Invited Comment

Apoptosis: potential role in renal diseases

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Introduction

The rapid expansion of the literature on apoptosis in renal journals reflects the growing interest in this subject in kidney pathophysiology. Even though apoptosis has been known for decades to occur in all tissues for the orderly disposal of unnecessary or unwanted cells, only very recently have scientists begun to link this physiological process to the pathogenesis of renal diseases. Along with its well-known role in renal morphogenesis, where embryonic structures are progressively replaced by more mature architectures, there is now evidence that apoptosis intervenes in such diverse processes as the formation of renal cysts, glomerular and interstitial inflammation, scarring and sclerosis of the kidney. Moreover, even distant events such as the clonal selection of lymphocytes producing autoreactive antibodies, occurring largely by apoptosis, may influence the kidney through the formation of immune complexes and/or triggering autoimmune reactions leading to glomerulonephritis (GN). In the following brief commentary, we summarize our current understanding of the potential implications of apoptosis for renal diseases.

The cellular and molecular biology of apoptosis

The cellular content of any tissue is regulated by a balance between cell replication and cell loss. Under physiological conditions, excess cells are cleared by apoptosis, a sequence of events including recognition of the cell, cessation of metabolic activity, disassembly and orderly disposal of cellular components and debris [1,2]. Interestingly, the process is often an active one, requiring transcriptional events and protein synthesis prior to nuclear fragmentation and packaging of DNA into ‘apoptotic bodies’, the hallmark of an apoptotic cell. The goal of the process is ‘sequestration’ of cytoplasmic components, which could be harmful if released into the extracellular environment, as in the case of enzymes, or potentially immunogenic, triggering autoreactive responses leading to inflammation [1,2]. Thus, in a healthy organism, deletion of large numbers of cells occurs without perturbation of the surrounding environment. This ordinarly applies to cell populations with high turnover, such as leucocytes or intestinal epithelial cells. Also chemical or physical damage to the tissue may trigger apoptosis, below a certain threshold of injury. Above that level, cell disruption occurs, with the release of proinflammatory components, which in turn amplify damage. Such an alternative modality of cell loss, with obvious negative implications for survival of the organism, is termed necrosis. Typical examples of this situation are UV or radiation damage, heat or cold exposure and direct trauma. All these events initially trigger apoptosis, accompanied or replaced at later stages by tissue necrosis [1,2].

Apoptosis is generally initiated by activation of one or more cellular ‘switches’, which are usually membrane receptors, such as the protein encoded by the gene Fas [3,4]. Circulating ligands for this receptor, belonging to the tumour necrosis factor (TNF) superfamily, act as ‘death signals’, triggering a cascade of events amplified by ‘death promoter’ genes, such as Bax/Bad [5–7] (Table 1). Alternatively, cell cycle arrest in G0–G1 could be induced by p53, a gene product that senses DNA damage and induces WAF-1/Cip1-encoded p21 to block cyclin-dependent kinases [8–10]. The cellular content of any tissue is regulated by a balance between cell replication and cell loss. Under physiological conditions, excess cells are cleared by apoptosis, a sequence of events including recognition of the cell, cessation of metabolic activity, disassembly and orderly disposal of cellular components and debris [1,2]. Interestingly, the process is often an active one, requiring transcriptional events and protein synthesis prior to nuclear fragmentation and packaging of DNA into ‘apoptotic bodies’, the hallmark of an apoptotic cell. The goal of the process is ‘sequestration’ of cytoplasmic components, which could be harmful if released into the extracellular environment, as in the case of enzymes, or potentially immunogenic, triggering autoreactive responses leading to inflammation [1,2]. Thus, in a healthy organism, deletion of large numbers of cells occurs without perturbation of the surrounding environment. This ordinarly applies to cell populations with high turnover, such as leucocytes or intestinal epithelial cells. Also chemical or physical damage to the tissue may trigger apoptosis, below a certain threshold of injury. Above that level, cell disruption occurs, with the release of proinflammatory components, which in turn amplify damage. Such an alternative modality of cell loss, with obvious negative implications for survival of the organism, is termed necrosis. Typical examples of this situation are UV or radiation damage, heat or cold exposure and direct trauma. All these events initially trigger apoptosis, accompanied or replaced at later stages by tissue necrosis [1,2].

