apoptosis, and could contribute to septic and nephrotoxic ARF. The lethal effect of LPS appears to be mediated through cytokine induction. LPS increases Fas expression in tubular cells and whole kidney and, in conjunction with TNF, sensitizes to FasL-induced apoptosis [15,16]. However, no direct toxic effect of LPS could be observed in cultured tubular cells [16].

Cyclosporin A and acetaminophen also increase Fas expression in tubular epithelium [31]. However, in contrast to deprivation of survival factors or inflammatory cytokines, they do not sensitize to FasL-induced death. Thus, we have to postulate that these nephrotoxins lack a putative effect of the inflammatory mediators on the intracellular death signal transduction pathways form the Fas receptor.

In addition, cyclosporin A and acetaminophen decrease the expression of BclxL [32]. Indeed, BclxL appears to play a central role in the regulation of tubular epithelial cell survival. Proapoptotic stimuli as diverse as deprivation of survival factors, activation of death receptors and nephrotoxins decrease the expression of BclxL. In addition, enforced expression of BclxL protects form apoptosis induced by serum deprivation, TNF or FasL and cyclosporin A, acetaminophen or HMGCoA inhibitors [15,20,32]. *In vivo*, changes in BclxL expression are observed in tubular epithelial cells in ARF [15]. Strikingly, both upregulation or downregulation of BclxL were noted in individual tubular cells. This fits with the notion that, in acute tubular injury, some cells survive and later repopulate the tubules. We postulate that competition for survival factors results in the patchy expression of BclxL.

However, further differences are apparent in the intracellular death pathways activated by individual nephrotoxins. While caspase-3 inhibitors prevent apoptosis induced by cyclosporin A, they failed to protect tubular cells from acetaminophen apoptosis [4,33]. The pancaspase inhibitor zVAD prevented apoptosis in both models, but cells did not survive in the long-term. Thus, the specific caspases that promote apoptosis are stimulus-specific in tubular cells, and this may have therapeutic consequences. We are currently exploring in detail the intracellular pathways activated by both nephrotoxins. A consistent picture is emerging. Both cyclosporin A and acetaminophen activate caspases-3 and -9. However, while mitochondrial injury is prominent in cyclosporin-treated cells, endoplasmic reticulum damage predominates in acetaminophen tubular cytotoxicity [31].

5. Targeting apoptosis

Current evidence suggests that apoptosis and its regulatory molecules contribute to the pathogenesis of ARF. From a therapeutic point of view we might be interested in prolonging parenchymal cell survival in the early phase of acute tubular injury, without interfering with the recovery of normal renal function.

The key to any successful therapeutic manipulation of apoptosis lies in limiting the interference to the cell type we want to manipulate and to a defined time period. Otherwise, we risk unintended side effects derived from interference with physiological apoptosis taking place during

renal healing or in the every day function of other organs. For instance, the systemic antagonism of Fas can result in autoimmunity in mice [34]. A theoretical risk of promoting neoplasia can be predicted if there are no temporal limits to antagonism of apoptosis. Mutations in apoptosis regulatory proteins that favor cell survival are common in a variety of neoplasias [13].

There are different theoretical approaches to achieve cell specificity. The ideal one would be to define molecular pathways that are activated only under pathological conditions. However, there is not enough information on this subject. Another would be a cell-specific delivery of the drug. Gene therapy using cell-specific promoters holds promise in this regard. Finally, if cell-specificity is not achieved, we might choose a non-specific inhibitor of apoptosis for a limited period of time. This limited period of time would be chosen according to the time frame of maximal apoptosis in the target cell population. To date, this has been the only approach explored in experimental kidney disease. The fact that the kidney is an excretory organ can also be used to our advantage. Drugs that are eliminated by the kidney and become concentrated in urine can be used to increase the tubular cell specificity of drug delivery. To further promote tubule cell-specific delivery we may take advantage of the presence of specific transporters in renal cells.

