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The Role of Necrotic cell death in the pathogenesis of immune mediated nephropathies

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Abstract

Necrosis, an inflammatory form of cell death, has been considered to be an accidental death and/or cell death due to injury. However, the literature in the last decade has established that necrosis is a regulated form of cell death, and that inhibition of specific molecular pathways leading to necrosis can block it and reduce inflammation. Since necrotic lesions are observed in several immune mediated human pathologies, in this review we will discuss the impact that this form of programmed cellular demise has in the pathology of immune mediated nephropathies.

Keywords

Nephritis; Autoimmunity; Cell Death; Necrosis

1. Cell death

Classically cell death has been divided into two categories: 1) Apoptosis or programmed cell death, a regulated form of cell death, and 2) Necrosis, accidental and pro-inflammatory cell death. The term ‘programmed cell death’ was first used by Lockshin et al. while describing the breakdown of the intersegmental muscles of silkworms [1]. With histological studies of ischemic liver, Kerr et al distinguished two types of cell death: classical necrosis, and “apoptosis”, which involved a process of formation of cytoplasmic bodies that often contained fragmented nuclear material. The latter was suggested to be a basic programmed phenomenon [1; 2; 3; 4]. Apoptosis and necrosis were thought of as two opposing mechanisms, necrosis being a purely accidental and passive cell death characterized by swelling of cytoplasm without nuclear disintegration, whereas apoptosis as a highly regulated form of cell death.

Laster et al. [5] observed that tumor necrosis factor induced two different forms of cell death in various cell types. One form had classical features of apoptosis and the second had

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characteristics of necrosis. This observation suggested that necrosis could in fact be a programmed form of cell death, regulated by defined set of signaling molecules. Following this initial observation, several studies have provided evidence that necrosis could be in fact a regulated process, and led to the concept of 'regulated necrosis'. In 2005 Degterev et al [6] coined the term 'Necroptosis' to define a form of regulated non-apoptotic cell death with characteristic morphological features of necrosis.

Recently a new form of cell death in neutrophils has been reported. Neutrophils release chromatin in the form of neutrophil extracellular traps, and the form of cell death is known as 'NETosis' [7; 8]. NETosis has been reported to be distinct from necrosis and apoptosis and as independent of caspase activation, however the exact molecular pathways leading to this form of cell death are not yet completely understood [8]. As mast cells [9] have also been reported to undergo this form of cell death, it is sometimes referred to as 'ETosis' to include both cell types [10].

2. Regulated necrosis: Molecular pathways

Several enzymes such as Receptor Interacting Protein kinase (RIP) and Poly (ADP Ribose) polymerase (PARP-1) have been shown to play a role in the induction and execution of programmed necrosis (Figure 1 and Figure 2 illustrate their respective molecular pathways). The resulting cell death is a consequence of complex interactions between several molecular and biochemical processes occurring within the cell. The major executioners are believed to be calcium and reactive oxygen species (ROS), which cause damage to proteins, lipids, DNA, and cause loss of cell integrity and death [11].

Death receptor ligands stimulate apoptosis by default. However, if caspase activation is hampered, those ligands can induce necrosis. Ligation of TNF receptor 1 (TNFR1) in the absence of caspase activity induces the assembly of a complex consisting of Receptor interacting protein kinase 1 and 3 (RIP1 and RIP3), which has recently been referred to as 'necrosome'. This complex results in a regulated form of necrosis- Necroptosis, characterized by the involvement of RIP1 and/or RIP3 [12]. Although the role of Fas associated death domain adaptor protein (FADD) in TNFα induced necrosis is not clear yet, using TNFR1-associated death domain protein (TRADD) deficient mice Pobezinskaya et al [13] showed that TRADD is required for TNFα induced necrosis. TRADD is necessary to recruit RIP1 to TNFR complex in mouse embryonic fibroblasts. During this form of cell death, RIP1 and RIP3 interact through their RIP homotypic interaction motifs (RHIM) [12; 14]. The kinase activity of RIP1 is indispensible for the interaction. RIP1 is shown to be an important mediator of regulated necrosis. However, virus associated necrosis has been shown to proceed independently of RIP1 [15]. It is possible that viruses induce a form of cell death different from necroptosis observed with TNF stimulation. Further evidence for the essential role of RIP-1 is provided by the observation that inhibition of enzyme activity of RIP1 by small molecule inhibitor Necrostatin inhibits TNFα-induced necrosis [6].