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### Table 1. Genes involved in apoptosis of mammalian cells

<table>
<thead>
<tr>
<th>Genes involved in apoptosis of mammalian cells</th>
<th>References</th>
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<tbody>
<tr>
<td>Proapoptotic death signals</td>
<td>[1,2,4]</td>
</tr>
<tr>
<td>c-myc (myelocytoma oncogene)</td>
<td>[1–4,12,17,21,22,56,62,63,66]</td>
</tr>
<tr>
<td>Fas (APO-1, CD95)</td>
<td>[1,2,4]</td>
</tr>
<tr>
<td>Tumour necrosis factor (TNF, Fas ligand, gld)</td>
<td>[1,2,4]</td>
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<tr>
<td>Hid</td>
<td>[1,2,4,8]</td>
</tr>
<tr>
<td>p53</td>
<td></td>
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<tr>
<td>E1A/E1B</td>
<td></td>
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<tr>
<td>Death promoters</td>
<td>[7]</td>
</tr>
<tr>
<td>Bad</td>
<td></td>
</tr>
<tr>
<td>Bax</td>
<td>[5–7]</td>
</tr>
<tr>
<td>Bak (bcl-2 homologous antagonist/killer)</td>
<td>[12]</td>
</tr>
<tr>
<td>Bcl-x&lt;sub&gt;S&lt;/sub&gt;</td>
<td>[16]</td>
</tr>
<tr>
<td>Cystine proteases</td>
<td>[8–11,25]</td>
</tr>
<tr>
<td>ced-3, ced-4 (Caenorhabditis elegans genes, encode cystine proteases)</td>
<td></td>
</tr>
<tr>
<td>Anti-apoptotic survival promoters</td>
<td>[5–7,15–17,26,50,53,54,56,63,64]</td>
</tr>
<tr>
<td>Bcl-2 (B-cell follicular lymphoma, ced-9)</td>
<td>[7]</td>
</tr>
<tr>
<td>Bcl-x&lt;sub&gt;L&lt;/sub&gt;</td>
<td></td>
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Whatever the technique used to mark fragmented DNA, fluorescence-activated cell sorting or direct microscopy are useful to quantitate the percentage of cells involved.

The time required for a cell to progress from ‘priming’ for apoptosis, to nuclear fragmentation, to removal of debris by surrounding cells and/or macrophages is variable under most circumstances, between 1 and 6 h. It should be borne in mind that morphologically normal cells may be already primed for apoptosis, so that underestimation of the percentage of dying cells usually occurs, unless sensitive techniques such as TUNEL are employed. Under physiological conditions, only a minor fraction of a given cell population is undergoing apoptosis. This notwithstanding, over several hours or days even minor apoptosis may lead to extensive remodelling of an anatomical structure or renewal of a replicating tissue [1,2].

A number of genes appear to be involved in the early phase of apoptosis, controlling activation and progression of the cell to DNA fragmentation [3–10,14–17]. Each cell appears committed to apoptosis by expression of the entire genetic machinery needed, although a balance between ‘survival factors’ and proapoptotic factors decides its functional status. As the process is critical and irreversible, much as a ‘self-destruction’ device inscribed into a cell’s genome, it is understandable how so many levels of control come into play before a cell is directed toward apoptosis. Table 1 lists proapoptotic and anti-apoptotic genes as they have been progressively characterized in various organisms and tissues, including the mammalian kidney. Studies are already surfacing on the expression of Fas, Bcl-2 and Bax in human kidney disease, so that it is reasonable to envisage a role for many, if not all, of these genes as players in processes such as proliferative nephritides and glomerulosclerosis.

