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Cell death in the pathogenesis of systemic lupus erythematosus and lupus nephritis

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Abstract

Nephritis is one of the most severe complications of systemic lupus erythematosus (SLE). One key characteristic of lupus nephritis (LN) is the deposition of immune complexes containing nucleic acids and/or proteins binding to nucleic acids and autoantibodies recognizing these molecules. A variety of cell death processes are implicated in the generation and externalization of modified nuclear autoantigens and in the development of LN. Among these processes, apoptosis, primary and secondary necrosis, NETosis, necroptosis, pyroptosis, and autophagy have been proposed to play roles in tissue damage and immune dysregulation. Cell death occurs in healthy individuals during conditions of homeostasis yet autoimmunity does not develop, at least in part, because of rapid clearance of dying cells. In SLE, accelerated cell death combined with a clearance deficiency may lead to the accumulation and externalization of nuclear autoantigens and to autoantibody production. In addition, specific types of cell death may modify autoantigens and alter their immunogenicity. These modified molecules may then become novel targets of the immune system and promote autoimmune responses in predisposed hosts. In this review, we examine various cell death pathways and discuss how enhanced cell death, impaired clearance, and post-translational modifications of proteins could contribute to the development of lupus nephritis.

Introduction

Systemic lupus erythematosus (SLE) is a heterogeneous autoimmune disorder characterized by the presence of pathogenic autoantibodies, immune complex formation and deposition in various organs, profound innate and adaptive immune dysregulation and inflammation, and a wide range of clinical manifestations including kidney involvement (1, 2). A characteristic of lupus is the production of antibodies (Abs) recognizing nucleic acids and proteins binding to nucleic acids. Among them, synthesis of anti-double-stranded (ds)DNA Abs is considered a hallmark feature of SLE (3, 4).

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Lupus glomerulonephritis (LN) is one of the most common and severe complications in SLE and a major cause of morbidity and mortality (5, 6). LN affects predominantly younger individuals and is frequently observed in children (7). Various mechanisms have been proposed in the pathogenesis of this complex lupus complication and both innate and adaptive branches of the immune system appear to contribute to LN (8-11).

Dysregulated cell death and defective clearance of dying cells have been proposed to contribute to autoantigen generation and induction of autoantibodies and other aberrant immune responses in SLE and in LN specifically (12). Indeed, dysregulation in various cell death processes (e.g. apoptosis, primary and secondary necrosis, NETosis, necroptosis, pyroptosis and autophagy) and the response of the immune system to these processes have been implicated in the pathogenesis of LN (12, 13). This review will focus on the putative mechanisms by which various mechanisms of cell death can promote immune dysregulation and renal disease in SLE.

Apoptosis

Apoptosis is a silent form of cell death that is active during both physiological and pathological conditions and plays a critical role in homeostasis of tissues experiencing a high rate of turnover, as observed during embryogenesis and development (14). Apoptosis also plays a key role in the immune system by eliminating autoreactive T cells and B cells during positive and negative selection to prevent autoimmunity (15). Apoptosis can be initiated by ligation of cell surface receptors such as Fas or tumor necrosis factor (TNF) receptor or due to cellular stress (12). Once activated, a series of enzymatic reactions leads to changes in membrane phospholipid expression, DNA fragmentation, post-translational modifications of histones, and membrane blebbing (16). Apoptotic cells express “eat me” signals, which include phosphatidylserine and phosphatidylethanolamine exposure on the membrane outer leaflet (14). Phosphatidylserine can be recognized directly by phagocytic cells expressing scavenger receptors leading to clearance or it can bind to opsonizing agents to enhance phagocytosis. Uptake of apoptotic cells occurs very rapidly and leads to an anti-inflammatory effect with the release of transforming growth factor beta (TGF-β) (17). Various defects in the apoptotic cell death pathway or in clearance of apoptotic material have been implicated in SLE subjects and in mouse models **(Table 1)** (12).

One of the earliest reports linking impaired apoptosis to SLE was the identification of mutations in Fas receptor and Fas ligand (FasL) in MRL/*lpr-lpr* and C3H/HeJ-*gld/gld* mice, respectively (18-20). Both mice strains develop similar disease phenotypes characterized by hypergammaglobulinemia, autoantibody production, glomerulonephritis, and arthritis (19-21). Mutations in *Fas* or *FasL* have been identified in humans that develop autoimmune lymphoproliferative syndrome (ALPS) (21, 22) but the incidence of renal damage in this condition is extremely rare (23). Based on these findings, the role of Fas/FasL in the development of lupus nephritis appears stronger in mouse models of SLE compared to human SLE.

Other apoptotic signaling molecules including B cell lymphoma 2 (Bcl-2), Bim, transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI), B

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cell-activating factor (BAFF), phosphatase and tensin homolog (PTEN), and p53 have also been linked to lupus nephritis (15). Bcl-2 is an anti-apoptotic protein reported to be elevated in glomeruli and serum in patients with LN, although the significance of this is unclear (24). Immunized transgenic mice overexpressing *BCL2* under the control of immunoglobulin heavy chain enhancer exhibit autoantibodies and develop immune complex-glomerulonephritis (25). Bim is a member of the Bcl-2 family that promotes apoptosis and mice with a combined deficiency in Bim and Fas develop a lupus-like disease with renal damage caused by increased infiltration of B cells and macrophages, apoptotic cells and deposition of immune complexes (26). BAFF is a cytokine essential for B cell survival and maturation and SLE patients have elevated circulating BAFF levels that positively correlate with disease activity (27, 28). Mice overexpressing BAFF manifest lupus-like disease characterized by enhanced germinal center formation, splenomegaly, autoantibodies and immune-complex glomerulonephriits (29). In humans, LN patients treated with Belimumab, a BAFF neutralizing antibody, have shown greater reduction in proteinuria, normalization of anti-dsDNA and complement levels, and renal function improvement compared to those that received standard of care therapy (30). One of the key receptors for BAFF that has also been shown to potentially play a role in renal disease in lupus patients is TACI. In a 2010 study examining 73 Chinese SLE patients for expression of BAFF and BAFF receptors, SLE patients had elevated numbers of $CD19^{+}TACI^{+}$ B cells compared to healthy controls and lupus nephritis patients expressed the highest numbers of these cells (28). Targeting TACI, instead of BAFF, has been shown to protect against autoimmune kidney disease while maintaining the B cell population (31). PTEN is a tumor suppressor protein that negatively regulates the phosphoinositide 3-kinase (PI3K)-AKT pathway and loss of this protein has been shown to promote autoimmunity (32). Mice with a specific deletion of *Pten* in $Foxp3^{+}$ regulatory T cells (T_{reg}) lose immune tolerance and develop a systemic autoimmune-like phenotype characterized by immune complex LN. Tumor suppressor p53 protein has been known to play a critical role for the prevention of tumorigenesis but recent evidence has suggested that p53 also has a vital function in inhibiting autoimmunity (33-39). Kawashima et al showed that mice with a specific deletion of p53 in T cells develop inflammatory diseases including glomerulonephritis that is associated with a reduction in splenic T_{reg} cells (40). Moreover, p53 interacted with the FoxP3 promoter driving the expression of this gene and promoted the differentiation of regulatory T cells. Apoptosis is a finely tuned machine that requires proper functioning of both pro-apoptotic and anti-apoptotic proteins. Based on the previous findings, aberrant expression and function of these proteins can result in decreased apoptosis and lead to an autoimmune-like phenotype in both mice and humans likely through the accumulation of autoreactive immune cells. In addition, increased apoptosis has also been observed in SLE and may also contribute to the development of nephritis.