In cell culture experiments and in extrarenal pathology successful approaches to modulation of apoptosis have included cytokines, decoy receptors, neutralizing antibodies, peptide inhibitors of caspases, gene transfection of wild-type genes or dominant negative mutants and antisense oligodeoxynucleotides and siRNA. Studies in renal tubular epithelial cells have demonstrated the feasibility and effectivity of gene transfer strategies to promote the expression of Bcl2 or BclxL and prevent tubular epithelium apoptosis [5,15]. Experience in human ARF is limited to the use of the survival and growth factor IGF-1. Two approaches that target apoptosis have been tried in animal models. The first is to administer or antagonize cytokines (reviewed in [14]). Given the multifunctional nature of most cytokines, such approaches, even if successful, do not necessarily implicate apoptosis as the mode of action. The second involves the inhibition of proteases. However, current inhibitors are not specific enough to warrant that the therapeutic result is the consequence of apoptosis inhibition, even when a decreased rate of apoptosis is observed. Inhibition of proteases has been reported to improve the evolution of experimental ARF. The pan caspase inhibitor zVAD prevented renal function impairment at an early time point (24 hr) when administered at the time of reperfusion in an ischemia–reperfusion acute tubular injury model [35]. The drug was much less effective if administered 2 hr later. Longer follow-up studies are needed to exclude the possibility that zVAD is only retarding cell death and favoring more injurious necrotic cell death. Interestingly, inhibition of caspases also reduces renal inflammation. The authors hypothesized that inhibition of tubular cell death led to decreased inflammation. However, there is currently a controversy on the mechanisms of the beneficial effect of caspase inhibition. An alternative hypothesis suggests that caspase inhibition reduces inflammation (for example, through inhibition of caspasae-1β production) and, secondarily, prevents inflammatory cell-induced tubular cell injury. The relationship between apoptosis and inflammation is complex. Apoptosis of leukocytes clearly contributes to clearance of inflammation. However, in particular contexts, inhibition of leukocyte apoptosis may accelerate recovery from an inflammatory stimulus, as has been demonstrated in bacterial peritonitis in mice, where neutrophils rescued from apoptosis contribute to clearance of bacteria [36,37]. Additional information on the role of apoptosis in ARF has been derived from mice with genetic defects in apoptosis regulatory genes, such as *fas*, *caspase-1*, and *caspase-12*. The deficit of any of these proteins protected tubular cells from apoptosis in the course of ARF. However, renal function was not evaluated in experiments performed in *fas*-deficient mice, there are discrepancies on the effect of caspase-1 deficiency on renal function, and *caspase-12* deficiency was reported to protect from a clinically irrelevant toxin, tunicamycin (reviewed in [14]).

6. Future research

At present there is evidence that apoptosis participates in ARF. Stimuli that induce renal tubular cell apoptosis in culture also induce renal injury *in vivo*, apoptosis has been observed during ARF, the expression and/or activity of apoptosis modulatory molecules changes in the course of ARF and caspase inhibition improved renal function in at least some experimental models of ARF. However, there is an incomplete understanding of the molecular regulation of apoptosis in renal cells. In particular, a thorough evaluation of the role of newly described apoptosis regulatory molecules is warranted in order to search for stimulus and cell-specific apoptosis pathways activated in the course of renal disease. In addition, experimental results linking interference with apoptosis to a therapeutic effect are scarce and not definitive. Future research should focus on the definition of the molecular targets as well as the optimal time frame for therapeutic intervention. Special consideration should be given to optimizing modes of local delivery of apoptosis modulatory therapies so as to target only specific cell populations during a limited period of time.

Acknowledgments

The author's research has been financed by grants from FISSS 98/0637 and 01/0199, Comisión Interministerial de Ciencia y Tecnología (SAF 97/0071), Fundación

Conchita Rábago, Comunidad de Madrid (08.4/0007/1999 1, 08.2/0030/2000), Sociedad Española de Nefrología, Instituto Reina Sofia de Investigaciones Nefrológicas.