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**Fig. 1.** DNA fragmentation on agarose/ethidium bromide gel electrophoresis. Lane 1, DNA size markers; lane 2, integral genomic DNA. Note the ‘laddering’ of DNA in lanes 3 and 4 as a result of endonuclease activation in cultured human proximal tubular epithelial cells.

Cell culture level or in kidney biopsies, DNA fragmentation can be easily seen as chromatin condensation, even before the budding of apoptotic bodies from a dying cell. Staining of DNA with either propidium iodide, acridine orange or Hoechst 33258 dye is helpful in revealing condensed nuclear areas in otherwise normal cells (Figure 2). More accurate techniques for the identification of apoptosis rely on tagging of fragmented DNA by the enzyme terminal-transferase (TdT), as in the widely used in situ hybridization assay or TUNEL (TdT-mediated UTP nick-end labelling).
**In vitro and animal studies**

Cell culture is a convenient tool for the study of apoptosis and its regulation. Savill and co-workers pioneered this field, reporting the rapid appearance of apoptosis in monolayer cultures of glomerular mesangial cells upon withdrawal of growth factors from the culture media [18,19]. Obviously, most apoptotic cells are found in cytopsins of floating, detached cells. Supplementing the culture media with serum or purified growth factors, particularly insulin-like growth factor 1 (IGF-1), prevented this phenomenon, confirming the ‘survival factor’ activity of these polypeptides [18,19]. These studies, in conjunction with earlier literature in cell culture from other organs, have led to the appreciation of the need for survival factors to support viability, not only proliferation of cells. If a cell becomes deprived of life-permissive growth factors, it will progress automatically to apoptosis. This phenomenon should have profound implications for the in vivo situation, where matrix-bound growth factors and autocrine loops between neighbouring cells are likely to convey anti-apoptotic signals in a viable tissue [20].

Consistent with the general model outlined above, Gonzalez-Cuadrado et al. were able to induce apoptosis of mesangial cells by application of an agonistic anti-Fas antibody. In these cells, induction of Fas and Fas-ligand gene expression occurs in response to a number of agents, such as TNF, interleukin-1β, interferon-γ, or *Escherichia coli* lipopolysaccharide (LPS) [21,22].

RGD (the Arg–Gly–Asp amino acid sequence)-containing peptides, typical of fibronectin and vitronectin, have been recently shown to stimulate apoptosis of human mesangial cells, possibly through expression of ICE-1 [11,23,24]. RGD peptides have relevance to the binding of integrins such as αvβ3, and this finding may indicate that fibronectin and vitronectin are important regulators of the survival of mesangial cells [23,24]. Moreover, it has been recently demonstrated that antibodies to β1-integrins induced apoptosis of epithelial cells [25], and that the expression of the α4β1 integrin, but not the closely related α β, which binds fibronectin on the same RGD motif, suppress apoptosis through the Bcl-2 pathway in Chinese hamster ovary (CHO) cells [26]. The strict link between interstitial glycoproteins, integrins and apoptosis suggests a potential role for interstitial fibrils in modulating cell survival during fibrogenesis and scarring.

Particular interest has been attracted by genes involved in protection against reactive oxygen species (ROS) or superoxide radicals, metabolic byproducts of oxidative metabolism in aerobic cells. ROS activate poly(ADP) ribose transferase, with resulting depletion of NAD/NADH and ATP leading to cell death. This has been reported in many cell systems, including cultured glomerular cells [27–32]. Clearly, much of the toxicity associated with the release of ROS at sites of inflammation is mediated by stimulation of apoptosis, with obvious relevance to glomerular disease. This may well be the case in co-culture models using either apoptotic leucocytes being phagocytosed by mesangial cells, or conversely exploiting monocyte adhesion to induce mesangial cell cytotoxic damage and apoptosis [33–35].

