HHS Public Access

Author manuscript

Clin Immunol. Author manuscript; available in PMC 2018 December 01.

Published in final edited form as:

Clin Immunol. 2017 December ; 185: 74–85. doi:10.1016/j.clim.2016.10.007.

The contribution of the programmed cell death machinery in innate immune cells to lupus nephritis

FuNien Tsai, MS[a], **Harris Perlman, PhD**[a], and **Carla M. Cuda, PhD**[a,*]

[a]Northwestern University, Feinberg School of Medicine, Department of Medicine, Division of Rheumatology, 240 East Huron Street, Room M300, Chicago, IL 60611, USA

Abstract

Systemic lupus erythematosus (SLE) is a chronic multi-factorial autoimmune disease initiated by genetic and environmental factors, which in combination trigger disease onset in susceptible individuals. Damage to the kidney as a consequence of lupus nephritis (LN) is one of the most prevalent and severe outcomes, as LN affects up to 60% of SLE patients and accounts for much of SLE-associated morbidity and mortality. As remarkable strides have been made in unlocking new inflammatory mechanisms associated with signaling molecules of programmed cell death pathways, this review explores the available evidence implicating the action of these pathways specifically within dendritic cells and macrophages in the control of kidney disease. Although advancements into the underlying mechanisms responsible for inducing cell death inflammatory pathways have been made, there still exist areas of unmet need. By understanding the molecular mechanisms by which dendritic cells and macrophages contribute to LN pathogenesis, we can improve their viability as potential therapeutic targets to promote remission.

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic and systemic multi-factorial autoimmune disease believed to be initiated by both genetic and environmental factors, which in combination trigger disease onset in susceptible individuals. According to the Alliance for Lupus Research, approximately 1.5 million Americans suffer from lupus, with more than 16,000 new cases reported annually across the country, making it a highly prevalent autoimmune disease. SLE mainly affects women of reproductive age; African American women are three times more likely than Caucasian women to develop SLE and Latina women tend to present the most aggressive disease activity. The diverse manifestations of SLE result from chronic immune dysregulation and pathogenic autoantibody production, culminating in progressive end-organ injury to multiple organs, including the skin, central nervous system and kidney.

*Corresponding Author: Carla M. Cuda, PhD, Northwestern University, Feinberg School of Medicine, Department of Medicine, Division of Rheumatology, 240 East Huron Street, Room M360F, Chicago, IL 60611, USA, c-cuda@northwestern.edu, Phone: 312-503-4971, Fax: 312-503-0994.

2. Lupus nephritis

Damage to the kidney as a consequence of lupus nephritis (LN) is one of the most prevalent and severe of these outcomes, as LN affects up to 60% of SLE patients and accounts for much of SLE-associated morbidity and mortality [1]. Glomerular deposition of immune complexes in the kidney is considered the initiator of the resultant inflammation in LN. These deposited immune complexes derive from circulating anti-nuclear, anti-C1q, and crossreactive anti-glomerular autoantibodies [2–4], opsonized apoptotic particles, microparticles and neutrophil extracellular traps (NETs) [5, 6]. DNA particulates that can reside within NETs can be resistant to degradation by DNAses, and nephritic kidneys are enriched for antibodies with anti-DNA activity [7]. However, not all anti-DNA antibodies are pathogenic, and a number of non-DNA-binding antibodies contribute to LN [8, 9].

Histological classification of LN-associated glomerular disease via light microscopy of kidney biopsy sections has yielded five subtypes, with class III (focal proliferative, <50% glomeruli affected), class IV (diffuse proliferative, >50% glomeruli affected) and class V (membranous) subtypes retaining the greatest potential to cause long-term damage [10, 11]. Renal damage initiated by pathogenic immune complexes depends on the location of deposition and the subsequent injured cell population, which both contribute to the classification of LN. Subendothelial deposits are the hallmark of class III and IV proliferative LN. Due to their access to the vascular space, these deposits activate myeloid cells via Fcγ receptor (FcγR) binding, thus enabling these myeloid cells to enter the kidney [12]. In contrast, subepithelial deposits associated with class V disease injure podocytes and provoke a less severe inflammatory response than subendothelial deposits; however, should the glomerular basement membrane rupture, subepithelial deposits can access the entire glomerulus [10].