Another mediator of regulated necrosis is Poly (ADP-Ribose) Polymerase-1 (PARP-1), which is activated in response to moderate DNA damage and facilitates repair. PARP-1 catalyzes the conversion of NAD+ into nicotinamide and poly(ADP-ribose) polymers

(PAR). The poly (ADP-ribosyl-)ation of nuclear proteins allows DNA repair, and cell survival is the outcome. Extensive DNA damage, however, leads to over-activation of PARP-1. The excessive activation of PARP-1 causes NAD+ depletion. Subsequent ATP depletion results in irreversible bioenergetic failure and necrosis [16]. Inhibition or deletion of PARP-1 inhibits necrosis [16; 17], and we showed previously that inhibition or absence of PARP-1 protects mice from immune mediated nephritis [18]. PARP-1 also acts as a co-activator of transcription factor NFκB. Indeed, NFκB activation during septic shock, ischemia/reperfusion injury or collagen-induced arthritis is greatly reduced after inhibition or in the absence of PARP-1 [19; 20; 21; 22].

Several mediators have been implicated in the execution phase of necrosis. Reactive oxygen species (ROS) generated during inflammation cause damage to cellular macromolecules including DNA. Oxidative stress will, therefore, lead to necrosis via a PARP-1 dependent pathway. ROS also modify proteins including oxidation of membrane phospholipids. Lipid peroxidation leads to leakage of Ca2+ and proteases by destabilizing mitochondrial, lysosomal, and endoplasmic reticular membranes. Increased intracellular Ca2+ leads to the opening of mitochondrial permeability transition (MPT) pore (MPTP), resulting in loss of mitochondrial membrane potential, swelling, and rupture of mitochondrial outer membrane. To date, three proteins are known to comprise the MPTP; the voltage-dependent anion channel (VDAC), the adenine nucleotide translocator (ANT), cyclophilin D (Cyp D: a mitochondrial peptidyl prolyl-*cis*, *trans*-isomerase) [23]. The role of Cyp D in MPT and induction of necrosis has been established convincingly with the use of Cyp D deficient mice [24; 25]. Cyp D dependent MPT also plays a major role in ischemia/reperfusion injury [26]. TNFα and zVAD.fmk treatment results in a mitochondrial defect in ADP transport through ANT, which is dependent on RIP1 [27]. Increased intracellular Ca2+ also activates calpains, which leads to release of cathepsins in the cytoplasm, and further contribute to the execution of necrotic cell death.

Interestingly inhibition of PARP-1 does not block TNF mediated RIP dependent necrosis and inhibition of RIP1/RIP3 does not prevent DNA damage induced PARP-1 mediated cell death [28]. The cell death pathways mediated by RIP-1/RIP3 and PARP-1, although apparently independent, may in fact be linked under certain circumstances. Xu et al showed that PARP-1 activation and necrosis requires activation of RIP-1 [29]. The mechanisms by which RIP-1 leads to activation of PARP-1, however, are not yet understood.

In addition to regulating necrosis, PARP-1 can form stable complexes with transcription factors such as p53 and *fos*. PARP-1 can act as a co-activator of transcriptional factor NFκB. Over-activation of PARP-1 enhances inducible nitric oxide synthase (iNOS) expression in an NFκB-dependent manner [30]. Inhibitors of PARP prevent the expression of pro-inflammatory agents such as iNOS, adhesion molecules, and neutrophil migration to inflammatory sites [30]. Furthermore, NFκB activity is impaired and iNOS, TNFα and IFNγ expression is reduced in PARP-1 deficient mice subjected to endotoxic shock [19]. Activation of pro-inflammatory cytokines and induction of reactive oxygen/nitrogen species following NFκB activation may in turn lead to necrosis and amplification of local inflammatory response. Inhibition of PARP-1 activity reduces secretion of pro-inflammatory cytokines as well as neutrophil migration to the inflammatory sites [16; 19; 31]. Moreover,

our recent unpublished data show that PARP-1 also regulates the active release of HMGB1 in both macrophages and mouse mesangial cells. PARP-1 may, therefore, have profound modulatory effect on inflammatory response.

3. Immune Mediated Nephropathies

3.1 Lupus nephritis

Lupus GN is among the most devastating chronic effects of lupus disease. It is the leading cause of long-term disability, and ranks high as a cause of morbidity and mortality in SLE patients. The pathological manifestations of lupus GN are very diverse and have been re-classified [32]. Of the six classes defined by WHO, classes III-V are characterized by the presence of necrotic lesions, either segmental or global with distinct signs of necrotic cell death [32].