References

[1] Liano F, Pascual J, and the Madrid Acute Renal Failure Study Group. Epidemiology of acute renal failure: a prospective, multicenter, community-based study. Madrid Acute Renal Failure Study Group. Kidney Int 1996;50:811–8.
[2] Solez K, Morel-Maroger L, Sraer JD. The morphology of ''acute tubular injury'' in man: analysis of 57 renal biopsies and a comparison with the glycerol model. Medicine (Baltimore) 1979;58:362–76.
[3] Olsen TS, Olsen HS, Hansen HE. Tubular ultrastructure in acute renal failure in man: epithelial necrosis and regeneration. Virchows Arch A: Pathol Anat Histopathol 1985;406:75–89.
[4] Ortiz A, Lorz C, Catalán MP, Ortiz A, Coca S, Egido J. Cyclosporine A induces apoptosis in murine tubular epithelial cells: role of caspases. Kidney Int 68 (Suppl):S25–9.
[5] Takeda M, Kobayashi M, Shirato I, Osaki T, Endou H. Cisplatin-induced apoptosis of immortalized mouse proximal tubule cells is mediated by interleukin-1 beta converting enzyme (ICE) family of proteases but inhibited by overexpression of Bcl-2. Arch Toxicol 1997;71:612–21.
[6] Cihlar T, Ho ES, Lin DC, Mulato AS. Human renal organic anion transporter 1 (hOAT1) and its role in the nephrotoxicity of antiviral nucleotide analogs. Nucleosides Nucleotides Nucleic Acids 2001;20: 641–8.
[7] Meier P, Dautheville-Guibal S, Ronco PM, Rossert J. Cidofovir-induced end-stage renal failure. Nephrol Dial Transplant 2002;17: 148–9.
[8] Shimizu A, Yamanaka N. Apoptosis and cell desquamation in repair process of ischemic tubular necrosis. Virchows Arch B: Cell Pathol Incl Mol Pathol 1993;64:171–80.
[9] Ueda N, Kaushal GP, Shah SV. Apoptotic mechanisms in acute renal failure. Am J Med 2000;108:403–15.
[10] Lieberthal W, Levine JS. Mechanisms of apoptosis and its potential role in renal tubular epithelial cell injury. Am J Physiol 1996;271(3 Pt 2):F477–88.
[11] Green DR. Apoptotic pathways: the roads to run. Cell 1998;94:695–8.
[12] Ortiz A. Apoptotic regulatory proteins in renal injury. Kidney Int 2000;58:467–85.
[13] Strasser A, O'Connor L, Dixit VM. Apoptosis signaling. Annu Rev Biochem 2000;69:217–45.
[14] Ortiz A, Justo P, Catalán MP, Sanz AB, Lorz C, Egido J. Apoptotic cell death in renal injury: the rationale for intervention. Curr Drug Targets: Immune, Endocr Metab Disord 2002;2:181–92.
[15] Ortiz A, Lorz C, Catalán MP, Danoff TM, Yamasaki Y, Egido J, Neilson EG. Expression of apoptosis regulatory proteins in tubular epithelium stressed in culture or following acute renal failure. Kidney Int 2000;57:969–81.
[16] Ortiz-Arduan A, Danoff TM, Kalluri R, González-Cuadrado S, Karp SL, Elkon K, Egido J, Neilson EG. Regulation of Fas and Fas ligand expression in cultured murine renal cells and in the kidney during endotoxemia. Am J Physiol 1996;241:F1193–201.
[17] Alvarez Arroyo MV, Suzuki Y, Yagüe S, Lorz C, Jimenez S, Soto C, Barat A, Belda E, Gonzalez Pacheco FR, Deudero JJP, Castilla MA, Egido J, Ortiz A, Caramelo C. Role of vascular endothelial growth factor in tubular cell protection against acute cyclosporine toxicity. Transplantation 2002;74:1618–24.