Infiltrating inflammatory cells enter the kidney through glomerular and interstitial blood vessels and contribute in tissue injury. Lymphocytes participate in local effector functions and adaptive immune responses to incite inflammation and promote perpetuation of kidney disease [13, 14]. A recent single-centre prospective observational study shows that treatment with a biologic designed to deplete $CD20^+$ B cells, rituximab, in conjunction with low dose intravenous methyl prednisolone and MMF allows for the elimination of oral steroids and their negative side effects [15]. Despite these observations, clinical trials for rituximab remain inconclusive, potentially owing to the continued reliance on oral steroids despite a planned taper, failure to achieve the primary endpoint and patient variability in genetic variants that influence LN through mechanisms independent of B cell activation [15–18]. Although lymphocytes are necessary for LN, professional phagocytic cells of the innate immune system, including dendritic cells and macrophages, have surfaced as critical cell populations in the pathogenesis LN. Deposited immune complexes activate FcγRs to promote the activation of dendritic cells and macrophages [19]. Depending on their internal structure, FcγRs can either activate or inhibit downstream signaling upon ligation to immune complexes [20]. Human FcγRI, IIa, IIc and III and murine FcγRI, III and IV contain an ITAM (immunoreceptor tyrosine-based activation motif) that promotes activating signals [21]. In contrast, FcγRIIB contains an ITIM (immunoreceptor tyrosine-based inhibitory motif) that promotes inhibitory signals [22]. Polymorphisms and/or copy number

variants in multiple FcγR genes are linked to SLE susceptibility and associated with LN [23–27]. There is an accumulation of immune complexes bound to activating FcγRI and FcγRIV SLE-prone mice [28], and deletion of FcγRI in a murine model of SLE results in protection from immune complex accumulation in the kidney [28]. In contrast, FcγRIIB$^{-/-}$ mice develop severe SLE-like nephritis [29]. Immune complexes also have the ability to activate the complement cascade [30] or to directly activate intrinsic glomerular cells, inducing inflammatory chemokine and cytokine release [31]. Further, should immune complexes contain nucleic acids, they can also activate endosomal Toll-like receptors (TLRs), including TLR7 and TLR9, thus increasing the inflammatory response [32]. While dendritic cells and macrophages can descend from a common progenitor and maintain overlapping functions, including antigen presentation and participation in T cell homeostasis, these phagocytes retain distinct roles not only within the immune system, but also in the context of disease [33–35].

2.1. Dendritic Cells in LN

Dendritic cells play a critical role in the regulation of the adaptive immune response and consist of two major categories: myeloid dendritic cells and plasmacytoid dendritic cells. Both myeloid and plasmacytoid dendritic cells are derived from a dendritic cell precursor in the bone marrow, while inflammatory dendritic cells, similar to inflammatory macrophages, originate from monocytes [33]. Dendritic cells can function to protect against renal injury; in acute immune-mediated disease, dendritic cells can be anti-inflammatory [36]. However, should renal inflammation become chronic, dendritic cells can adopt a pro-inflammatory behavior [36]. Dendritic cells are among the infiltrating cells in the nephritic kidney, and this chronic inflammatory environment will induce their maturation, wherein they can produce inflammatory cytokines and stimulate rather than tolerize effector T cells to perpetuate kidney disease [37, 38]. Studies show that CD141^{high} and CD1c^{+} subsets of the myeloid dendritic cell population, as well as CD303^{+} plasmacytoid dendritic cells, are numerically increased in patients with LN, in particular class III/IV LN, and this presence correlates with kidney fibrosis [39–41]. Increased dendritic cell presence in the kidney also correlates with decreased peripheral circulating dendritic cell subsets [42]. During nephritis in murine models of SLE, resident renal CD103^{+} dendritic cells that are the best antigen-presenting cells do not expand their population; however, CD11c^{high} myeloid dendritic cells accumulate in mass quantities in the nephritic kidney, yet their function is unknown [37]. A clear type I interferon signature is detected in nephritic kidneys [43, 44]. This finding potentially implicates plasmacytoid dendritic cells in LN pathogenesis, as this population is a major producer of type I interferon [45, 46]. However, studies also suggest that resident renal cells are capable of producing type I interferon and can thus contribute to the observed type I interferon signature [47]. Taken together, these data suggest that dendritic cells play a vital role in the pathogenesis of LN and highlight the necessity for delving further into their functionality within the kidney.