Glomerular necrosis is a feature of class III and IV lupus nephritis although not observed in pure mesangial proliferative (class II) or membranous (class V) lupus nephritis. It consists of a focus of smudgy fibrinoid obliteration of the glomerular tuft, which is often associated with any or all of the following: deposition of intracapillary fibrin, glomerular basement membrane rupture or gap formation, and apoptosis of infiltrating neutrophils forming pyknotic or karyorrhectic nuclear debris. Necrotizing lesions are typically segmental, but more than one glomerular lobule may be affected, particularly in diffuse proliferative lupus nephritis class IV. As in other forms of glomerulonephritis in which necrotizing lesions are common (e.g., pauci-immune crescentic glomerulonephritis), early cellular crescents frequently directly overlie the affected lobules. The lesions of active glomerular disease for class III and class IV are similar and the two classes are distinguished based on the percentage of glomeruli affected [32; 33].

3.2 IgA Nephropathy

The characteristic feature is the deposition of IgA_1 subclass (with or without complement C3) in the glomeruli. A defective O-glycosylation of serine threonine and proline-rich hinge region of IgA_1 subclass appears to play a central role. IgA nephropathy occurs most commonly between the ages of 10 and 40 years. Most studies show a male predominance, with an overall average male:female ratio of approximately 2:1 [34; 35]. Another disease associated with glomerular IgA deposits is Henoch-Schönlein purpura (HSP). HSP is a more systemic form of disease involving IgA mediated vasculitis and is often associated with infectious agents such as streptococci and mycoplasma [36].

Classes III, IV, V of IgA nephropathy are characterized by necrotic lesions along with glomerular hypercellularity (mesangial or endocapillary) and cresent formation. The renal histopathology in HSP is virtually indistinguishable from IgA nephropathy. The glomerulonephritis follows the deposition of IgA containing immune complexes on mesangial cells or through the binding of IgA to specific receptors on mesangial cells in absence of antigen. The binding of IgA activates mesangial cells to secrete cytokines such as IL-6, platelet aggregating factor, fibronectin and transforming growth factor [37; 38; 39]. Enhanced TGF-β release and matrix protein synthesis favor progression toward sclerosis.

3.3 Anti-glomerular basement membrane nephritis

Anti-glomerular basement membrane disease/Goodpasture's disease is a rare pulmonary-renal syndrome. The pathogenic features incorporated in the diagnostic criteria include cresentic glomerulonephritis with the majority of glomeruli showing crescents and linear IgG deposits often accompanied by complement C3. Half of the patients present with alveolitis and pulmonary hemorrhage. The circulating auto-antibodies (autoAbs) can be detected by ELISA and are directed against the non-collagenous domain of alpha 3 chain of type IV collagen [α3(IV)NC1] [40]. The antigen is found only in specialized basement membrane such as kidney, lung, choroids plexus, retina and cochlea. The autoAbs react with a conformational epitope which is most likely formed from the combined amino and carboxyl epitopes. The disease can be transferred from patients to animals by transferring antibodies [41]. Serum transfer from diseased mice to syngenic recipients leads to development of disease [42]. There is a well established experimental autoimmune glomerulonephritis in which a anti-basement glomerulonephritis animal model can be induced by active immunization of susceptible strains of rat/mice with glomerular basement membrane or α3(IV)NC1 [43; 44]. Autoreactive T cells have been shown to be both necessary and sufficient for disease development. Th1 cytokines (IFNγ, IL12), but not Th2 (IL10, IL4) cytokines play a major role in susceptibility [42; 44; 45]. Susceptibility to disease depends on both genetic and environmental factors.

Glomerular fibrinoid necrosis and crescent formation are the histologic hallmarks of acute anti-GBM glomerulonephritis [46; 47]. Even though the glomerular binding of anti-GBM antibodies is always diffuse and global, at the time of biopsy, glomerular tuft necrosis more often is segmental rather than global [48].

3.4 Pauci-immune glomerulonephritis

Pauci-Immune glomerulonephritis is a form of rapidly progressive glomerulonephritis that is characterized by almost complete absence of immunoglobulin deposits (as assessed by immunofluorescence). Pauci-immune necrotizing glomerulonephritis can be broadly divided into two subgroups: 1) associated with Anti-Neutrophil Cytoplasmic Antibodies (ANCAs), and 2) ANCA independent (also called idiopathic crescentic GN). ANCA associated GN includes granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and Churg-Strauss syndrome (CSS) [49]. *GPA;* this form is characterized by granulomatous lesions and vasculitic disease manifestations. Granulomatous lesions are found in respiratory tract, while vasculitic manifestations are found primarily in lung and kidney (glomerulonephritis). In particular GN is reported in 38% to 70% of patients [50].

