Targeting Cell Death Pathways for Therapeutic Intervention in Kidney Diseases

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Summary: Precise regulation of cell death and survival is essential for proper maintenance of organismal homeostasis, development, and the immune system. Deregulated cell death can lead to developmental defects, neuropathies, infections, and cancer. Kidney diseases, especially acute pathologies linked to ischemia-reperfusion injury, are among illnesses that profoundly are affected by improper regulation or execution of cell death pathways. Attempts to develop medicines for kidney diseases have been impacted by the complexity of these pathologies given the heterogeneous patient population and diverse etiologies. By analyzing cell death pathways activated in kidney diseases, we attempt to differentiate their importance for these pathologies with a goal of identifying those that have more profound impact and the best therapeutic potential. Although classic apoptosis still might be important, regulated necrosis pathways including necroptosis, ferroptosis, parthanatos, and mitochondrial permeability transition–associated cell death play a significantly role in kidney diseases, especially in acute kidney pathologies. Although targeting receptor-interacting protein 1 kinase appears to be the best therapeutic strategy, combination with inhibitors of other cell death pathways is likely to bring superior benefit and possible cure to patients suffering from kidney diseases. Semin Nephrol 36:153-161 © 2016 Elsevier Inc. All rights reserved.

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Kidney disease is a relatively common ailment that is associated with significant morbidity and mortality. It typically is classified as either chronic kidney disease (CKD) or acute kidney injury (AKI), but recently it has been postulated that AKI and CKD are interconnected syndromes such that CKD is a risk factor for AKI and AKI is a risk factor for the development of CKD.[1] Data from the National Health and Nutrition Examination Survey in the United States show that, in adults aged 20 or older, the overall prevalence of CKD is approximately 14%, and studies have shown that the risk of death, hospitalizations, and cardiovascular events increase as kidney function decreases.[2,3] The incidence of AKI, which typically occurs in the hospitalized setting, is estimated to be 406.5 per 100,000 patient-years and has been increasing significantly, with AKI estimated worldwide to occur in one in three children and in one in five adults with acute illness.[4,5] The importance of this increase cannot be underestimated because AKI is associated with increased morbidity and mortality, with the worldwide unadjusted mortality in AKI estimated to be 23.9% in adults and 13.8% in children.[5]

Outside of therapies related directly to end-stage renal disease and its complications, there are few therapies that have been found to be beneficial in the treatment of either CKD or AKI. This is because of the complexity and/or length of the clinical trials required for showing a benefit as well as an incomplete understanding of the underlying pathophysiology of the disease. Recently, data from experimental models of both CKD and AKI have highlighted the importance of pathways associated with programmed cell death in these diseases. This review focuses on these specific pathways and their potential contribution to the pathophysiology of CKD and AKI.

CELL DEATH PATHWAYS IN KIDNEY PATHOLOGIES

Extrinsic and Intrinsic Apoptotic Pathways

Cell death can be performed by multiple modalities, with apoptosis and necrosis representing the best-studied pathways. Apoptosis is a carefully orchestrated cell death program that relies on caspases – cysteine-dependent, aspartyl-specific proteases.[6-8] Caspase-dependent apoptotic cell death can be initiated by extrinsic or intrinsic stimuli. Intrinsic cell death is activated by cellular stress, developmental cues, or growth factor withdrawal, which can lead to disruption of internal cellular integrity including damaging mitochondria[9,10] (Fig. 1). The critical regulators of the intrinsic mitochondrial cell death pathway are the Bcl-2 family of proteins in which the pro-apoptotic initiators such as Bim or Bid and effectors such as Bak and Bax counteract the inhibitory action of the

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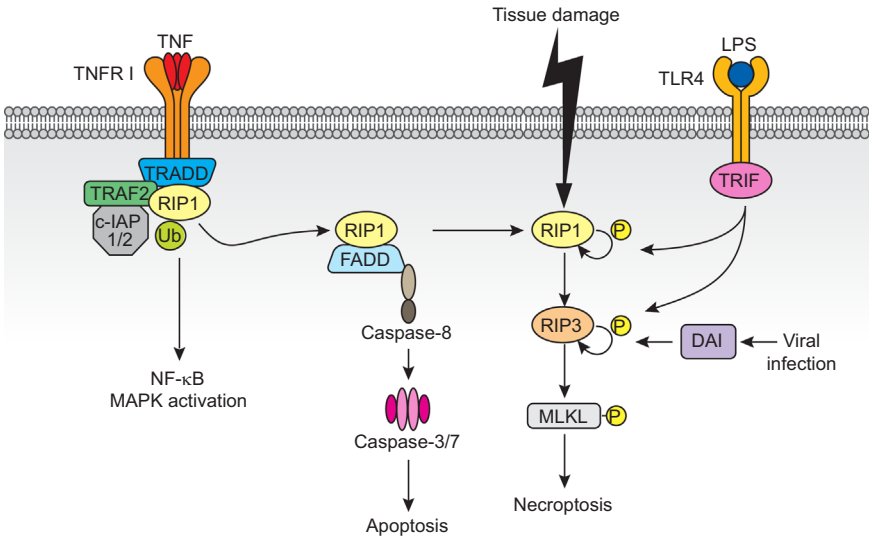