2.2. Macrophages in LN

Depending on the environmental composition, activated monocytes can differentiate into two main macrophage subtypes: classically activated (M1 infiltrating and inflammatory macrophages) and alternatively activated (M2 tissue resident and trophic macrophages). M2

macrophages can be further categorized into subsets according to the applied stimuli and the consequential transcriptional alterations [48, 49]. Studies within the past decade suggest that murine macrophages stimulated with IFNγ, LPS and granulocyte-macrophage colony stimulating factor (GM-CSF) can become classically activated (M1 macrophages). M1 activation results in the production of proinflammatory cytokines, including TNFα, IL-1β, IL-12, IL-18 and IL-23; production of nitric oxide and reactive oxygen species; antigen presentation; expression of chemokine receptors CCR1 and CCR5; promotion of type 1 T helper (T_H1) and type 17 T helper (T_H17) cell responses; thus providing an effective mechanism of pathogen killing [49]. Murine macrophages skewed towards an M2 phenotype by fungal cells, immune complexes, parasites, complement components, apoptotic cells, macrophage colony stimulating factor (M-CSF), IL-4, IL-13, IL-10, and TGFβ can be subdivided into four groups depending on the stimuli; M2a, considered to be pro-fibrotic; M2b, considered to be immunity-regulating; M2c; considered to be deactivated, remodelling or anti-inflammatory; and M2d are a distinct group unlike M2a-c [49]. Murine M2 macrophages produce IL-10, arginase 1, chitinase-like protein 3 (also known as phagocytosis, extracellular matrix production, apoptotic cell clearance, wound healing and/or anti-inflammatory activities [49]. However, macrophages have been found to exhibit phenotypic plasticity [50, 51]. Changes in the environmental milieu can promote crossover between each group, allowing for an extensive variation in their phenotype [50, 51]. Only within the past three years has the M1–M2 paradigm been recognized as a set of well-defined molecular events that are highly reproducible under controlled conditions *in vitro*, but have little to no relevance *in vivo* [52–54]. Thus, *in vivo*, populations of macrophages can share both M1-like and M2-like characteristics.

Detection of macrophages in nephritic kidneys, especially when found at a repeat biopsy, correlates with poor prognosis [55]. However, macrophages can play essential roles in both kidney injury and repair [56, 57]. Murine kidneys can present with both tissue resident interstitial macrophages, which are $CD11b^{low}F4/80^{bright}$, derived from fetal yolk sac precursors, and the predominant macrophage population and infiltrating inflammatory macrophages, which are $CD11b^{high}F4/80^{low}$, derived from monocyte precursors and constantly replenished by monocytes [56, 58]. Tissue resident interstitial macrophages may be capable of self-renewal [59], and in murine models of LN, this population increases in number and activation and develop matrix metalloproteinase and cathepsin activity, indicating they may contribute to irregular tissue remodeling [58, 60]. Upon recruitment from the peripheral blood to the kidney, infiltration macrophages exhibit a proinflammatory phenotype during acute inflammation, but have the capacity to switch to a healing phenotype to enhance the resolution of inflammation [56, 61]. Failure by macrophages to switch from a pro-inflammatory to an anti-inflammatory phenotype or to eliminate apoptotic cells can cause chronic inflammation, wherein macrophages continue to amplify disease [62]. In support of this argument, administration of poly (I:C) to pre-nephritic SLE-prone mice promotes macrophage infiltration into the kidney and accelerates proliferative LN [63]. Treatment with chlodronate-loaded liposomes not only diminishes the poly (I:C)-induced macrophage infiltration but also the ensuing intraglomerular proliferative lesions and crescent formation, thus indicating that macrophages are the key mediators of the LN [63]. However, in LN there may not exist a clear segregation of macrophage phenotype (M1 or

M2) due to the aberrant activation of macrophages induced by the surrounding complex inflammatory milieu [64]. For example, in a different murine model of SLE, induction of apoptosis in circulating monocytes by chlodronate-loaded liposomes, and the ensuing decrease in monocyte-derived macrophages, accelerates, rather than prevents, the development of LN, potentially owing to a decrease in macrophage clearance of apoptotic cells and the subsequent increase in circulating self-antigen [65, 66]. The differing outcomes of the aforementioned macrophage depletion experiments presumably stem from the inherent plasticity of macrophages and their designated function within the diseased kidney at the time of their deletion as well as the context of LN pathogenesis in the chosen SLE disease model.