ROS levels are controlled by Bcl-2, which encodes a protein capable of inhibiting radiation-, heat shock protein- or glutathione peroxidase deficiency-induced apoptosis [15,16]. The Bcl-2 gene product inhibits apoptosis by promoting the activity of mitochondrial...
Apoptosis in renal diseases

Relevance of apoptosis to renal disease

If one looks at the basic events leading to pathologic changes of the kidney, it is easy to envisage how the balance between proliferating and dying cells is critical. Proliferative changes, such as those seen in post-infectious diffuse proliferative GN, rapidly progressive GN, mesangial proliferative nephritides, lupus WHO class IV nephritis, or renal transplant rejection are likely to reflect a dominance of mitotic events in glomerular cells or infiltrating leucocytes. Resolution of the lesion—whenever applicable—requires an increased rate of cell removal, possibly by apoptosis, so that inflammation is minimized. Any inadequacy in the rate of apoptosis would favour proliferation of resident cells, cellular infiltration and inflammation, and slow down the recovery of these subjects.

The situation is the opposite when glomerulosclerosis and/or scarring is considered. Here, cellular depletion is the hallmark of disease, with replacement of glomerular, tubular or interstitial structures by amorphous, fibrous material. The existing literature already provides evidence of apoptosis in heterogeneous renal diseases characterized by fibrosclerotic evolution. Obviously, the presence of cells with nuclear fragmentation may simply be an epiphenomenon, and harder evidence is necessary to link renal sclerosis to primary alterations of apoptosis.

Apoptosis and cystic diseases

Polycystic kidney disease, like other cystic disorders, results from disorderly proliferation of epithelial cells of tubular segments, with fluid accumulation, disruption of surrounding structures and interstitial fibrosis [45]. The autosomal dominant inherited form of the disease results from abnormalities of the PKD1 gene, encoding a 460 kDa protein, polycystin, which plays a role in differentiation of epithelial cells. It appears that malfunction of polycystin results in altered proliferation and fluid secretion into cysts, with perturbed viability of epithelial and interstitial cells [45,46]. Increased rates of apoptosis have been described by Woo in several structures of kidneys altered by cystic transformation, including the glomerulus, cyst walls, and both cystic and non-cystic tubules [47]. This finding was confirmed by Lanoix et al., who noted elevated rates of epithelial proliferation, parallel to increased expression of the proto-oncogene, c-myc. Bcl-2 mRNA and protein were also increased, along with stable levels of Bax and p53, in the face of increased apoptosis [48]. Winyard et al. examined human pre- and post-natal samples of polycystic kidneys [49], confirming increased rates of apoptosis. These investigators noted similar changes in the polycystic cpk/cpk mouse model, thus strengthening the hypothesis that apoptosis may represent a primary defect leading to cell loss and altered architecture of the residual structures [49].

Notably, cystic transformation of the kidney can be induced in transgenic mice overexpressing the proto-oncogene c-myc, parallel to increased levels of the Bcl-2 gene and protein. As mentioned earlier, mice deficient for Bcl-2 also develop multicystic renal disease [50].

Studies in the rat anti-Thy 1.1 nephritis model by Baker et al. have shown clearly that mesangiolysis, a typical early feature of this experimental lesion, is mediated by apoptosis of mesangial cells [19]. Clearance of apoptotic cells occurs via ingestion by neighbouring mesangial cells or professional macrophages [18,36,37]. Other ways of eliminating excess cells during resolution of inflammation include migration, as in the case of neutrophils [38]. After a few days, apoptosis subsides, being replaced by proliferation of mesangial cells, which rapidly restores the architecture of the glomerulus. It is of interest that the appearance of growth factors at the site of the lesion, either produced by infiltrating leucocytes or released by platelets, correlates well with the offsetting of apoptosis in the proliferative phase of the anti-Thy 1.1 nephritis [39].

