Apolothesis in tubulointerstitial renal disease

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Introduction

Tubulointerstitial injury and fibrosis play a critical role in the progression of renal disease such that there is a striking correlation between the severity of the tubulo-interstitial pathological changes and the subsequent development and progression of chronic renal failure [1]. Apoptosis has been well documented in both human renal diseases and experimental animal models of renal injury [2–7]. In many instances, unchecked apoptosis over time results in a slowly progressive loss of resident renal cells, culminating in renal tubular atrophy and hypocellular fibrotic tubulointerstitial scarring (reviewed in [8,9]). This brief article focuses upon the role of the Fas death receptor (CD95), cell cycle regulatory proteins and extracellular proteins in tubulointerstitial cell apoptosis in an attempt to give the reader a flavour of the varied factors that may influence cell death in the tubulointerstitial compartment of the kidney.

Life and death signals

Cells constantly receive signals from the local microenvironment, many of which may be viewed as promoting either cell survival or death (Table 1). Such signals may be cell lineage specific, such as certain growth factors, or more general, such as the fundamental requirement for an adequate supply of oxygen and nutrients. These apparently conflicting signals are integrated at the level of individual cells which then decide whether to live or die. In extremely adverse biological circumstances, cell death may be mediated by necrosis which is markedly proinflammatory in view of the inevitable spillage of phlogistic intracellular contents. Cells in both physiological and pathological circumstances (e.g. embryogenesis or acute inflammation) preferentially die by undergoing apoptosis. Apoptosis is characterized by stereotypical morphological changes and, unlike necrosis, is injury-limiting since apoptotic cells are usually ingested rapidly and degraded by local or infiltrating phagocytes without the release of proinflammatory mediators [10–12]. However, apoptosis is a double-edged sword and, although it may result in the beneficial deletion of cells such as infiltrating leukocytes or excess numbers of tubular cells during tubular remodelling, it may also be responsible for the undesirable deletion of resident renal cells during inflammation or post-inflammatory scarring [8,13,14].

Is the fate of tubulointerstitial cells amenable to study in vivo?

The identification of proliferating tubulointerstitial cells may be ascertained accurately by double immunostaining for markers of proliferation [e.g. bromodeoxyuridine (BrdU) or proliferating cell nuclear antigen (PCNA)] together with cell type-specific markers (e.g. smooth muscle actin for the interstitial myofibroblast). However, double-labelling of apoptotic interstitial cells with cell-specific surface markers and TUNEL staining is fraught with hazard since studies of apoptosis in both renal development and renal inflammation indicate that the majority of apoptotic cells actually lie within other cells as a consequence of rapid recognition and phagocytosis [15,16]. This strongly militates against using a double-labelling strategy to study levels of apoptosis within individual populations of cells within the interstitial compartment. However, it is important to note that tubular cell apoptosis is amenable to accurate and quantifiable study.

The cell surface death receptor Fas (CD95)

The Fas death receptor is a member of the tumour necrosis factor (TNF) receptor family and may be expressed by renal tubular cells, interstitial fibroblasts and infiltrating leukocytes; all of which may also express Fas ligand (FasL, CD95L) [17,18]. Binding of Fas ligand to cell surface Fas leads to activation of the caspase protease cascade with subsequent cleavage of numerous intracellular proteins resulting in the rapid demise of the cell (reviewed in [19]). A substantial

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body of experimental data indicates a role for Fas in mediating apoptosis in tubulointerstitial disease (reviewed in [20]). Work by Schelling and co-workers has demonstrated a role for Fas in two murine models of chronic renal failure as well as hypoxic renal tubular cell apoptosis in vitro [21,22]. The latter is particularly intriguing in view of recent speculation about the role of chronic hypoxia in the progression of renal disease [23]. Studies involving lpr mice, which express a non-functional Fas receptor, have also been informative, indicating that Fas is involved in distal tubular cell apoptosis in both murine renal ischaemia reperfusion injury and experimental hydronephrosis [24,25].