CD169 (sialoadhesin), a sialic acid-binding immunoglobulin-like lectin, is an adhesion molecule restricted to macrophages that serves as a biomarker for a type I IFN-signature associated with SLE and whose expression is induced by IFNα [67]. Whereas CD169 deficiency is sufficient to ameliorate murine autoimmune neuropathy, suggesting a functional contribution of this molecule to autoimmune pathologies [68], LN severity and disease progression in a murine model of SLE were unaffected by CD169 deficiency [69]. However, in SLE, CD169-expressing monocytes within the glomeruli correlate with LN disease severity [70], suggesting a utility for this molecule not as a therapeutic target for, but as a biomarker of, LN disease severity [71]. Together these data indicate that macrophages are critical mediators of LN pathology, as they can drive both the aberrant inflammation and resolution of disease. Moreover, macrophages in organs other than the kidney may also participate in the pathogenesis of LN.

2.2.1. Splenic marginal zone macrophage populations in the initiation of LN—

The spleen is the largest secondary lymphoid organ in the mammalian body and plays important roles in the filtration of blood and pathogen defense. The follicular marginal zones (MZ) of the spleen are transitional sites that separate the white pulp from the blood-filled sinuses of the red pulp. Within the splenic MZ, two highly specialized macrophage populations, along with a subset of B cells, function in concert to play a vital role in host defense. The anatomy of the MZ slows down blood flow, thus allowing pathogens in the peripheral circulation to be phagocytosed by both marginal metallophilic macrophages (MMM) and MZ macrophages (MZM). Also contained with the reticular framework of the MZ are the MZ B cells (IgM^+ $CD21^{high}$ $CD23^{low}$ $CD1d^+$ in mice) [72], which can transport immune complexes into the follicle to potently activate T cells [73]. MMM exist as a thin band of cells within the follicle located beneath $MAdCAM\text{-}1^+$ cells that line the marginal sinus. MZM are in close physical contact with MZ B cells [74], and together these two populations create powerful cellular network for the capture of antigen, including immune complex, pathogens and apoptotic cells. Further, it has been suggested that the maintenance of both the MMM and MZM populations requires an intact MZ B cell population [75]. Thus, MZ macrophages and MZ B cells require cell-to-cell contact and communication to maintain the integrity of the MZ structure [75].

Under steady-state conditions, apoptotic cells and debris that escape clearance by local phagocytes are cleared by MMM and MZM, thus preventing autoantigens from entering the follicle. Efferocytosis is a process whereby phagocytes, including MMM and MZM, engulf

and eliminate apoptotic cells to promote the resolution of inflammation. Recognition of apoptotic cells is based on a number of factors [76]: (1) Modification of lipid localization on the plasma membrane. PS predominately located on the inner leaflet of the plasma membrane is rapidly externalized during apoptosis, and increased exposed PS are recognized as ‘eat-me’ signals by scavenger receptors CD36 and MerTK [77, 78]. (2) Oxidation of cell surface lipid. Besides CD36, other scavenger receptors such as class A scavenger receptor (SR-A), CD14 and CD68 have an affinity for oxidized lipids that will then enhance antigen capture and distribute signals to phagocytes [79–82]. (3) Reduction of surface ‘don’t eat me signals’ and opsonization of the cell by serum proteins, including members of the complement cascade (C1q, C3, C4) [76]. Following proper recognition, phagocytes internalize the apoptotic cells by rearranging their cytoskeleton and then ingesting the material, which is then accompanied by the release of anti-inflammatory mediators to prevent local inflammation [77]. However, failure to properly distinguish these cells from nearby live cells can lead to severe autoimmune disease [77]. Mice deficient in MerTK are unable to clear apoptotic cells and develop SLE-like disease [83]. Further, Over 90% of patients with C1q deficiency develop SLE [84], owing to reduced circulating C1q, C3 and C4 in the serum of SLE patients [85]. C1q-deficient mice also develop SLE-like disease, including glomerulonephritis [84, 86].