Enhanced apoptosis contributes to development of nephritis

Accelerated apoptosis in SLE can potentially overwhelm the host clearance mechanisms and result in an accumulation of apoptotic debris that can undergo secondary necrosis (12). Secondary necrotic cells lose the integrity of the plasma membrane and release nuclear autoantigens that can lead to immune complex formation, their glomerular deposition, and

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development of nephritis (14). Apoptosis of kidney cells, defective clearance, and release of nucleosomes may lead to development of nephritis but whether or not increased apoptosis of glomerular cells contributes to renal pathology is controversial (3, 41). Soto et al reported a decrease in apoptotic cells from the glomerulus and tubulointerstitium in LN biopsies compared to control kidneys (42). In addition, renal cells from LN patients had enhanced proliferation without an increase in apoptosis. It is worth noting that the apoptotic cell numbers from control kidneys was higher than apoptotic renal cell numbers from healthy subjects from previous similar studies (42, 43). Faurschou et al found that kidney biopsies from both lupus nephritis patients and healthy controls did not express apoptotic glomerular cells (44). However, one-third of the LN biopsies expressed low levels of apoptotic tubular cells that positively correlated with interstitial inflammation. In lupus-prone NZB/NZW F1 (NZB/W) mice, the appearance of circulating anti-dsDNA antibodies and glomerular deposits did not correlate with the activation of apoptotic pathways in the kidneys, but rather, correlates with the downregulation of *Dnase1* gene expression (45). Seredkina et al suggests that severe nephritis may develop due to the decreased expression of DNase1 that leads to an accumulation of chromatin, subsequent immune complex formation and deposition in glomerular membranes. However, Kalaaji et al demonstrated that nucleosomes released from apoptotic intraglomerular cells deposited in glomerulus basement membranes (GBM) and were targeted by nephritogenic lupus antibodies (46, 47). Unlike the results from Seredkina et al, Kalaaji demonstrated intraglomerular cell death that correlates with anti-dsDNA Ab in nephritic NZB/W mice (45, 47). Lupus nephritis patients have been reported to have increased numbers of apoptotic glomerular cells and infiltrating neutrophils compared to healthy controls, in correlation with anti-dsDNA Ab levels, complement consumption, and cell proliferation (41). Takemura et al reported the presence of apoptotic cells in the mesangial area and glomerular capillaries from LN patients and this positively correlates with the expression of Fas antigen (48). Bcl-2 expression was upregulated in mesangial cells and infiltrating leukocytes from LN patients and this correlates with the expansion of glomerular cells and degree of proteinuria. These authors postulated that increased Bcl-2 expression may contribute to the hypercellularity of glomerular cells and prolonged survival of infiltrating leukocytes in LN (48). Increased apoptosis of interstitial inflammatory cells, renal tubular epithelial cells, and glomerular parenchymal cells has been reported in lupus nephritis patients in association with enhanced expression of apoptosis-related proteins Fas, Bax, and caspase-3 (49). In summary, it is debatable whether or not increased apoptosis of glomerular cells is a significant source of circulating and/or tissue nucleosomes promoting glomerulonephritis. It is unclear why there are significant discrepancies when determining if renal cells from LN patients undergo increased apoptosis but one potential explanation could be the type of experimental method used to quantify this process (44, 51).

Accelerated apoptosis has also been observed in SLE for various key immune cells including phagocytes (monocytes, macrophages, neutrophils, and immature dendritic cells) that are critical for clearance (52). Autoreactive T cells in SLE patients induce apoptosis in autologous monocytes through TNF-related ligands (53). In NZB × SWR (SNF_1) lupus-prone mice, induction of accelerated macrophage apoptosis using clodronate liposomes results in increases in anti-dsDNA and anti-nucleosome antibody levels and enhanced proteinuria and LN features (54). SLE patients have increased numbers of circulating

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apoptotic neutrophils compared to healthy control donors and this positively correlates with disease activity and anti-dsDNA levels (55). Serum from SLE patients can induce apoptosis in antigen presenting cells (APCs) and lymphocytes and is associated with complement consumption (56, 57). In summary, SLE patients experience accelerated apoptosis of immune cells that are critical for clearance of apoptotic debris. This can potentially result in inefficient removal of dying cells and chronic exposure of intracellular autoantigens.

Defects in clearance mechanisms contribute to nephritis

Conflicting results have been observed when apoptotic cells are administered to mice with regards to immunogenicity (58, 59). While apoptosis is considered a silent form of cell death, defects in apoptotic cell clearance may result in secondary necrosis and lead to autoimmunity. The apoptotic clearance program is a highly redundant and multi-tiered system and defects in apoptotic cell receptors and bridging molecules have been observed in SLE. The TAM receptor protein tyrosine kinase subfamily includes Mer, Tyro3, and Axl and they detect ligands bound to phosphatidylserine on the membrane of dying cells and are involved in their removal (60). TAM-deficient mice develop an autoimmune-like syndrome with renal immune complex deposition (61, 62). Class A scavenger receptors macrophage receptor with collagenous structure (MARCO) and scavenger receptor A (SR-A) also recognize apoptotic cells and mice deficient in these receptors develop autoantibodies following transfer of apoptotic cells (63). In lupus-prone NZB/W mice and in SLE patients, autoantibodies against SR-A and MARCO are present and detected before onset of disease and may play a putative role in reduced uptake of dying cells (63).

In addition to phosphatidylserine exposure, proper recognition and clearance of apoptotic cells requires their opsonization by serum proteins including C-reactive protein (CRP), serum amyloid protein (SAP), pentraxin-related protein (PTX3), IgM, mannose binding lectin (MBL), and complement C1q (12). CRP and SAP are short pentraxins produced by the liver in response to interleukin 6 (IL-6) and PTX3 is a long pentraxin that is generated from a variety of tissues after TLR stimulation and in response to inflammatory cytokines (64). CRP interacts with polysaccharides and phosphocholine exposed on apoptotic cells and microbes and mediates activation of the classical pathway of complement (65). CRP also opsonizes cells and mediates their removal by interacting with the Fc receptor on phagocytic cells (14). Abnormalities in CRP function and expression have been observed in SLE (66-69). SLE patients produce autoantibodies against CRP and this correlates with disease activity, anti-dsDNA, and LN (66, 67, 69). Genome-wide linkage studies have revealed that CRP maps to a locus associated with SLE and polymorphisms in the CRP locus are associated with development of SLE, autoantibodies and low CRP expression (70). CRP can improve murine lupus and its associated nephritis (71, 72).

SAP is another acute phase reactant and opsonin that is critical for the removal of apoptotic cells (73). SAP binds to DNA and chromatin exposed in apoptotic blebs and solubilizes chromatin released during necrosis (74). As observed with CRP, defects in SAP lead to murine lupus-like disease including glomerulonephritis (75). SLE patients also develop anti-SAP Abs that correlate with disease activity and are reduced with improved clinical outcome

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(76). Exogenous administration of SAP has a therapeutic effect in mice, including decrease in immune-complex deposition and prevention of LN (77).

PTX3 binds to nuclear antigens exposed on the cell membrane in apoptotic cells (78) and regulates autoimmunity by sequestering cell debris that would otherwise be internalized by APCs. Similar to CRP and SAP, autoantibodies against PTX3 are detected in SLE patients and correlate with disease activity (79). *Ptx3*-deficient mice that are crossed with *Fas*-deficient (lpr) C57BL/6 mice develop autoimmune lung disease but no glomerulonephritis (80). In summary, the pentraxins CRP, SAP, and PTX3 play critical roles in the clearance of apoptotic cells and dysregulation in the function of these molecules may promote autoimmunity.

MBL is a serum pattern recognition receptor that recognizes and opsonizes carbohydrate moieties present on microorganisms, resulting in complement activation (81). The role of MBL in the lupus pathogenesis is potentially complex as high expression results in complement activation and tissue damage while low levels lead to defective apoptotic cell clearance (82, 83). Variants in the *MBL2* gene result in MBL deficiency, predisposition to SLE, and increased risk of LN (84-86). IgM is also involved in the opsonization and clearance of dying cells and low serum IgM levels have been reported in SLE patients (87). Finally, C1q is a member of the classical complement pathway and an opsonin that binds to apoptotic cells and mediates their removal by phagocytic cells (88). Deficiencies in C1q have been linked to SLE (89). SLE patients may have anti-C1q Abs in association with LN, complement consumption, autoantibodies, and disease activity (90, 91). C1q-deficient mice develop immune complex nephritis and accumulation of renal apoptotic bodies (92). Together, these results suggest that recognition and opsonization of apoptotic cells is highly critical for their clearance and prevention of autoimmune disease. Although significant redundancy exists in proteins involved in the clearance of apoptotic cells, the functional loss of just one protein may be sufficient to promote activation of the immune response.