MPA: Rapidly progressive glomerulonephritis (RPGN) is the major clinical feature of MPA with 80% to 100% of patients presenting with renal manifestations [51; 52]. The hallmark finding on biopsy is focal segmental necrotizing glomerulonephritis. Glomerular crescents are seen in approximately 80% patients [51].

CSS: Renal involvement in CSS is very infrequent (less than quarter of CSS patients). Similar to other forms of ANCA associated GN, the characteristic glomerular lesion of CSS

is focal segmental glomerulonephritis with necrotizing features. Renal disease, however, is considered milder and rarely causes renal failure [53; 54].

The hallmark histologic lesions of acute pauci-immune ANCA glomerulonephritis are crescents and fibrinoid necrosis, which occur at the same frequency irrespective of the presence or absence of associated systemic vasculitis [55; 56; 57; 58]. Foci of fibrinoid necrosis often contain neutrophil granule constituents indicating neutrophil activation and degranulation at these sites [59]. Crescent formation appears to begin adjacent to foci of segmental necrosis. This extremely lytic necrosis is similar to focal lytic lesions in many other small vessels in ANCA-associated vasculitis [59].

ANCA negative GN: Approximately 10-30% patients with Pauci-immune are negative for ANCA. Although the exact mechanism of crescentic glomerulonephritis observed in these patients is not known, neutrophils seem to play an important role. [60; 61]. The subsequent activation and degranulation of neutrophils may result in necrotic cell death of glomerular cells. Although, the ANCA negative GN shows higher incidence of chronic glomerular lesions as opposed to acute lesions in ANCA positive, a clear distinction in renal pathologies in these two forms of pauci immune GN has not been established yet.

Both ANCA glomerulonephritis and anti-GBM glomerulonephritis have extensive fibrinoid necrosis, focal destruction of Bowman's capsule, and disordered crescents. Pauci-immune biopsies especially those with Wegener's granulomatosis, have focal hemorrhagic papillary necrosis that is caused by leukocytoclastic angiitis affecting the medullary vasa recta [49].

3.5 Membranous Glomerulonephritis

Although glomerular lobulation, mesangial hypercellularity, segmental scars, inflammation, and necrosis are not common features of idiopathic membranous Glomerulonephritis (MGN), necrotic lesions are often seen in secondary forms of MGN, and more commonly are seen with a systemic disease [62].

4. Programmed necrosis in Nephritis

The nephropathies described above are distinct forms of GN. However the pathophysiological features such as fibrinoid necrosis are shared by the majority of these diseases. Crescent formation is often observed close to necrotic foci. The forms of GN show presence of clear signs of necrotic cell death, pointing to the notion that regulated necrosis may play an important pathogenic role. Several immunological and pathological features of renal inflammation can mediate or induce necrosis in the kidney (Table 1). We describe below some of the pathways leading to necrotic cell death in the kidney.

4.1 Complement system

Renal inflammation in autoimmune diseases results from deposition of immune complexes in the kidney or binding of autoantibodies to antigens on the renal intrinsic cells. These immune-complexes fix complement C1q further leading to activation of the complement cascade. The complement activation results in the release of several components such as complement C5a that act as chemoattractants for leukocytes and amplify inflammation. The

final step of complement activation is the formation of complement C5-9 membrane attack complex (MAC). MAC binds to cell surface and creates pores in the cell membrane. The cell loses membrane integrity and undergoes necrotic cell death [63]. The complement cascade induces cellular injury, rupture of plasma membrane and lysosomal membranes, leading to necrosis. This necrosis increases inflammation. Complement activation and deposition is a common phenomenon in lupus nephritis, ANCA vasculitits, Goodpasture, HSP, and IgA nephropathy [64; 65; 66; 67; 68]. The autoAb deposition in the kidney either passive or through the binding of Abs to the autoAg expressed in the kidney, leads to complement activation. Lower C3 levels are consistently used in classification or activation criteria features of systemic lupus erythematosus with nephritis [69], further exemplifying the importance of complement activation.