Apoptotic bodies in the circulation are targeted to the MZ and are ingested by MMM and MZM, indicating that the removal of apoptotic cells by MMM and MZM is critical to prevent inflammatory pathology and fatal autoimmune disease in both mice and humans. MMM are characterized by the specific expression of CD169 [74]. CD169 binds to sialic-acid expressed on the surface of pathogens and is involved in cell-cell adhesion as well as cell-pathogen interaction [87]. Studies show that deletion of $CD169^{+}$ macrophages in CD169-DTR mice by injection of diphtheria toxin caused delayed clearance of injected dying cells in the MZ of the spleen [88]. MZM express MARCO (**Ma**crophage **R**eceptor with **Co**llagenous Structure) and SIGN-R1 (mouse homologue of DC-SIGN) [74]. The capture of apoptotic cells can be promoted by the interaction of C1q with SIGN-R1 on MZM [89, 90]. The layer of splenic $MARCO^{+}$ MZM is significantly reduced in patients with SLE compared to the dense layer found in non-SLE patients [91]. With age, BXD2 mice (derived from the cross of a C57BL/6 and DBA/2 mice) [92–94] and B6.*Sle1.Sle2.Sle3* [95] show a dramatic loss of MZM and development SLE-like disease. The loss of MZM was due to translocation of MZ B cells from the MZ into the follicle [91, 94]. The absence of MZM leads to increased loading of apoptotic cell antigens on MZ B cells which then translocate more antigens into the follicle, thus resulting in T cell activation and inflammatory cytokine production [93].

The spleen can clear immune complex-associated apoptotic cells as described above. However, the spleen is considered pathogenic in LN, as cells from draining lymph nodes, including macrophages, T and B cells home to the spleen. Therefore, removal of the spleen has been postulated as a potential therapeutic strategy to reduce or prevent LN. In the murine model of immune complex-induced glomerulonephritis, experimental nephrotoxic serum nephritis (NTS), splenectomy does not impact disease, as kidney damage, circulating antibody levels and immune complex deposition in the glomeruli remain unchanged [96]. In

the BAFF transgenic murine model of SLE, low affinity self-reactive B cells, in particular MZ B cells, are expanded and these mice develop nephritis [97]. However, splenectomized BAFF transgenic mice are not protected from nephritis, indicating that splenocyte populations are not the drivers of kidney inflammation [97]. In contrast, splenectomy in a spontaneous murine model of SLE at 2 weeks of age significantly reduced proteinuria, indicating diminished kidney damage [98]. The efficacy of splenectomy in patients is equally inconclusive. Patients with glomerulopathy exhibit decreased proteinuria and marked histological improvement in the kidney following splenectomy [99]. Another study suggests an increased risk for the development of SLE associated with splenectomy [100]; however, this study requires further analysis, as factors that could have independently led to SLE development in these patients were not taken into consideration [100, 101]. Therefore, these inconclusive results suggest that the efficacy of the splenectomy as a viable therapy has yet to be determined. Taken together, further investigation is required to understand the key mechanistic roles of splenic MZ macrophage populations in prevention of murine SLE-like nephritis and human LN.

3. Programmed cell death pathways in dendritic cells and macrophages are implicated in LN

Programmed cell death pathways, including apoptosis, are the central mechanisms for the controlled clearance of cells. As mentioned above, tissue inflammation can occur as a consequence of the failure to clear dying cells. The resulting inflammation is caused by the release of cellular contents and exposure to self-antigens that engage receptors for damage-associated molecular patterns (DAMPs), ultimately culminating in autoimmunity [77, 102]. Therefore, inefficient clearance of dying cells by dendritic cells and macrophages may contribute to a break in tolerance and lead to LN, in part by providing self-antigens that become components of immune complexes deposited in kidney. While the mechanisms underlying LN are not fully illuminated, aberrant programmed cell death is a fundamental player in its pathogenesis [103]. Theoretically, defects in programmed cell death signaling components within dendritic cells and macrophages may have detrimental downstream effects on disease. In recent years, inflammatory functions have been ascribed to molecules classically involved in programmed cell death through the study of both human samples and murine models. Here we discuss these newly discovered mechanisms associated with programmed cell death signaling mediators, with a focus on the dendritic cell and macrophage populations, in the development of LN.