Once phagocytic cells have recognized apoptotic cells, they must be efficiently ingested to prevent immune system activation. Defects in phagocytosis have been observed in lupus (93). SLE patients have an accumulation of apoptotic cells in lymph node germinal centers likely due to a reduction in tingible body macrophages that specialize in the removal of dead cells (93). Defects in the differentiation of myeloid progenitors into macrophages may potentially lead to phagocytosis defects in SLE (60). Macrophages derived from SLE monocytes display impaired uptake of apoptotic material (94, 95). Lupus-prone mouse macrophages have been reported to display impaired lysosomal maturation that can lead to the recycling and accumulation of nuclear antigens to the cell surface that can potentially activate autoreactive lymphocytes (96). Impairments in lysosomal acidification can promote leakage of nuclear contents into the cytosol resulting in activation of the cytosolic sensor for dsDNA and inflammasome protein absent in melanoma 2 (AIM2) and sensor for IgG, tripartite motif-containing protein 21 (TRIM21). Activation of AIM2 results in another form of cell death called pyroptosis and release of IL-1β (mentioned below), while stimulation of TRIM21 can lead to type I IFN production, a phenomenon that promotes immune dysregulation in SLE (97, 98). Together, these results suggest that defective uptake and

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processing of apoptotic cells in SLE can result in activation of innate and adaptive immune responses.

Apoptosis-associated histone modifications in LN

Apoptosis is characterized by chromatin condensation and DNA fragmentation. Post-translational modifications of histones alter the structure and function of chromatin during apoptosis (99). Most histone modifications occur at the N-terminus and include serine and threonine phosphorylation, lysine acetylation and ubiquitination, lysine and arginine methylation and ADP ribosylation. Histone phosphorylation weakens its interactions with DNA and promotes structural chromatin reorganization (100) and DNA fragmentation (101-104).

Acetylation of lysine residues on histones results in structural chromatin changes leading to an open conformation that activates gene transcription (105). Histone acetylation also promotes increased accessibility to nucleases and DNA fragmentation (99). Addition and removal of acetyl groups on histones is mediated by histone acetyltransferases (HAT) and histone deacetylases (HDAC). HDAC inhibitors delivered at high concentrations induce apoptosis (106, 107). Conversely, hypoacetylated histone H4 has been associated with early apoptosis (108). Histone methylation represses transcription and hypermethylated histone H4 has been linked to apoptosis (109). Ubiquitination targets proteins for proteasomal degradation and promotes protein-protein interactions (12). Histone H2A deubiquitination is also associated with chromatin condensation in apoptosis (110, 111). Poly(ADP-ribosyl)ation is involved in many signaling pathways including DNA repair and apoptosis and is characterized by the addition of poly(ADP-ribose) (PAR) residues by poly(ADP-ribose) polymerases (PARPs) (12). Chemical inhibition of poly(ADP-ribosyl)ation prevents DNA cleavage and cell death, suggesting the critical role of poly(ADP-ribosyl)ation in apoptosis (112-115). In summary, many types of post-translational histone modifications are generated during the apoptotic process. Various post-translational modifications that take place during apoptosis could create neoantigens that become targets for autoantibody formation (12, 116). Indeed, experiments performed by several groups suggest that apoptosis-induced post-translational histone modifications are targets for autoimmune responses in SLE patients and mice (117-120). Plasma from SLE patients and lupus-prone mice contains autoantibodies specific for modified histones that target acetylated residues in H2B and H4, methylated H3, and ubiquitinated H2A. Deposition of histone H3 is observed in kidney sections of MRL/*lpr* mice and glomerular ubiquitinated histone H2A has been reported in a significant proportion of patients with LN (120, 121). In summary, SLE patients generate autoantibodies targeting modified histones and this could promote immune complex formation and glomerulonephritis. Indeed, modified histones have been reported to be more immunogenic compared to unmodified histones (117, 122). Lupus-prone mice treated with a triacetylated histone H4 peptide have enhanced mortality, proteinuria, and glomerular IgG deposition when compared to mice treated with a nonacetylated histone H4 peptide (117). Bone marrow-derived DCs exposed to acetylated nucleosomes undergo maturation and activate syngenic T cells. Apoptotic microparticles, which expose modified nucleosomes at the cell surface (123-125), are found in both SLE patients and mice (125-127). Apoptotic microparticles from MRL/*lpr* mice express elevated levels of modified

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chromatin and induce enhanced maturation of DCs than BALB/c mice (125). DNASE1L3 is a serum enzyme that is critical for the degradation of chromatin in microparticles precluding autoantibody recognition of microparticle DNA and humans and mice lacking DNASE1L3 develop SLE-like disease (127-131). Microparticles from SLE patients express apoptosis-related histone modifications while these were absent in microparticles from healthy individuals (126). Microparticles from SLE patients activate pDCs and myeloid DCs that results in the induction of proinflammatory cytokines and type I IFN and also primes neutrophils for neutrophil extracellular trap (NET) formation (126). Based on this evidence, increased apoptosis-induced histone modifications in SLE may have immunostimulatory roles and contribute to the pathogenesis of LN

Necrosis

In contrast to apoptosis, primary and secondary necrosis are considered inflammatory modalities of cell death. Primary necrosis is often induced by cellular injury caused by ATP depletion, heat-shock or freeze/thaw, toxins, oxidative stress, and other noxious insults (14, 132, 133). Necrosis can also be induced by inhibition of apoptosis combined with blockade of autophagy and/or caspase inhibition (134-138). Apoptotic cells can become secondary necrotic cells after phagocytes fail to clear the dying cells (132, 133). Necrotic cell death is characterized by ROS production, mitochondria hyperpolarization, lysosomal membrane disintegration, cellular and organelle swelling, and plasma membrane rupture (133). Necrotic cell death is considered inflammatory because loss of plasma membrane integrity promote release of autoantigens and damage associated molecular pattern (DAMPs) that serve as chemoattractants for inflammatory cell recruitment (139, 140). To prevent further inflammation, rapid clearance of necrotic cells is critical. Necrotic cells differ from apoptotic cells in the way they are internalized by macrophages (132, 141). While apoptotic cells are ingested by phagocytosis, necrotic cells are cleared by macropinocytosis (132, 141). Both apoptotic and necrotic cells depend on the externalization of phosphatidylserine for phagocyte recognition (142-144). CRP, SAP, C1q, and DNase I are also critical for clearance of necrotic cells (145-147). Unlike apoptosis, where complement binding is a late event, complement binding to necrotic cells occurs early on (146). In contrast to apoptosis, genes required for necrosis have yet to be defined although receptor-interacting serine/threonine-protein kinase 1 and 3 (RIP1 and RIP3) appear to be critical for a type of programmed necrotic cell death called necroptosis (137, 148, 149). Necrosis can be a programmed occurrence in healthy individuals during development and intestinal epithelial cell homeostasis (137, 150, 151). In SLE, accelerated primary necrosis or accelerated apoptosis resulting in secondary necrosis, defective clearance of necrotic cells, and post-translational modifications during necrosis may play an important role in the development of LN.

Accelerated primary or secondary necrosis in LN

As previously mentioned, accelerated apoptosis leading to secondary necrosis has been observed in SLE patients and mice and promotes autoimmunity and renal damage (41, 46, 47, 49, 53-55, 152, 153). Necrosis is frequently observed in subjects with LN and is associated with enhanced serological activity and proteinuria compared to LN patients that do not display necrosis (154). Nucleosomes can induce necrosis in lupus and control

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lymphocytes both *in vitro* and *in vivo* (155). Due to the enhanced secondary necrosis observed in SLE, nucleosomes can accumulate and induce necrosis in neighboring cells, thereby resulting in an amplification loop of nucleosome release and immune dysregulation (155).