Another setting of increased apoptosis is represented by the remnant kidney model employing 5/6 nephrectomy in the rat. Sugiyama et al. have reported the rapid appearance of TUNEL-positive cells in otherwise normal glomeruli subject to the functional overload that eventually leads to glomerulosclerosis in the remnant kidney [40]. Damage to tubular epithelial cells by filtered proteins in nephrotic patients may represent another example of an apoptotic stimulus leading to progressive nephron loss. Recent studies in vitro and in vivo suggest the potential of proteinuria to trigger apoptosis. Native serum albumin complete with its lipidic components elicited apoptosis of glomerular and tubular cells [41]. Cultured human proximal tubular epithelial cells incubated with native albumin, at concentrations mimicking those encountered in nephrotic syndrome, underwent apoptosis [41]. Fatty acid-free albumin was ineffective, confirming a role for the lipid mediator proposed by Kees-Folt [42]. This observation was confirmed in vivo, in a model of protein overload proteinuria [43]. The large amounts of filtered exogenous albumin induced apoptosis of both tubular and mesangial cells. This effect was mediated by stimulation of inducible nitric oxide synthetase (iNOS) gene transcription, in turn responsible of the overexpression of the p53 tumour suppressor gene [43,44]. The relationship between filtered albumin, enhancement of iNOS and apoptosis was confirmed by the suppression of p53 expression and apoptosis in rats treated with albumin and a non-specific inhibitor of iNOS, 1-nitroso-arginine. As these models are relevant to the non-immunologic progression of renal disease in humans, the information is potentially important and awaits confirmation from renal biopsies.
Both conditions are associated with increased apoptosis in cystic epithelia and surrounding interstitial cells, pointing to its role as a common denominator for the formation and enlargement of cysts.

**Apoptosis and glomerulonephritis**

The initial reports in this field are predictably broad-spectrum investigations of the phenomenon of apoptosis in a variety of histological lesions. Soto et al. examined two proliferative forms of GN, namely post-streptococcal GN and lupus nephritis [51]. This work employed proliferating cell nuclear antigen (PCNA)/cyclin staining to assess the percentage of dividing cells, parallel to TUNEL of apoptotic cells. The findings are unequivocal, with simultaneous changes in proliferation and cell death throughout the course of the usually resolving post-infectious nephritis. On the other hand, diffuse proliferative lupus nephritis was characterized by an imbalance between proliferating cells and apoptosis, with the latter not matching the actual proportion of PCNA-positive cells [51]. This resulted in a progressive increase in glomerular cellularity. Only minor increments of the number of apoptotic cells have been observed in mesangio proliferative nephritides, possibly accounting for the increased cellularity of these diseases. Of course, one should keep in mind the long time-frame of the evolution of these lesions, in which even marginal changes in the rate of apoptosis may lead with time to significant remodelling of the glomerulus [52].

Studies on apoptosis-related gene expression in experimental or human nephritides are beginning to appear. Nakopoulou et al. have examined the distribution of Bcl-2 oncoprotein in human nephritides, noting its prevalent accumulation in tubular and interstitial areas, with modest expression in the glomerulus [53]. Only in rapidly progressive GN and transplant rejection, abundant Bcl-2 was seen at the site of cellular crescent formation. In contrast to these findings, Takemura et al. reported in situ hybridization extensive positivity of the glomerulus for both Fas and Bcl-2 in lupus nephritis and other forms of GN, with an obvious correlation with apoptosis [54].

**Apoptosis and glomerulosclerosis**

Sugiyama and co-workers examined renal biopsies from patients with focal glomerulosclerosis and found some analogies with remnant kidneys of rats subject to 5/6 nephrectomies [40]. Evident TUNEL-positive cells were found in the developing fibrous material which accounts for the typical lesion of these diseases, although this is certainly not sufficient to conclude that dysregulated apoptosis accounts for their pathogenesis. Mechanical or cytotoxic damage to resident glomerular cells, most likely epithelial visceral cells, may account both for the production of excess matrix and blockade of their turnover. Apoptosis may be normal, providing a non-inflammatory means of removing otherwise damaged cells.