3.1. Extrinsic Pathway of Apoptosis in LN

The apoptotic machinery can determine the fate of a cell. While ligation of death receptors triggers death, activation of death receptors by their cognate ligands may also trigger cellular proliferation and inflammation [104]. Apoptosis occurs via two pathways, an extrinsic pathway involving transduction of an apoptotic signal following aggregation of a death receptor, such as Fas, TNF receptor 1 (TNF-R1) or TNF-related apoptosis inducing ligand (TRAIL) receptor R1 and R2, to its ligand, Fas ligand (FasL), TNFα or TRAIL, respectively, and an intrinsic pathway that signals through the mitochondria and is regulated by the Bcl-2 family (discussed in detail below). In the extrinsic pathway, binding of a death

ligand, such as homotrimeric Fas ligand (FasL), to its cognate receptor Fas, leads to recruitment of Fas-associated death domain protein (FADD). FADD will then recruits the cysteine-aspartic acid enzyme pro-caspase-8, and aggregation and homodimerization of pro-caspase-8 results in its autocatalysis and/or activation and induces the degradative phase of apoptosis through the activation of caspase-3/7, coordinators of downstream apoptotic cellular processes [105]. Cellular FADD-like IL-1β-converting enzyme (FLICE)-inhibitory protein (FLIP) is a catalytically inactive homolog of caspase-8 and acts as an endogenous regulator of the apoptotic pathway at the level of caspase-8 activation. FLIP is also recruited by FADD upon Fas activation and can either inhibit or potentiate binding of FADD and caspase-8 depending on its concentration [106, 107]. An alternative pathway of Fas-induced cell death involves cross-talk with the intrinsic pathway mediated by activating the Bcl-2 pro-apoptotic protein Bid [108, 109], which is cleaved by caspase-8 following Fas ligation. Cleaved Bid is then targeted to the mitochondria and results in the induction of the intrinsic apoptotic pathway [110].

3.1.1. Fas

Here, we examine Fas and its downstream signaling molecules in phagocytic cell populations of the innate immune system in the context of LN in both humans and mice (TABLE 1).

Human—Variants of genes that encode for both the death receptor Fas and its ligand, FasL, are associated with the pathogenesis of SLE, with the -670 FAS polymorphism directly linked to development of LN [111, 112].

Mouse—Mice that possess a mutation in the death receptor Fas (*lpr*) develop normally, but with age exhibit splenomegaly, lymphadenopathy, hypergammaglobulinemia, autoantibodies, the presence of double negative T cells ($CD3^+CD4^-CD8^-B220^+$) and severe glomerulonephritis, with development of advanced SLE-like disease being highly dependent upon strain background [113]. The autoimmune-prone MRL strain possessing the *lpr* mutation (MRL.$Fas^{lpr/lpr}$) develop the most severe SLE-like disease [114]. Deletion of dendritic cells with defective Fas signaling in MRL.$Fas^{lpr/lpr}$ mice ameliorates kidney disease, thus revealing a requirement for dendritic cells in the expansion and differentiation of T cells and subsequent onset of kidney damage [115]. Deletion of macrophages with defective Fas signaling in MRL.$Fas^{lpr/lpr}$ mice via congenital deletion of colony-stimulating factor (CSF-1) or its receptor, CSF-1R, ameliorates kidney disease due to a decrease of both renal infiltration and intrarenal proliferation [116]. MCP-1 is chemokine with potent monocyte attracting activity, and its receptor, CCR2, is expressed by circulating inflammatory monocytes, as well as T cells. Deletion of either MCP-1 or CCR2 in MRL.$Fas^{lpr/lpr}$ mice improves renal disease owing to a decrease in both macrophage and T cell infiltration [117, 118]. Further, in MRL.$Fas^{lpr/lpr}$ mice, targeting of CX3CR1, the receptor for fractalkine expressed on macrophages and important for trafficking into tissues, improves renal disease as a result of reduced macrophage infiltration [119]. The advent of conditional gene deletion has allowed cell-specific dissection of Fas deficiency within the dendritic cell and macrophage populations. $CD11c^{cre}Fas^{flox/flox}$ mice, in which Fas is deleted in conventional, but not plasmacytoid, dendritic cell populations, develop several