Defective clearance of necrotic cells in LN

Due to the inflammatory nature of cell death via necrosis, rapid clearance of dying cells is critical to prevent inflammation propagation and tissue damage (14). Necrotic cell clearance defects have been reported in SLE (132, 156). C1q and MBL are involved in macropinocytosis uptake of both apoptotic and necrotic cells and decreased C1q and MBL, reported in SLE, may lead to impaired macropinocytosis of necrotic cells, immune dysregulation and renal damage (86, 87, 89-91). Defects in expression and activity of CRP and SAP also contribute to defective clearance of necrotic cells (66, 68, 76). Some lupus patients have defective serum DNase I activity (157, 158) and they tend to have higher disease activity, and higher autoantibody levels when compared to SLE patients with normal enzyme activity (158). In mice, DNase I deficiency results in a lupus-like syndrome with glomerular immune complex deposition and glomerulonephritis (157). In summary, defects in the clearance of necrotic cells may potentiate immune dysregulation and organ damage in LN.

Post-translational modifications in necrosis

Little is known about the various post-translational modifications that occur during necrosis and their contribution to the development of LN. During programmed cell death, PARP is inactivated and cleaved by caspase-3 resulting in apoptosis (159). PARP is also cleaved in necrotic cells in a caspase-independent manner (160). Autoantibodies to PARP have been detected in SLE (161, 162) and they do not inhibit its catalytic activity but, rather, prevent caspase-3-mediated cleavage that results in decreased apoptosis (163). Collectively, the decreased clearance of apoptotic cells can result in cells undergoing secondary necrosis and the release of nucleosomes. Additionally, defects in the uptake of primary necrotic cells can also promote autoantigen externalization. Nucleosomes can induce primary necrosis in neighboring cells and this can result in enhanced autoantigen release, inflammation, and epitope spreading. Autoantibodies generated against nuclear components can inhibit PARP cleavage leading to prolonged survival of autoreactive cells that can mount an autoimmune response (163).

NETosis

An additional mechanism by which nuclear autoantigens may be modified and released to the extracellular space is through a specialized form of neutrophil cell death called NETosis (164). In response to microbial stimuli but also to a variety of sterile inflammatory signals (activated platelets, endothelial cells, crystals, autoantibodies, immune complexes and various proinflammatory cytokines), neutrophils can extrude a meshwork of nuclear material bound to neutrophil granular proteins (including LL-37, neutrophil elastase (NE), and myeloperoxidase (MPO)) (165-175). After recognition of a microbial insult, induction of

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NETosis typically requires hydrogen peroxide production by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and superoxide dismutase (176). Hydrogen peroxide is consumed by MPO, which mediates the release of NE from azurophilic granules into the cytosol and its translocation to the nucleus (177), cleaving histones and promoting chromatin decondensation (174). Chromatin decondensation is also promoted by the activation and nuclear localization of peptidylarginine deiminase 4 (PAD4), an enzyme that citrullinates histones, leading to disruption in the electrostatic interactions of histones with DNA (178, 179). The nuclear and granular membranes become permeable and this allows for the formation of cytoplasmic complexes of granular proteins and chromatin (180). Once the plasma membrane ruptures, chromatin fibers decorated with granular proteins are extruded from the cell in the form of NETs (165). NETs can also be induced in a NADPH oxidase-independent manner dependent on calcium-activated small conductance potassium (SK) channel member SK3 and mitochondrial ROS (167). In fact, patients with chronic granulomatous disease lack NADPH oxidase activity but can still develop autoimmunity and have the ability to form immunogenic NETs through enhanced mitochondrial ROS production and promotion of interferogenic responses by extrusion of oxidized mitochondrial DNA (181). NETs can also induce IFN-α by activating TLRs on pDCs (182). DNase I is an important enzyme for the degradation of NETs and C1q also plays a key role in opsonizing NETs for clearance by macrophages (183, 184). NETs are considered dual-edged swords in that NET induction and clearance may result in a protective antimicrobial effect but excessive NET formation and inefficient removal could lead to tissue damage and autoantigen modification and externalization (185). Excessive NET formation promoting tissue damage has been proposed in sepsis, psoriasis, diabetes, atherosclerosis, and SLE, among others (175, 186-189). This next section will discuss how enhanced NETosis, defective clearance of NETs, and post-translational modifications of proteins during NETosis may contribute to the development of lupus LN.

Enhanced NETosis in SLE may promote tissue damage

Neutrophils from SLE patients and lupus-prone mice are more prone to form NETs than neutrophils from healthy controls (175, 182, 190, 191). Neutrophils exposed to RNP immune complexes undergo enhanced NETosis through the induction of mitochondrial ROS (181). NET-derived self-DNA complexed with neutrophil-derived antimicrobial peptides such as LL-37 or human neutrophil peptide (HNP) activate pDC TLR9 and induce IFN-α (191). SLE patients generate autoantibodies that bind antimicrobial peptides and this can further enhance NET formation. These findings reveal a putative pathogenic amplification loop in SLE where neutrophils become primed to undergo NETosis after exposure to type I IFNs and other inflammatory stimuli, thereby releasing immunostimulatory nucleic acids that further activate type I IFN production.

SLE patients express a distinct subset of proinflammatory neutrophils, called low-density granulocytes (LDGs) (54, 192, 193) that have a heightened capacity to form NETs (175) and enhanced capacity to synthesize mitochondrial ROS (181). This leads to heightened externalization of immunostimulatory molecules (175, 181). Furthermore, LDG NETs are enriched in oxidized mitochondrial DNA that promotes type I IFN responses in target cells through a cGAS-STING-mediated pathway (181). Analysis of kidney biopsies from patients

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with LN have revealed the presence of NETs and infiltrating netting neutrophils in the glomeruli (175), which positively correlates with higher levels of circulating autoantibodies and enhanced activity index in kidney biopsies. As such, LDGs' enhanced ability to spontaneously form NETs leads to enhanced externalization of modified autoantigens and immunostimulatory molecules that may promote vascular and renal damage. NETs (and LL-37 expressed in NETs) can also induce inflammasome activation, pyroptosis, and release of IL-1β and IL-18 in human and murine macrophages, further amplifying NETosis (171).

Enhanced NETosis has also been observed in the NZM2328 and MRL/*lpr* murine models of lupus (190, 194). Given that PAD4 has been implicated in NET formation, lupus-prone mice have been treated with PAD chemical inhibitors (Cl-amidine or BB-Cl-amidine) and found to have improved vascular function, reduced type I IFN signatures, glomerular NETosis, renal inflammation and immune complex deposition (190, 194). These results suggest that enhanced NETosis in lupus mice promotes endothelial and renal damage and that targeting this cell death pathway may be explored as a potential therapeutic option for the treatment of kidney disease. In addition, inhibition of NETosis through mitochondrial ROS scavengers in vivo in lupus-prone mice also decreased renal inflammation and immune complex deposition (181). Overall, these observations implicate aberrant NET formation in the pathogenesis of LN.

Defective clearance of NETs contributes to renal disease

Previous studies have suggested that SLE patients have an impaired ability to degrade NETs and proposed that this impairment contributes to the development of LN (157, 158, 184, 195). DNase I is the major endonuclease found in circulation involved in degrading NETs and, as mentioned above, impaired activity of this enzyme leads to lupus-like disease in mice and humans (157, 184, 196). The correlation between DNase I deficiency and increased prevalence of LN was also confirmed in humans as SLE subjects with renal involvement were reported to have significantly reduced DNase I activity (157). Impaired DNase I activity in humans can be linked to mutations and polymorphisms in DNase I, the presence of DNase I specific inhibitors and anti-NET antibodies, and binding of C1q, LL-37, and HMGB1 to NETs to prevent degradation (184, 191, 195-201). While a previous phase I study of DNase I in patients with LN revealed no change in serum markers of disease activity (202), it is possible that more effective preparations of the enzyme may prove efficacious in future trials.