Cell cycle regulatory proteins

Linkage between apoptosis and the cell cycle is becoming increasingly apparent, with cells destined to undergo apoptosis often exiting the cell cycle from the G1 phase [26]. Cell cycle regulatory proteins such as the cyclin-dependent kinase inhibitors p27 and p21 (which inhibit cell cycle progression) and cyclin-dependent kinase 2 (cdk2, which facilitates cell proliferation) play an important role in renal disease (reviewed in [27]). Interestingly, recent data indicate that p27, p21 and cdk2 can also modulate apoptosis in both renal and non-renal cells [28–30]. For example, p27 knockout mice exhibit markedly increased levels of both tubular cell proliferation and apoptosis compared with wild-type controls in experimental hydrenephrosis [31]. It is important to note that the effect of the absence of such ‘apoptosis-modulating proteins’ may vary according to the nature of renal injury. In this regard, no differences in tubular cell death were discernible between p21 knockout and wild-type mice in experimental hydronephrosis; a result quite unlike that seen in cisplatin nephropathy in which p21 knockout mice develop markedly increased levels of tubular cell apoptosis and necrosis, worse renal function and have a higher mortality [30–32].

Extracellular proteins

Extracellular proteins may provide important survival signals for cells, and inhibition of adhesion may induce apoptosis. Osteopontin (OPN) is a multifunctional adhesive protein, a tubular cell survival factor and a macrophage chemoattractant (reviewed in [33]). OPN is expressed at low levels by tubules in normal kidney but is up-regulated rapidly in almost all forms of renal injury. In experimental hydronephrosis, OPN knockout mice are significantly protected from macrophage infiltration and collagen deposition compared with wild-type mice. However, despite marked amelioration of interstitial inflammation and scarring, OPN knockout mice actually develop significantly increased levels of tubular cell apoptosis, thus illustrating the critical importance of exogenous survival factors [34]. Furthermore, recent work suggests that the collagens present within the normal kidney provide important survival signals to renal cells, signals which are not provided by the interstitial collagens which accumulate during renal scarring [35,36]. Linkage between apoptosis and the cell cycle is becoming increasingly apparent, with cells destined to undergo apoptosis often exiting the cell cycle from the G1 phase [26]. Cell cycle regulatory proteins such as the cyclin-dependent kinase inhibitors p27 and p21 (which inhibit cell cycle progression) and cyclin-dependent kinase 2 (cdk2, which facilitates cell proliferation) play an important role in renal disease (reviewed in [27]). Interestingly, recent data indicate that p27, p21 and cdk2 can also modulate apoptosis in both renal and non-renal cells [28–30]. For example, p27 knockout mice exhibit markedly increased levels of both tubular cell proliferation and apoptosis compared with wild-type controls in experimental hydrenephrosis [31]. It is important to note that the effect of the absence of such ‘apoptosis-modulating proteins’ may vary according to the nature of renal injury. In this regard, no differences in tubular cell death were discernible between p21 knockout and wild-type mice in experimental hydronephrosis; a result quite unlike that seen in cisplatin nephropathy in which p21 knockout mice develop markedly increased levels of tubular cell apoptosis and necrosis, worse renal function and have a higher mortality [30–32].

Other factors

There are obviously many other factors involved in tubulointerstitial cell death. For example, proteinuria has been implicated in tubular cell apoptosis, whilst interstitial macrophages may induce tubular cell damage and death [37,38]. Hypoxia, ischaemia, reactive oxygen species, nitric oxide, angiotensin II, cytokines such as TNF-α and transforming growth factor-β, as well as cellular expression of members of the Bcl-2 family, may play an important role in determining renal cell fate.

Conclusion

The fate of tubulointerstitial cells during inflammation and scarring is decided by the balance between survival and death signals. Recent exciting work has indicated that widespread renal cell apoptosis in murine renal ischaemia/reperfusion injury may be inhibited by exogenous administration of either caspase inhibitors or insulin-like growth factor 1 [39]. Therefore, despite
the complexity of this biological battleground, there are grounds for hope that therapeutic interventions will be developed either to augment apoptosis of injurious cells such as inflammatory leukocytes or to prevent apoptosis of resident renal cells thereby reducing renal injury and preserving organ function.

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References