4.2 ROS

Reactive oxygen species are generated by immune cells as well as tissue cells such as mesangial cells in the glomeruli [70; 71]. ROS act as a source of stimulation for immune cells. ROS induce cell death in cells either through the apoptotic or necrotic pathways. ROS can also act as second messengers and play an important role in regulating signal transduction pathways in immune cells. For example, ROS can regulate calcium response in endothelial cells [72; 73]. ROS can induce necrosis and further amplify inflammation. The activation of complement also recruits inflammatory cells such as neutrophils and macrophages, which generate inflammatory mediators including reactive oxygen species and reactive nitrogen species [74]. This initiates an extensive inflammatory response in the kidney. Reactive oxygen and nitrogen species cause damage to DNA, which activates PARP-1. Excessive PARP-1 activation then causes pro-inflammatory necrotic cell death through bioenergetic failure and thus serving as a positive feedback signal to inflammation. The recruitment of inflammatory cells as well as proliferation of mesangial cells results in crescent formation. Cellular crescents containing predominantly macrophages are associated with Bowman's capsule rupture, and are prone to progress to fibrosis [75].

The loss of vascular permeability following infiltration of immune cells usually leads to fibrin deposition, generation of micro-thrombi and fibrinoid necrosis [76; 77; 78]. Due to lack of aerobic respiration, thrombi might create an environment ischemic and therefore with limited energy. Caspase activation is an energy dependent process and therefore, might not be favored during ischemia because of the energy-depleted environment. The lack (or reduced) activation of caspases including caspase 8, which is a negative regulator of necroptosis may facilitate necrosis rather than apoptosis, and result in inflammation.

4.3 Pro-inflammatory cytokines in the kidney

TNFα and IL1 are two major cytokines implicated in the pathogenesis of kidney disease [79; 80; 81; 82; 83; 84]. Although initially the source for TNFα was considered to be infiltrating leukocytes, Timoshanko et al showed that the source of TNFα is in fact the intrinsic renal cells [85]. TNF-α plays a key role in the development of GN [81; 82; 84], which has further been confirmed by the inability to induce anti-GBM GN in TNF-αβ-deficient mice [83]. Blockade of TNF-α has also been shown to reduce inflammation and scarring in experimental crescentic GN [82]. Treatment of lupus prone New Zealand Black x

New Zealand White F1 (NZBxNZW F1) mice with TNF receptor type II (TNFRII) Ig prolonged survival and inhibited secretion of proinflammatory cytokines by renal cells [86]. TNF receptor triggering in the absence of caspase activation is conducive of necrosis, therefore the micro-thrombi formed in the kidney, the low energy availability during inflammation and a high local concentration of TNFα may lead to cell death through the necrotic pathways rather than apoptosis, and thus necrosis may play a potential pathogenic role in nephritis.

5. Necrosis in amplification of inflammation

Necrosis is a highly pro-inflammatory form of cell death, and results in the release of 'alarmins' or 'danger signals' such as heat shock proteins, uric acid, ATP, DNA, and nuclear proteins that alert and activate the innate immune system [11; 87]. These alarmins activate the immune system through several pattern recognition molecules such as Toll-like receptors (TLR) and Nod-like receptors (NOD). Heat shock protein 60 (Hsp60) is released by nephritic kidneys and exogenous administration of Hsp60 results in increased severity of nephrotoxic serum induced nephritis in mice [88]. Another such danger signal is High Mobility Group Box I (HMGB1) protein. Receptor of Advanced Glycation End Products (RAGE) and TLR4 are the putative receptors for HMGB1 [89; 90].

HMGB1 expression has been associated with the formation of granulomas in adenine-induced nephropathy in rats and mice [91]. In patients with chronic kidney disease (CKD) HMGB1 levels negatively correlated with glomerular filtration rate [92]. HMGB1 levels correlated with levels of pro-inflammatory cytokines/markers such as TNFα and IL 6, suggesting HMGB1 as predictor of disease severity. Serum levels of HMGB1 were significantly higher in patients with GPA that had active disease rather than patients in remission [93]. Therefore HMGB1 may be a useful marker for disease activity in GPA. In contrast patients with microscopic polyangiitis had comparable levels of HMGB-1 regardless of disease activity, suggesting that HMGB1 may be useful in discriminating between different forms of ANCA associated vasculitides [93]. However more studies are needed as Bruchfeld et al did not detect any differences in HMGB1 levels between different forms of ANCA-associated vasculitis (AAV) [94]. Interestingly the latter study also showed that HMGB1 is increased in AAV patients with renal manifestations, and the levels decrease during remission. HMGB1 has also been shown to be upregulated in the sera of patients with Henoch-Schönlein purpura nephritis and IgA nephritis [95]. Other danger signals released by dying cells that have been implicated in renal inflammation include S100 family of proteins and uric acid [96; 97; 98].