Collectively, these data imply that impaired DNase I activity and enhanced externalization of autoantigens and antimicrobial peptides promotes IFN production, inflammasome activation/pyroptosis, autoantibody formation, and prevents degradation of NETs that creates an amplification loop for inflammation and tissue damage.

NETosis-derived post-translational modifications in SLE

Various post-translational modifications of cellular proteins occur during NETosis and the enhanced externalization of these proteins, combined with defective clearance, may promote disruptions in adaptive immunity that further drive SLE pathogenesis (117, 119, 120, 203).

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SLE NETs contain histone modifications that are also observed during apoptosis (203). SLE NETs express higher levels of acetylated H4-K8, 12, 16, acetylated H2B-K12, and tri-methylated H3-K27 compared to NETs from healthy donors. These modified histones were targeted by autoantibodies in SLE and administration of a triacetylated histone H4 peptide in lupus-prone mice led to increased mortality and renal damage (117, 119, 120). Hypoacetylated H4-K8, K12, K16, and H2B-K12 and hypomethylated H3-K27 were found in unstimulated SLE neutrophils and induction of NETosis resulted in a significant enhancement in histone acetylation and methylation when compared to healthy control neutrophils. These results may indicate that SLE neutrophils are more susceptible to NETosis-induced histone modifications than healthy donor neutrophils (203). Hyperacetylated histones in NETs can upregulate the activation marker CD71 on macrophages (203). These results indicate that many histone modifications that occur during apoptosis are also observed during NETosis.

PAD4 mediates citrullination of histones H1, H2A, H3, and H4 during NETosis (204, 205). Citrullinated histone H1 is present in NETs and autoantibodies specific for citrullinated histone H1 are present in lupus sera (204). Autoantibodies targeting histone H1 appear to be specific for SLE and correlate with disease activity (206). In addition to histones, the antimicrobial peptide LL-37, which is externalized in NETs, was also reported to undergo citrullination in lung tissues from individuals with chronic obstructive pulmonary disorder (COPD) (207). Citrullinated LL-37 has an impaired ability to kill various bacteria (208) and this could potentially be implicated in the enhanced susceptibility of patients with autoimmunity to develop secondary bacterial infections (209). Whether citrullination of other proteins during NETosis impairs distinct immunogenicity or tissue damage potential in SLE remains to be determined. NETosis also results in the translocation of hypopolarized mitochondria to the cell surface that mediates the externalization of oxidized mitochondrial DNA, which is both proinflammatory and interferogenic (181). Collectively, enhanced NETosis and defective clearance of NETs occur in SLE patients and the enhanced externalization of modified autoantigens and antimicrobial peptides contributes to the production of type I IFN and autoantibodies specific for NET components that may promote the development of autoimmunity.

Pyroptosis

Pyroptosis is an inflammatory form of programmed cell death that occurs in response to danger signals and it is triggered by inflammasome activation, resulting in release of IL-1β and IL-18 and in externalization of cellular material (13). The canonical inflammasome is a multi-protein complex found in the cytosol that includes members of the nucleotide-binding domain and leucine-rich repeat-containing (NLR) family and AIM2 and is dependent on caspase 1. The noncanonical inflammasome is a cytosolic LPS sensor that signals through caspase 11. Inflammasome activation is completed in two steps with the first step being recognition of the pathogen-associated molecular pattern (PAMP) or DAMP by TLRs or RLRs, activation of NF-κB, synthesis of pro-IL-1β and pro-IL-18, and upregulation of inflammasome proteins (13). The second step involves the assembly of the inflammasome, conversion of procaspase-1 to caspase 1, and cleavage of pro-IL-1β and pro-IL-18 into their active secreted form that mediates inflammation (210). In addition, caspase 1 also triggers

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DNA fragmentation, nuclear condensation, lysosome exocytosis, disappearance of organelles, pore formation in plasma membrane, cellular swelling, and disintegration of the plasma membrane, all characteristic of pyroptosis (13). IL-1β signals through the IL-1 receptor and activates NF-κB that results in the production of proinflammatory mediators including cyclooxygenase-2 (COX-2) and IFN-γ (211). IL-18 signals mainly through the p38 MAPK pathway and mediates production of IL-1α, IL-6, and IL-8 (211). Additionally, IL-1β and IL-18 can induce NETosis to amplify the inflammatory response (171, 173). Pyroptosis can also result in the release of HMGB1 and this alarmin may induce inflammation by the production of proinflammatory cytokines, recruitment of immune cells through chemotaxis, and further induction of pyroptosis in macrophages (13, 212). Moreover, HMGB1 forms complexes with and increases the immunogenicity of DNA, histones, and LPS (213-215). Pyroptosis can lead to the release of undigested lysosomal contents that may include microbial products, previously phagocytosed autoantigens, and antimicrobial peptides (13). These factors may induce an inflammatory reaction that possibly could contribute to lupus flares. Pyroptosis also results in the release of intact nuclei that can potentially serve as source of autoantigens for the formation of anti-nuclear antibodies (13, 216, 217). Inflammasome activation also externalizes the adaptor ASC that displays ‘prionoid’-like activity and propagates the inflammatory response after internalization by neighboring cells. Moreover, patients and mice with autoimmune disease generate autoantibodies to ASC specks (218). These studies suggest that pyroptosis results in the externalization of various molecules that can potentiate the inflammatory response and potentially serve as a source of autoantigens.

Because pyroptosis is an inflammatory form of cell death involving release of self-antigens, rapid and efficient clearance of cells is crucial to prevent chronic inflammation and autoimmunity. Similar to apoptosis and necrosis, macrophages undergoing pyroptosis also expose phosphatidylserine on their surface for macrophage uptake (219). Pyroptotic cells release ATP as a “find-me” signal for recruitment of macrophages. Excess externalization of ATP can result in further activation of the NLRP3 inflammasome and lead to release of proinflammatory mediators (220).

NLRP3 is the best characterized inflammasome protein that recognizes various microbes and microbial products but also crystals, ATP and pore-forming toxins (210). Dysregulated NLRP3 inflammasome activation has been implicated in various diseases (221-230) including SLE (171, 231, 232). Given the inflammatory nature of this form of programmed cell death and the externalization of nuclear material, this next section will discuss how accelerated pyroptosis, defective clearance, post-translational modifications during pyroptosis could contribute to the break in tolerance and lead to renal damage in lupus.

Enhanced pyroptosis in lupus nephritis

Numerous studies have reported that enhanced pyroptosis of human and murine macrophages in SLE may contribute to the development of nephritis and other lupus manifestations (171, 231, 232). Kahlenberg et al demonstrated that both LL-37 and NETs containing LL-37 activate the NLRP3 inflammasome in both human and murine macrophages that results in the secretion of IL-1β and IL-18. LL-37 requires P2X7 receptor-

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induced potassium efflux to activate NLRP3. SLE LDGs with their heightened capacity to form NETs can externalize higher levels of LL-37 that can further activate the inflammasome (175). Importantly, macrophages derived from SLE patients have a lower threshold for activation, greater caspase-1 cleavage, and enhanced production of IL-1β and IL-18 compared to control macrophages once they are exposed to NETs (171). IL-18 can induce NET formation potentially providing a feed-forward inflammatory loop where NETs induce activation of the inflammasome and release of proinflammatory mediators that induce NETosis in neighboring neutrophils.

It has also been shown that the inflammasome is involved in the development of nephritis in murine models of lupus (231-233). Kidneys from MRL/*lpr* mice have enhanced protein expression of various inflammasome components compared to kidneys from control mice (234). Yuan et al demonstrated that MRL/*lpr* mice treated with isoflurane had reduced renal NLRP3 inflammasome expression and activation, proteinuria, autoantibodies, and renal inflammatory markers (231). P2X7 receptor plays a critical role in the activation of the NLRP3 inflammasome and release of IL-1β by binding extracellular ATP and inducing pore formation that results in the efflux of intracellular K^+ (235). Zhao et al treated MRL/*lpr* mice and the accelerated model of IFN-adenovirus administration to NZM2328 mice with a P2X7 inhibitor, brilliant blue G (BBG), and observed reduced renal injury and marked improvement in survival compared to untreated mice (232). Together, these data demonstrate P2X7-mediated NLRP3 inflammasome activation is enhanced in both MRL/*lpr and* NZM2328 AdIFN-α mouse models of glomerulonephritis and targeting P2X7 may ameliorate renal disease.