Figure 1. Multiple cell death stimuli converge on the RIP1 and RIP3 kinases. TNF binding to TNFR1 triggers the assembly of the receptor-associated complex, leading to the ubiquitination of RIP1 by c-IAP1/2 and the activation of nuclear factor-κB (NF-κB) and mitogen-activated protein kinase (MAPK) signaling pathways. Subsequently, nonubiquitinated RIP1 moves to cytoplasm to join FADD and caspase-8 to stimulate caspase-3/7 activation and apoptosis. In cases in which caspase-8 is inhibited, RIP1 associates with RIP3 into there necrosome where their kinase activity and autophosphorylation leads to MLKL phosphorylation and induction of necroptosis. Other stimuli such as tissue damage, Toll-like receptor signaling, or viral infection also can induce necroptotic signaling by activating RIP1 and/or RIP3 through various adaptors such as TRIF and DAI. DAI, DNA-dependent activator of IFN-regulatory factors; TRAF, TNF receptor associated factor; TRIF, TIR (Toll/interleukin-1 receptor) domain-containing adaptor protein; Ub, ubiquitin.

anti-apoptotic proteins Bcl-2, Bcl-x_L, and Mcl-1.[11] Tipping of the balance in favor of pro-apoptotic Bcl-2 proteins leads to cytochrome C release, formation of the apoptosome complex around Apaf-1, and activation of caspase-9. Activated caspase-9 subsequently activates caspase-3 and caspase-7, leading to cell death.[12] The role of the mitochondrial apoptotic pathway in renal injury was examined using Bax- or Bak-deficient mice. In the mouse model of ischemic acute kidney injury, knockouts of Bax or Bak attenuated renal tubular cell apoptosis and partially protected from kidney injury without significantly affecting necrotic tubular damage.[13,14] These results likely reflect the limited role of intrinsic apoptosis during ischemic acute kidney injury.

The extrinsic cell death pathway is initiated by binding of death ligands from the tumor necrosis factor (TNF) family to death domain–containing TNF receptors (TNFRs), causing their aggregation and recruitment of the receptor-associated, death-inducing signaling complex[15] (Fig. 1). Death receptors 4 and 5 and Fas recruit adaptor protein Fas-associated death domain (FADD) and caspase-8, which triggers caspase-8 activation and consequent activation of effector caspases-3 and -7.[16] TNFR1 and death receptor 3 engage additional proteins in their receptor complexes including TNFR-associated death domain, receptor-interacting protein (RIP1), TNFR-associated factor 2, and cellular inhibitors of apoptosis (c-IAP)1 and c-IAP2.[17,18] c-IAP1 and c-IAP2 ubiquitinate RIP1 with a variety of linkages, most prominently K63- and K11-linked polyubiquitin chains, within the TNFR1 receptor-associated complex.[19] This prevents the formation of the cytosolic pro-apoptotic complex (complex II) that is deprived of TNFR1 but engages FADD and caspase-8, and consequently blocks caspase-8 activation.[17] Removal of c-IAP proteins or ubiquitin moieties from RIP1 by deubiquitinating enzymes A20 or CYLD allows the formation of a fully functional complex II, caspase-8 activation, and cell death.[20,21] An additional brake on this pathway is achieved by the inhibitory caspase-8–like molecule FLICE-inhibitor protein (FLIP), which counters activation of the death-receptor apoptotic pathway by competing with caspase-8 for recruitment into the death receptor complex with FADD.[17,22] These two apoptotic pathways are not insulated from each other, but rather interact through caspase-mediated amplification of death signal and via proteolytic cleavage of Bid, which can further enhance extrinsic death signaling through stimulation of the mitochondrial pathway.[23] Both intrinsic and extrinsic apoptotic pathways converge at the activation of effector caspases-3 and -7, leading to the cleavage of hundreds of cellular proteins and consequent cell death.[24]

Although the superfamily of TNF ligands and TNFR receptors greatly influences survival and inflammatory response during renal injury, the contribution (s) of individual ligands or receptors are not completely clear. It seems that separate blockade or genetic ablation of Fas, TNFR1, or TRAIL affords some protection, with Fas potentially playing a more