The identification of danger signals released by necrotic cells as mediators of renal inflammation strongly supports the notion that regulated necrosis plays an important role in the pathogenesis of immune mediated nephritides.

Lupus patients that lacked DNase-1 activity and therefore, the ability to degrade NETs, had severe renal disease [99], suggesting NETosis as a contributing factor in lupus nephritis. NETs have been reported in kidney biopsies from ANCA glomerulonephritis and lupus nephritis patients [100; 101]. NETosis is generally considered pro-inflammatory and may

contribute to renal inflammation by providing accessible nuclear antigens for IC deposition. Recently IgA was shown to enhance NETosis through FcαRI ligation [102], although relevance of this activation in nephropathies was not investigated.

Finally there has been a growing interest in this form of cell demise and investigators have demonstrated in both animal models and patients that regulated necrosis is implicated in the pathophysiology of several other inflammatory diseases. During pancreatitis, most cell death was found to be necrotic rather than apoptotic and the degree of necrosis correlates with the severity of the disease [103]. In a murine model of pancreatitis, He, S et al showed that RIP3 deficient mice are resistant to cerulein-induced pancreatitis [104]. Nec-1 treatment protects against ischemia reperfusion (IR) injury in vivo, suggesting a possible role for Necroptosis in IR injury. Gunther et al showed a direct evidence for regulation of necroptosis by caspase 8 in inflammatory bowel disease (IBD) [105]. The authors show that TNFα induces epithelial necroptosis in a RIP3 dependent manner, and this cell death is inhibited by activation of caspase 8, thus suggesting a role for necroptosis in the pathogenesis of IBD [105]. Mice deficient in FADD develop chronic skin inflammation, which is triggered by RIP3, induced necroptosis [106].

6. Conclusions

Necrosis plays an important role in the pathogenesis of several inflammatory diseases, including immune mediated nephritides. The immune response to initial damage to the tissue induces necrosis and this necrotic cell death further amplifies the inflammatory response through the release of mediators of inflammation, thus forming a pathogenic feedback loop (Figure 3). Although a significant progress has been made in identifying the danger signals released by injured/dying/dead cells and their role in amplifying the inflammatory response, little effort has been made to regulate cell death to curb inflammation. Due the regulated nature of necrosis as opposed to accidental death, novel target are emerging to inhibit this form of cellular demise. Therefore, targeting necrotic cell death may prove to be an effective treatment for immune mediated nephropathies.

Abbreviations

ANT	adenine nucleotide translocator (ANT)
ANCA	Anti-Neutrophil Cytoplasmic Antibodies
AAV	ANCA-associated vasculitis
CSS	Churg-Strauss syndrome
CypD	cyclophilin D
FADD	Fas associated death domain adaptor protein
GPA	granulomatosis with polyangiitis
GBM	glomerular basement membrane
GN	Glomerulonephritis

HSP	Henoch-Schönlein purpura
HMGB1	High Mobility Group Box-1
iNOS	inducible nitric oxide synthase
MGN	membranous Glomerulonephritis
MAC	membrane attack complex
MPA	microscopic polyangiitis
MPTP	mitochondrial permeability transition pore
NAD	Nicotinamide adenine dinucleotide
α3(IV)NC1	noncollagenous domain of alpha 3 chain of type IV collagen
PAR	poly(ADP-ribose) polymers
PARP-1	Poly (ADP-Ribose) polymerase
ROS	reactive oxygen species
RIP	Receptor Interacting Protein kinase
RHIM	RIP homotypic interaction motifs
TNFα	Tumor necrosis factor alpha
TNFR1	TNF receptor 1
TRADD	Tumor necrosis factor receptor type 1-associated death domain protein
VDAC	voltage-dependent anion channel

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Highlights

The mechanisms of necrotic cell death are discussed.

The pathogenesis of glemerulonephritides is discussed.

The interplay between renal inflammatory triggers and necrotic cell death are discussed.

The potential benefits of inhibiting necrosis are proposed.