Mice lacking caspase-1 are protected from developing SLE and LN in the pristane-induced lupus model (233). In humans, microarray analysis from kidney biopsies from LN patients revealed upregulation of inflammasome-associated transcripts when compared to normal kidneys (236). Low levels of serum IL-1 receptor antagonist are associated with renal flares in SLE patients, suggesting that IL-1 signaling may play a pathogenic role in LN (237). Elevated levels of IL-18 have been described in sera and urine of SLE patients (238), particularly in patients with active LN (238, 239). Certain polymorphisms in the IL-18 gene are associated with SLE, increased expression, and development of kidney disease (238-243). Based on these data, heightened expression of IL-1β and IL-18, associated to inflammasome activation and death by pyroptosis, may play pathogenic roles in LN.

Defective clearance of pyroptotic cells

Impaired removal of pyroptotic cells can potentially lead to chronic exposure of potential autoantigens and break of self-tolerance in lupus. Wang et al provided some insight into pyroptotic cell clearance (219). Pyroptotic cells are efficiently internalized by human monocytic THP1-cell-derived macrophages and murine peritoneal macrophages and this process is also dependent on the expression of phosphatidylserine. In addition, pyroptotic cells release ATP as a “find-me” signal for macrophage recruitment. Since pyroptotic cells and apoptotic cells both externalize phosphatidylserine for recognition by phagocytes, defects in phagocytic removal of apoptotic cells could also play a role in the impaired removal of pyroptotic cells. C1q prevents procaspase-1 cleavage and caspase-1-mediated

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cleavage of pro-IL-1β in human monocyte-derived macrophages suggesting an inhibitory effect on inflammasome activation (244). Although previous literature has not reported the role of C1q in removal of pyroptotic cells, it would be interesting to determine if impaired C1q activity in SLE contributes to the dysregulated inflammasome activity previously mentioned.

At this time, there is not sufficient literature available supporting a link between post-translational modifications during pyroptosis and development of SLE and further work is needed.

Autophagy

Autophagy is a catabolic process that involves the recycling of aged cellular components and proteins into nutrients and amino acids to prolong survival and limit cellular stress (245, 246). Autophagy also plays a critical role in lymphocyte homeostasis and the innate and adaptive immune response (247). Three types of autophagy have been characterized and they include macroautophagy (hereafter called autophagy), microautophagy, and chaperone-mediated autophagy (CMA) (247). Macroautophagy is the best-understood autophagy pathway that involves the enclosure of a targeted portion of the cytoplasm into double-membrane vesicles (autophagosomes) that fuse with lysosomes (autolysosomes) leading to degradation (248). Microautophagy is the engulfment of cytoplasmic material by lysosomes and CMA is the selective uptake of cytosolic proteins into lysosomes that is mediated by chaperone proteins (249, 250). Although autophagy plays a critical role in promoting cellular survival, constitutive activation of this pathway can kill the cell in a process known as type II programmed cell death (247). According to the guidelines established by the Nomenclature Committee on Cell Death, autophagic cell death is cell death that is inhibited by genetic manipulation of at least two components from the autophagy pathway and verified using clonogenicity assays (251). Autophagic cell death is characterized by the presence of autophagosomes/autolysosomes, upregulation of autophagy-related genes (Atg) genes, a compromised plasma membrane, and lack of phagocyte recruitment (248, 252). Autophagic cell death has been shown to be induced by certain cytotoxic agents in the absence of an intact apoptotic pathway, in cancer cells in response to chemotherapy/radiation treatment, by dysregulated *RAS* oncogenic activity, and IFN-γ among others (138, 251, 253-256). A novel form of autophagic cell death that is dependent on Na^+, K^+-ATPase pump called autosis has also been described (251).

Although it is relatively unknown how cells dying from autophagy are cleared, a noncanonical form of autophagy dependent on ATG5 and ATG7 called microtubule-associated protein 1 light chain 3 alpha (L3C)-associated phagocytosis (LAP) is essential for efficient degradation of phagocytosed microbes and dead cells (245, 257, 258). LAP is induced after TIM4 recognizes phosphatidylserine on dead cells and this leads to the recruitment of the autophagy machinery (Beclin1, VPS34, and LC3) to the phagosome leading to lysosomal fusion, acidification, and subsequent degradation of the phagocytosed cargo (245, 257). Macrophages lacking ATG7 do not recruit autophagy machinery to the phagosomes and are unable to undergo acidification (257). This results in an inability to degrade the phagocytosed cargo and induction of proinflammatory cytokines. Previous

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genetic studies have linked polymorphisms in autophagy and LAP genes *ATG5* and *ATG7*, with SLE susceptibility (259-261). Given the critical role of LAP in processing and removing dead cell debris and defective removal of dying cells in SLE, this next section will examine how dysregulated autophagy and impaired LAP contribute to the development of nephritis.

Dysregulated autophagy may contribute to the development of SLE

Although previous literature has not reported the role of autophagic cell death in SLE, studies suggest that autophagy may be dysregulated in SLE (262-266). There are conflicting reports as to whether or not autophagy is defective or active in SLE (262-266). T cells from MRL/*lpr* and NZB/W mice display enhanced autophagy compared to control mice (266). In addition, autophagic vacuoles were elevated in specific subsets of T cells from SLE patients compared to healthy control and patients with other autoimmune diseases. Basal levels of autophagy are higher in $CD4^+$ T cells from SLE patients compared to healthy donors (262). However, T cells from SLE patients are resistant to autophagy induction (262). T cells from lupus patients also have enhanced expression of genes that negatively regulate the autophagy pathway including α-synuclein. Under serum starvation conditions to induce autophagy, T cells from SLE patients fail to induce autophagy, and instead, form aggregates of α-synuclein that have been shown to potentially serve a pathogenic role in other diseases (265, 267, 268). Collectively, these results suggest that T cells from SLE mice and humans have higher basal levels of autophagy that may potentially result in increased autophagic cell death. In addition, the lack of response to autophagy-inducing stimuli in T cells from SLE patients may result in decreased cell survival and increased apoptosis that can lead to increased autoantigen release (262). B cells from SLE patients and NZB/W mice have activated autophagy and inhibition of autophagy abrogates plasma cell development in mice and humans (264). These results suggest that autophagy may play a vital role in autoantibody formation in SLE. A majority of SLE patients express autoantibodies targeting a small GTPase family inhibitor, D4GDI, and treatment of T cells from healthy donors and SLE patients with α-D4GDI Ab induces autophagy (263). Chronic exposure to autophagy stimuli may lead to enhanced cell death and these authors suggested that repeated exposure to autoantibodies may lead to the selection of a T cell population that is resistant to autophagy induction in SLE.

Defective removal of dead cells by noncanonical autophagy may lead to nephritis

Defects in the LAP pathway have been shown to result in SLE-like disease in mice (258). LAP-deficient mice develop lupus-like disease characterized by increased circulating anti-dsDNA Ab, glomerular deposition of IgG and complement, glomerulonephritis, and IFN signature. LAP-deficient mice injected with apoptotic cells were capable of internalizing the dead cells but were unable to degrade the phagocytosed cargo resulting in induction of proinflammatory cytokines. LAP-sufficient mice generate IL-10 in response to administration of dying cells. TIM-4 deficient mice develop a similar phenotype characterized by the presence anti-dsDNA Ab, hyperactive lymphocytes, and impaired

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uptake and clearance of apoptotic cells (269). Together, these results suggest that recognition of dying cells by TIM-4 and their clearance by LAP is critical for prevention of autoimmunity.