The same concept applies to diabetic nephropathy in the rat, in which relevant areas of apoptosis have been reported by in situ apoptag labelling [55]. Control non-diabetic kidneys showed no significant percentage of apoptotic cells, providing a possible explanation for the reduced cellularity and fibrosis of diabetic nephropathy. Studies in cultured epithelial cells demonstrated down-regulation of the anti-apoptotic Bcl-2 protein, indicating one potential mechanism for the observed cell depletion [56]. Another likely mechanism involved in cell loss during the progression of diabetic nephropathy could be the enhancement of iNOS activity by non-enzymatically glycated products, particularly Amadori-configurated albumin [57]. Indeed, Amadori adducts of glycated albumin induce apoptosis of murine and human endothelial cells [58].

Nevertheless, as in the case of proliferative/inflammatory nephritides, the demonstration of a causative role of apoptosis rests in genetic manipulation of this process, in order to either trigger or dampen the pathologic changes occurring at the glomerular and/or interstitial level.

**Apoptosis and systemic lupus erythematosus (SLE)**

One of the most exciting avenues of research in the field of SLE is represented by the potential involvement of apoptosis in the pathogenesis of the disease [12,13]. The hypothesis has been put forward based on several observations. First, SLE is characterized by autoantibodies against DNA, which is hardly immunogenic under normal conditions. Interestingly, studies on the structure of the immune reactants in this disease have pointed to nucleosomes as the real target for autoantibodies. The high histone content of nucleosomes, a typical product of apoptosis, may also explain trapping of positively charged immune complexes at the level of the glomerular basement membrane (GBM) in lupus nephritis [59]. Glomerular mesangial cells also bind nucleosomes through a receptor-mediated mechanism [60]. Indeed, negatively charged single- or double-stranded DNA would be rejected by the similarly charged GBM. Second, there is evidence of a greater rate of spontaneous apoptosis in lymphocytes or mononuclear cells isolated from patients with SLE [12]. This would mean that such cells are 'primed' for apoptosis in vivo, although the process seems functionally blocked unless the cells are removed from serum and/or the native environment. Thus, researchers have speculated that defective apoptosis may account for exposure of normally sequestered nuclear antigens (nucleosomes, apoptotic bodies), with the induction of a deranged autoimmune response. Mice of the lpr and gld strains that spontaneously develop SLE exhibit abnormalities of the Fas and Fas ligand (gld) genes, controlling early steps of the apoptotic process. Interestingly, mice of the MRL/+/+ strain lacking the lpr gene develop milder disease later in life [61,62].
A third level of potential involvement of apoptosis in SLE is represented by the clonal expansion of autoreactive lymphocytes, eventually leading to autoantibody production. In a normal immune response, such aberrant clones would be deleted by apoptosis, in order to suppress potentially harmful autoreactivity. Evidence for the survival of ‘double-null’ CD4−CD8− cells signals an abnormality of the apoptosis process which may be part of a generalized disorder [12,15]. A circulating splice variant of the Fas receptor has been described in lupus, which may account for competitive inhibition of TNF/Fas ligand-dependent apoptosis [63]. There is also evidence for increased transcription of the Bcl-2 gene, an inhibitor of apoptosis via scavenging of ROS [64]. Thus, if one considers the initial reports of reduced apoptosis at the glomerular level in lupus nephritis, the possibility of a dual level of renal involvement exists: glomerular trapping of autoimmune complexes, followed by depressed anti-inflammatory mechanisms with impaired clearance of infiltrating cells, may induce the fulminant lesions (WHO class IV) occurring in flare-ups of the disease. Lesser degrees of impairment of apoptosis may favour more benign histological aspects, such as mild mesangial proliferation (class III), or immune deposit accumulation and GBM thickening (class V).