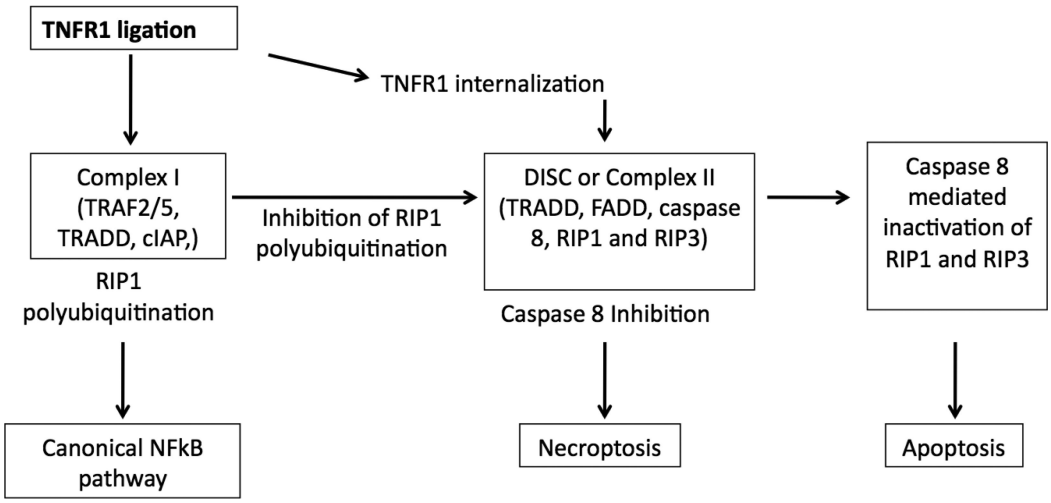

Figure 1. Molecular mechanisms of necroptosis. Complex I

Ligation of TNFR1 leads to formation of Complex I consisting of TRAF2/5, TRADD, cellular inhibitor of apoptosis proteins (cIAP) and polyubiquitination of RIP1, followed by activation of canonical NFkB pathway. **Complex II.** Internalization of TNFR1 leads to assembly of complex II consisting of TRADD, FADD, caspase 8, RIP1 and RIP3. Caspase 8 activates the classical caspase pathway and also inactivates RIP1 and RIP3, this leads to apoptosis. In the absence or inhibition of caspase 8, RIP1 and RIP3 are activated by phoshporylation and induce necroptosis.

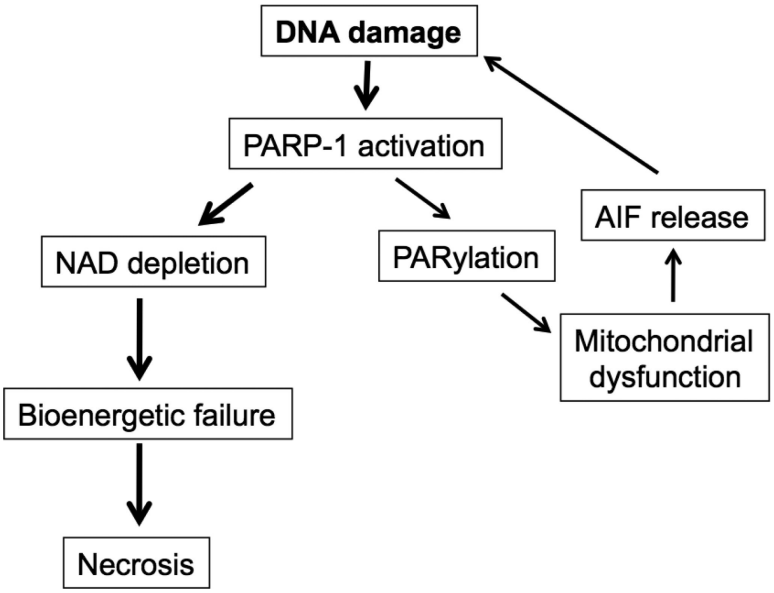

Figure 2. Molecular mechanisms of PARP-1 induced necrosis

Extensive DNA damage caused by radiation or during inflammation activates PARP-1, a DNA sentinel. PARP1 uses its enzymatic substrate NAD to generate Poly-(ADP-Ribose) polymers (PARs) through a process termed PARylation. PARylation transmits signals from the nucleus to the mitochondra, which in turn release apoptosis inducing factor (AIF). AIF tranlocates to the nucleus and induces more DNA damage, which further activates PARP-1. Depletion of NAD as a result of extensive PARP-1 activation leads to bioenergetic collapse and necrosis.