[18] Ortiz A, Lorz C, Egido J. New kids in the block: the role of FasL and Fas in kidney damage. J Nephrol 1999;12:150–8.
[19] Lorz C, Ortiz A, Justo P, González-Cuadrado S, Duque N, Gómez-Guerrero C, Egido J. Proapoptotic Fas ligand is expressed by normal kidney tubular epithelium and injured glomeruli. J Am Soc Nephrol 2000;11:1266–77.
[20] Blanco-Colio LM, Daehn I, Justo P, Lorz C, Ortiz A, Egido J. BCL-XL overexpression protects from apoptosis induced by HMG-Koa reeducates inhibitors in murine tubular cells. Kidney Int 2003;64:181–91.
[21] Let A, Basic MC, Walensky LD, Sorcinelli MD, Weiler S, Korsmeyer SJ. Distinct BH3 domains either sensitize or activate mitochondrial apoptosis, serving as prototype cancer therapeutics. Cancer Cell 2002; 2:183–92.
[22] Adams JM, Cory S. Life-or-death decisions by the Bcl-2 protein family. Trends Biochem Sci 2001;26:61–6.
[23] Loeffler M, Kroemer G. The mitochondrion in cell death control: certainties and incognita. Exp Cell Res 2000;256:19–26.
[24] Ferri KF, Kroemer G. Organelle-specific initiation of cell death pathways. Nat Cell Biol 2001;3:E255–63.
[25] Hacki J, Egger L, Monney L, Conus S, Rosse T, Fellay I, Borner C. Apoptotic crosstalk between the endoplasmic reticulum and mitochondria controlled by Bcl-2. Oncogene 2000;19:2286–95.
[26] Nakagawa T, Zhu H, Morishima N, Li E, Xu J, Yankner BA, Yuan J. Caspase-12 mediates endoplasmic-reticulum-specific apoptosis and cytotoxicity by amyloid-beta. Nature 2000;403:98–103.
[27] Thornberry NA, Lazebnik Y. Caspases: enemies within. Science 1998;281:1312–6.
[28] Lassus P, Opitz-Araya X, Lazebnik Y. Requirement for caspase-2 in stress-induced apoptosis before mitochondrial permeabilization. Science 2002;297:1352–4.
[29] Johnson DE. Noncaspase proteases in apoptosis. Leukemia 2000; 14:1695–703.
[30] Verhagen AM, Coulson EJ, Vaux DL. Inhibitor of apoptosis proteins and their relatives: IAPs and other BIRPs. Genome Biol 2001;2:3009.
[31] Justo P, Lorz C, Sanz A, Egido J, Ortiz A. Molecular pathways of CsA nephrotoxicity: a role for the endoplasmic reticulum (ER)? J Am Soc Nephrol 2002;13:549.A–50.A.
[32] Justo P, Lorz C, Egido J, Ortiz A. BclxL, but not caspase inhibition, increase long term cell survival in nephrotoxicity. J Am Soc Nephrol 2001;12:801A.
[33] Ortiz A, Lorz C, Catalan MP, Egido J. Different caspases are required for tubular cell death induced by nephrotoxins. J Am Soc Nephrol 1998;9:444A.
[34] Cheng J, Zhou T, Liu C, Shapiro JP, Brauer MJ, Kiefer MC, Barr PJ, Mountz JD. Protection from Fas-mediated apoptosis by a soluble form of the Fas molecule. Science 1994;263:1759–62.
[35] Daemen MA, van't Veer C, Denecker G, Heemskerk VH, Wolfs TG, Clauss M, Vandenabeele P, Buurman WA. Inhibition of apoptosis induced by ischemia–reperfusion prevents inflammation. J Clin Invest 1999;104:541–9.
[36] Catalán MP, Esteban J, Subirá D, Egido J, Ortiz A. Inhibition of caspases improves bacterial clearance in experimental peritonitis. Perit Dial Int 2003;23:123–6.
[37] Catalán MP, Reyero A, Egido J, Ortiz A. Acceleration of neutrophil apoptosis by glucose-containing peritoneal dialysis solutions: role of caspases. J Am Soc Nephrol 2001;12:2442–9.