The few clinico-pathological studies available thus far provide support for this working hypothesis, with an imbalance between abundant proliferating cells expressing cyclin-related antigens and TUNEL-positive cells, which one would expect to see particularly at sites of necrotizing lesions. Indeed, it is the severity of glomerular damage often encountered in flare-ups that may suggest failure of this basically anti-inflammatory pathway. Clearly, more work is necessary to relate morphological data to a potential involvement of apoptosis in SLE nephritis.

Apoptosis and transplant rejection

Transplant rejection is a typical example of multicellular interactions in which apoptosis might come into play by regulating lymphocyte subsets and/or deleting graft cells exposed to cytotoxic damage. A thorough study by Meehan et al. describes the pattern of apoptosis occurring in acute cellular rejection with focal lesions including endothelialitis, tubulitis and tubular necrosis [65]. Co-staining with GMP-17, a component of cytotoxic granules, allowed the identification of the cell populations undergoing apoptotic changes, which were mostly cytotoxic lymphocytes/macrophages. Only a limited number of resident graft cell were TUNEL-positive, suggesting that apoptosis is primarily responsible for the clearance on infiltrating cytotoxic T cells [66]. The expression of the apoptosis-related gene Fas was found to be significantly enhanced at the level of the tubular epithelium during acute allograft rejection, mostly in relationships with lymphocytic infiltrates [66]. Moreover, TUNEL-positive cells were observed in kidney graft biopsies showing features of cyclosporin (CsA) toxicity, as well as mild acute rejection and chronic allograft nephropathy [67]. The authors speculated that CsA may induce apoptosis of tubular cells, resulting in tubular atrophy and loss, typical features of chronic transplant nephropathy. The proapoptotic activity of CsA, evaluated mainly on T lymphocytes, is still debated. Recent in vitro experiments show that CsA promotes apoptosis of tubular, mesangial and endothelial cells, by acting on iNOS expression [68].

Therapeutic implications

Nephrologists have been dealing with apoptosis and manipulating the process for decades, often without being aware of the mechanism of action of immunosuppressants employed in renal diseases. Both corticosteroids and cytotoxic agents (cyclophosphamide, chlorambucil) induce apoptosis of leucocytes, resulting in deletion of autoreactive clones and/or depression of harmful immune responses. Alkylating agents are also proapoptotic in somatic cells, being employed to reduce the hyperplasia of capsular epithelial cells and fibroblasts in extracapillary, rapidly progressive GN. Adverse effects on bone marrow or the urinary tract, as in the case of cyclophosphamide-induced cystitis, are examples of the general toxicity of these agents. Now the introduction of more specific anti-rejection immunomodulators, such as cyclosporin, FK506 and mofetil mycofenolate, opens up new perspectives in the treatment of nephropathies. Also these agents rely on apoptosis of selected lymphocytic clones, although with more targeted action and less untoward effects on tissues. The goal of immunosuppression is to devise new compounds that may selectively trigger apoptosis of lymphocytes involved in autoimmune responses, without affecting immune defences in general, thus reducing the risk of infections and other side effects. The large number of genes serving as apoptosis ‘switches’ provides a list of potential targets for a more sensitive treatment of renal disease.

Conclusions

Apoptosis is undoubtedly involved in a variety of pathophysiological conditions of the kidney, ranging from morphogenesis to cyst formation, inflammation, and glomerular or interstitial scarring. Advances in this field yield the promise to interfere with the course and progression of disease in a more direct and selective way. Clearly, key to the development of new therapeutic strategies is the understanding of the molecular mechanisms of apoptosis in the kidney, and their possible dysregulation in renal diseases. The assumption that apoptotic pathways are identical in all organs needs experimental validation, with techniques that are presently available to many laboratories involved in renal research. The next few years will probably bring
relevant new information in this area, with promises for innovative diagnostic and therapeutic approaches to renal disease.

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