manifestations of systemic autoimmunity, including splenomegaly, hypergammaglobulinemia and auto-antibodies [120]. Though it was reported that leukocyte infiltration occurs in the liver, the authors did not mention whether kidney damage occurs in *CD11c*^{cre}*Fas*$^{flox/flox}$ mice [120]. Similar to *CD11c*^{cre}*Fas*$^{flox/flox}$ mice, mice that conditionally lack Fas in the myeloid cell compartment, which includes monocytes, macrophages and neutrophils (*LysM*$^{cre/cre}$*Fas*$^{flox/flox}$) [121], develop with age a SLE-like disease characterized by splenomegaly, hypergammaglobulinemia, autoantibodies and proinflammatory cytokine production [121]. Further, these mice develop SLE-like LN [121]. In *LysM*$^{cre/cre}$*Fas*$^{flox/flox}$ mice, the observed accumulation of peripheral monocytes/macrophages and granulocytes consequently increases both dendritic cell and T cell activation and disrupts their normal distribution, indicating an indirect role for Fas in myeloid cells on the activation status of other immune cells [121]. TLR activation is a critical step in the activation and functional determination of macrophages and is therefore central for development and persistence of SLE-like disease in mice [122]. *LysM*$^{cre/cre}$*Fas*$^{flox/flox}$ mice are more susceptible to death as compared to *Fas*$^{flox/flox}$ mice following high-dose LPS injection [121]. Thus, there is a heightened systemic reaction to TLR ligation resulting from loss of Fas in myeloid cells, suggesting that the death receptor Fas functions not only in initiating the extrinsic apoptotic pathway, but also in the maintenance of TLR activation. Thus, it is possible that defective Fas signaling in dendritic cells and macrophages may drive inflammation in the kidney.

3.1.2. FADD—Following the binding of FasL to its cognate receptor Fas, FADD is recruited to the complex.

Human: A study performed in 2007 found that expression of FADD is significantly decreased in PBMCs of SLE patients and negatively correlates with patient SLE activity index [123]. Expression of *FADD* was also found to be 2-fold higher in SLE patients who responded well to a 6-month regimen of corticosteroids plus mycophenylate mofetil or cycolophosphamide [124]. Together, these findings implicate decreased FADD expression in the severity of SLE.

Mouse: *CD11c*^{cre}*FADD*$^{flox/flox}$ mice develop systemic inflammation along with pro-inflammatory cytokines, including MCP-1, and increased macrophage, neutrophil and B cell populations. These phenotypes are attributed to the downstream effects of depletion of CD103^{+} dendritic cells within gut-associated lymphoid tissues due to the loss of FADD [125]. This same group also assessed the impact of myeloid cell-specific FADD-deficiency, and similar to *CD11c*^{cre}*FADD*$^{flox/flox}$ mice, *LysM*$^{cre/cre}$*FADD*$^{flox/flox}$ mice, which have nearly complete deletion of FADD in neutrophil and monocyte/macrophage populations, suffer from systemic inflammation along with pro-inflammatory cytokines, including MCP-1, and increased macrophage, neutrophil and B cell populations [126]. However, despite the systemic inflammation observed in *CD11c*^{cre}*FADD*$^{flox/flox}$ and *LysM*$^{cre/cre}$*FADD*$^{flox/flox}$ mice, kidney pathology was not assessed. FADD is able to sequester myeloid differentiation primary response gene 88 (MyD88), an adaptor protein that is essential for most TLR signaling, thereby hindering activation of the downstream transcription factor NFκB [127]. Disease in *CD11c*^{cre}*FADD*$^{flox/flox}$ mice is prevented by

global, but not dendritic cell-specific, deletion of MyD88 as well as oral antibiotic treatment [125]. Further global deletion of MyD88 rescues these phenotypes, indicating that the inflammation observed due to the loss of FADD is driven by MyD88 signaling and not a defect in death [126]. Since kidney pathology was not examined in mice with dendritic cell- or myeloid-cell specific FADD deletion, assessment of kidney damage in the context of cell-specific FADD deficiency merits investigation. Further, as elevated TLR signaling is linked to the pathogenesis of SLE, it is possible that the decreased level of FADD observed in patients with SLE allows for uncontrolled TLR signaling, though which cells are involved remain a mystery.