Post-translational modifications of histones in autophagy

Although previous literature has not examined the role of histone modifications during autophagy and their potential role in breaking tolerance in LN patients, post-translational modifications of histones plays a critical role in regulating autophagy (270). There are many histone modifications during autophagy that also occur during apoptosis but they serve opposing roles. H3K4 trimethylation, H3K9 dimethylation, H3K56 acetylation, and H4K16 acetylation repress autophagy, while H4K20 trimethylation promotes autophagy (270-278). At this time, it has not been reported whether autoantibodies targeting histone modifications that occur during autophagy exist in SLE.

Conclusions

Glomerulonephritis is one of the most common and serious clinical manifestations in SLE patients. Dysregulation in cell death pathways and in clearance of death material may promote enhanced synthesis of modified autoantigens that could promote autoimmunity in SLE. Maintaining homeostasis requires programmed cell death without compromising membrane integrity and their timely removal by scavenger cells. In SLE, accelerated cell death combined with the defective clearance of these dying cells leads to the externalization and accumulation of nuclear and cytoplasmic autoantigens **(Figures 1 and 2)**. In addition, post-translational modification of histones and other proteins increases their immunogenicity and may lead to autoantibody formation, induction of type I IFN responses and tissue damage **(Figure 3)**. Interestingly, the byproducts of one cell death pathway can induce activation of a different cell death pathway in a neighboring cell resulting in an amplification loop that exacerbates disease **(Figures 1 and 3)**. Moving forward, genetic and genomic analyses may further clarify the host's predisposition to mount dysregulated immune responses to death cells, to promote enhanced cell death or impaired clearance. Given the critical role that inflammatory cell death processes play in the pathogenesis of SLE, therapeutics that inhibit inflammatory forms of cell death, that enhance clearance or that limit certain deleterious posttranslational modifications may prove to be efficacious in the treatment of SLE. Previous groups have successfully inhibited NETosis and reduced disease activity by using molecules that scavenge ROS, inhibit PAD activation, modulate intracellular and extracellular calcium pools, block MPO activation, and disrupt the stabilization of the actin cytoskeleton (170). Given the critical role of DNASE1L3 in the degradation of DNA in circulating apoptotic microparticles and prevention of autoimmunity in mice (126), examining the effect of DNASE1L3 in SLE patients should be explored. Finally, HDAC inhibitors have been shown to modulate renal disease in various mouse models of lupus and should be further investigated in SLE patients (279-281).

List of Abbreviations

AIM2 absent in melanoma 2

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APC	antigen presenting cell
Atg	autophagy-related gene
BAFF	B cell-activating factor
Bcl-2	B cell lymphoma 2
CRP	C-reactive protein
DAMP	damage-associated molecular pattern
dsDNA	double stranded deoxyribonucleic acid
H2B-K12	histone H2B at lysine 12
HAT	histone acetyltransferase
HDAC	histone deacetylase
HMGB1	high mobility group box 1 protein
IL-1•	interleukin 1 beta
IFN	interferon
LAP	LC3 (light chain 3)-associated phagocytosis
LL-37	cathelicidin
LN	lupus glomerulonephritis
MARCO	macrophage receptor with collagenous structure
MBL	mannose binding lectin
MPO	myeloperoxidase
NADPH	nicotinamide adenine dinucleotide phosphate
NE	neutrophil elastase
NET	neutrophil extracellular trap
NLR	nucleotide-binding domain and leucine-rich repeat-containing
PAD4	peptidylarginine deiminase 4
PARP	poly(ADP-ribose) polymerase
pDC	plasmacytoid dendritic cell
PTEN	phosphatase and tensin homolog
PTX3	pentraxin-related protein
RIP1	receptor-interacting serine/threonine-protein kinase 1

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ROS	reactive oxygen species
SAP	serum amyloid protein
SLE	systemic lupus erythematosus
SR-A	scavenger receptor A
TACI	cyclophilin ligand interactor
TLR	toll-like receptor

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Highlights

- An imbalance in cell death and cell death clearance may promote autoantigen modification and availability to activate the innate and adaptive immune systems.
- Byproducts of one cell death pathway can induce other cell death mechanisms in adjacent cells.
- Aberrant cell death pathways have been implicated in the development of lupus nephritis.

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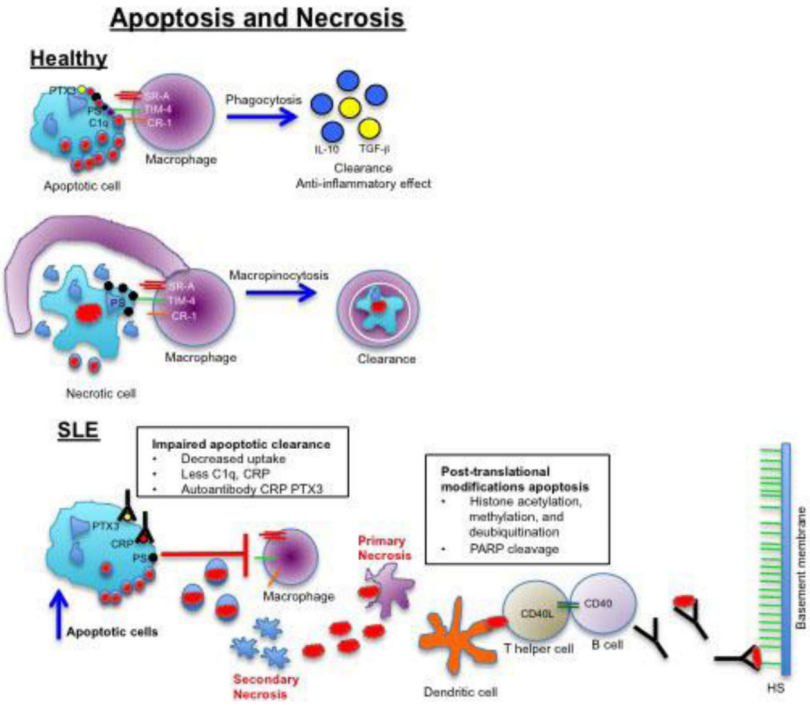

Figure 1. Potential role of apoptosis and necrosis in the development of lupus nephritis

In healthy patients, apoptotic cells are phagocytosed by macrophages after recognition of phosphatidylserine (PS) on the outer membrane leading to clearance and induction of anti-inflammatory mediators. Necrotic cells also expose PS on their membrane and are internalized by macrophages using macropinocytosis. In certain SLE patients, increased apoptosis and defective clearance of dying cells leads to secondary necrosis and release of nucleosomes (red oval structures). Circulating nucleosomes can induce primary necrosis in neighboring cells and can be internalized and presented by dendritic cells to autoreactive helper T cells that mediate autoantibody production by autoreactive B cells. Autoantibodies can form immune complexes with nucleosomes and bind to heparan sulfate (HS) on the glomerular basement membrane to induce glomerulonephritis.