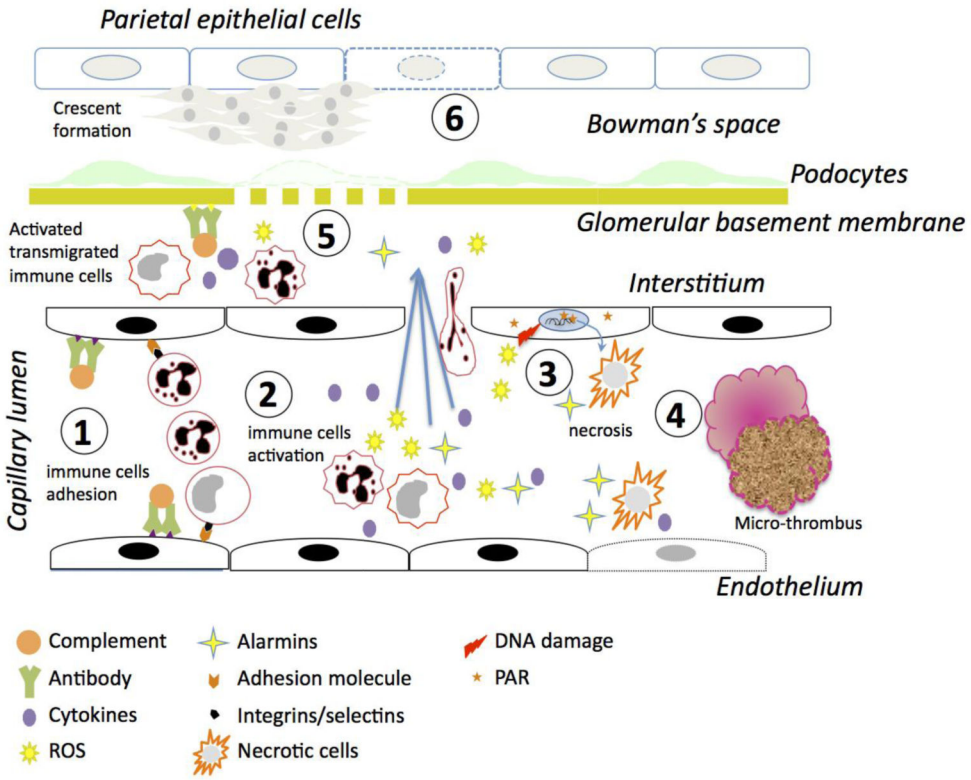

Figure 3. Role of necrosis in renal tissue injury

1. Deposition of immune complexes on the endothelial cells fixes complement and allows for the adherence and activation of monocytes and neutrophils through interactions between adhesion molecules and selectins/integrins. **2.** Activation of monocytes and neutrophils leads to release of pro-inflammatory cytokines, reactive oxygen species (ROS) activate endothelial cells and lead to endothelial dysfunction. The neutrophils and monocytes then migrate into the interstitium. **3.** The ROS generated causes DNA damage, leading to PARP-1 activation and necrosis of both leukocytes and endothelial cells. The necrotic cells release alarmins further activating leukocytes and endothelial cells. **4.** Endothelial dysfunction, leukocyte infiltration, and necrosis finally lead to micro-thrombi causing areas of local ischemia. Necrosis resulting from all these processes leads to a feed back loop that exacerbates the inflammatory response and induces further tissue damage. **5.** The leukocytes migrated into the interstitium get further activated by the immune complexes deposited on the glomerular basement membranes. Cytokines and inflammatory mediators released by the immune cells in the interstitium cause glomerular membrane rupture and loss of podocyte foot processes. **6.** The inflammatory mediators enter the Bowman's space, activate epithelial cells and finally lead to crescent formation.

Table 1

Nephritides	Pathological findings	Possible initial triggers of necrosis
Lupus Nephritis	-Mesangial proliferation, crescent formation, glomerular necrosis	-Complement activation
		-ROS generation by infiltrating cells
	-Granular mesangial orsubendothelial or subepithelial IgG deposits	-Cytokine secretion
IgA Nephropathy	-Glomerular hypercellularity (mesangial or endocapillary), acute tubular necrosis, and crescent formation	-Cytokine secretion by mesangial cells
	-Enhanced TGF-(3 release by mesangial cells leading to sclerosis	-ROS generation by infiltrating cells.
	-Linear IgA deposits	-Complement activation
Anti-GBM nephritis	-Wide spread glomerular crescents	- Complement activation
	-Glomerular fibrinoid necrosis	
	-Linear IgG deposits	
Pauci immune glomerulonephritis	- Crescents and fibrinoid necrosis often containing neutrophil granule constituents	-ROS generated by neutrophil activation
		-Cytokines and proteases released by neutrophils