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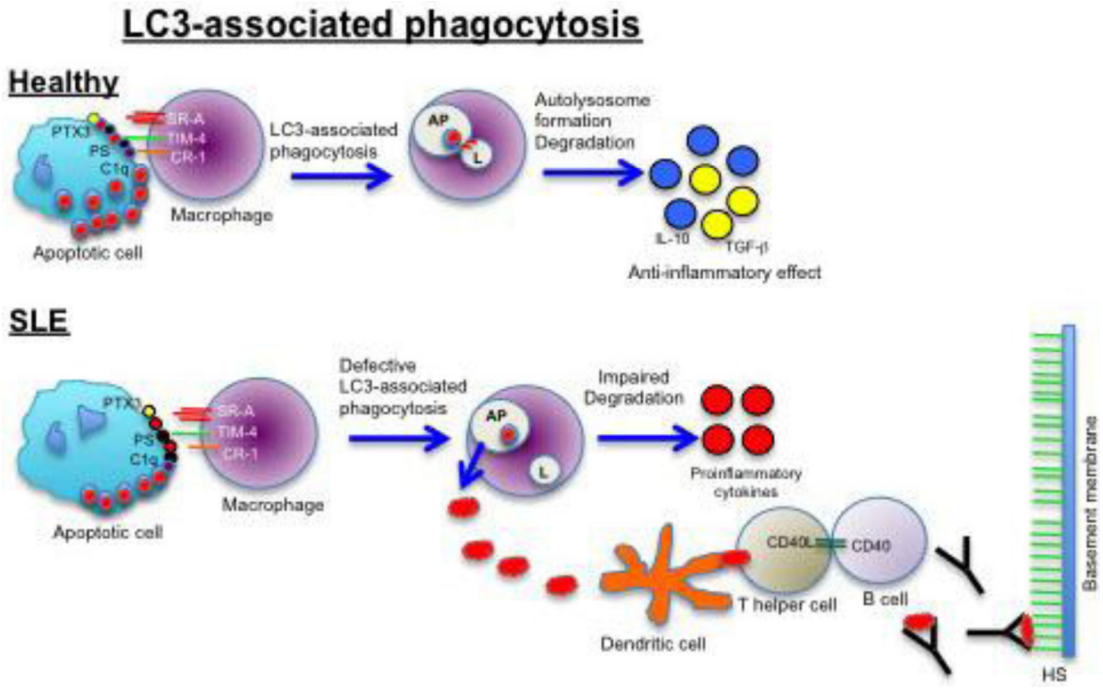

Figure 2. Putative role of LC3-associated phagocytosis (LAP) in the development of lupus nephritis

In healthy patients, engagement of the TIM-4 receptor leads to activation of LAP, recruitment of autophagy machinery (LC3) to autophagosomes (AP), fusion with lysosomes (L) and degradation of intracellular contents. In SLE patients, LAP can be defective leading to internalization of dying cells but impaired clearance that results in the release of nucleosomes and induction of proinflammatory cytokines, autoantibody formation, and kidney damage.

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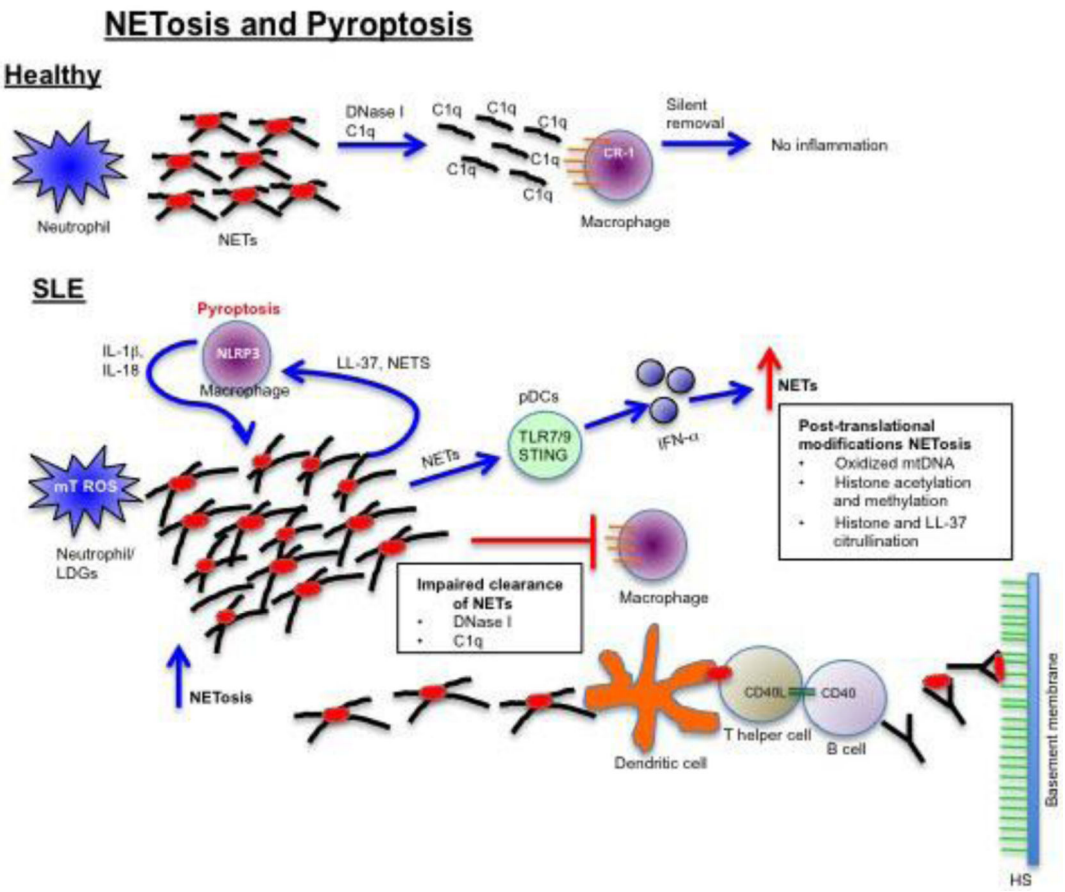

Figure 3. Putative role of NETosis and pyroptosis in the development of lupus nephritis

In healthy patients, NETs generated in response to sterile/microbial stimuli become opsonized by C1q and processed by DNase I leading to clearance by macrophages in the absence of inflammation. In SLE, neutrophils or low-density granulocytes (LDGs) have enhanced spontaneous NET formation that is driven by mitochondrial ROS. Due to DNase I or C1q deficiency, macrophages are unable to clear the NETs leading to activation of plasmacytoid dendritic cells (pDCs) and type I IFN, induction of pyroptosis in macrophages, autoantibody formation specific for modified NET proteins, and immune complex deposition in the glomerular basement membrane.

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Table 1

Cell death genes and autoimmunity

Gene	Encoded Protein	Cell Death Pathway	Mutant Phenotype
FAS or *FASLG*	Fas or FasL	Apoptosis	Lymphadenopathy, splenomegaly, autoantibody, hypergammaglobulinemia, glomerulonephritis
BCL2	Bcl-2	Apoptosis	Prolonged antibody response, ANA, immune complex deposition, renal disease
BCL2L11	Bim	Apoptosis	Splenomegaly, lymphadenopathy, glomerular damage, interglomerular proliferation
TNFSF13B	BAFF	Apoptosis	Expansion of mature B cells and effector T cells, anti-DNA, glomerular deposition
TNFRSF13B	TACI	Apoptosis	Deleting TACI in B cells prevents BAFF-induced kidney disease but $TACI^{-/-}$ mice develop fatal glomerulonephritis
PTEN	PTEN	Apoptosis	Anti-DNA, ANA, glomerular IgG deposition
TP53	P53	Apoptosis	Glomerulonephritis with depletion of splenic T_{reg} cells
TYR03/AXL/MERTK (TAM)	Tyro3, Axl, Mer	Apoptosis	Hyperproliferation of B and T cells, anti-DNA, kidney infiltrates of B and T cells, glomerular IgG deposition
SR-A/MARCO	SR-A/MARCO	Apoptosis	Anti-DNA and ANA
SAA1	SAP	Apoptosis and necrosis	Anti-DNA, inefficient degradation of long chromatin, glomerulonephritis
PTX3	PTX3	Apoptosis	Autoimmune lung disease
DNASE1L3	DNASE1L3	Apoptosis	Anti-DNA, ANA. splenomegaly, glomerular IgG deposition, glomerulonephritis
MBL2	MBL	Apoptosis and necrosis	Nephritis
C1QA	C1q	Apoptosis and necrosis	Decreased survival, autoantibody formation, glomerulonephritis, glomerular apoptotic cell bodies
CYBB	NOX2	NETosis, LAP	Splenomegaly, ANA, proteinuria, renal pathology
DNASE1	DNase 1	Apoptosis, necrosis and NETosis	ANA, glomerular immune complex deposition, glomerulonephritis
CYBB and *RUBCN*	NOX2 and rubicon	LAP	Proinflammatory cytokines, IFN signature, ANA, anti-DNA, immune complex deposition, renal damage
TIM4	TIM4	LAP	Anti-DNA, hyper-active lymphocytes, impaired uptake and clearance of dying cells