3.1.3. FLIP—Following recruitment of FADD, FLIP is then recruited by FADD and either inhibits or potentiates binding of FADD and caspase-8 depending on its concentration. FLIP is a catalytically inactive homolog of caspase-8 and acts as an endogenous regulator of the Fas pathway at the level of caspase-8 activation.

Human: Expression of the self-antigen Ro52/SSA that functions to increase cell death is increased in patients with SLE [128]. Ro52/SSA can negatively regulate the long form of FLIP (FLIP(L)) *in vitro*, as overexpression of Ro52/SSA reduces FLIP(L) and knockdown of Ro52/SSA results in the accumulation of FLIP(L) [129]. Peripheral blood B cells from patients with SLE present with significantly higher expression of FLIP, which correlates with SLE severity, as patients with active SLE show higher FLIP levels that patients with inactive SLE [130].

Mouse: Loss of FLIP in the conventional $CD8^+$ and $CD11b^-$ dendritic cell compartments ($CD11c^{cre}Flip^{flox/flox}$) promotes spontaneous development of an erosive inflammatory arthritis accompanied by autoantibodies to joint antigens that resembles another autoimmune disorder, rheumatoid arthritis [131]. Prior to the onset of arthritis, the dendritic cell populations, $CD8^+$ dendritic cells in particular, are significantly decreased in the thymus, spleen, and lymph nodes [131]. Although $CD11c^{cre}Flip^{flox/flox}$ mice are lymphopenic, autoreactive $CD4^+$ T cells are detected and correlate with reduced regulatory T cell numbers [131]. Another group reported that $CD11c^{cre}Flip^{flox/flox}$ mice develop neutrophilia, owing to excess availability of G-CSF, and splenomegaly. Contrary to the previous study, there is no impact on the peripheral dendritic cell number, but these cells are hyper-activated. FLIP-deficient dendritic cells are hyper-responsive to stimulation with TLR2, TLR4 and dectin-1 [132], yet these mice do not develop spontaneous arthritis [132–135]. In both studies, despite the systemic inflammation observed, the extent of kidney damage is unknown. Mice deficient in FLIP within the myeloid populations ($LysM^{cre/cre}Flip^{del/flox}$) show significantly reduced body weight and succumb to premature mortality by 3–5 weeks of age, demonstrating that expression of FLIP in myeloid cells is critical for postnatal survival [136]. $LysM^{cre/+}Flip^{del/flox}$ mice, which have complete deletion of FLIP in neutrophils, but only partial deletion of FLIP in monocyte precursors and peripheral monocytes, present increased numbers of circulating neutrophils accompanied by extensive multiorgan neutrophil infiltration [136]. FLIP is crucial for macrophage differentiation, as evidenced by the inability to differentiate ex vivo cultures of FLIP-deficient $c\text{-}Kit^+$ hematopoietic stem cells to macrophages and the fact that $LysM^{cre/+}Flip^{del/flox}$ mice show elevated levels of

circulating monocytes, yet show greatly reduced macrophage populations within tissues [136]. In particular, *LysM*$^{cre/+}$*Flip*$^{del/flox}$ mice show a reduced splenic MMM population [136]. Another group observed similar results when examining an alternate construct of FLIP deficiency (*LysM*$^{cre/cre}$*Flip*$^{flox/flox}$), which limits FLIP deficiency to the monocyte population [137]. Similar to *LysM*$^{cre/+}$*Flip*$^{del/flox}$ mice, the splenic MMM population is also deleted in *LysM*$^{cre/cre}$*Flip*$^{flox/flox}$ [137]. However, unlike *LysM*$^{cre/+}$*Flip*$^{del/flox}$ mice, *LysM*$^{cre/cre}$*Flip*$^{flox/flox}$ mice develop severe splenomegaly [137]. In both studies, analysis of the kidney is not included [136, 137]. As kidney pathology is not referenced in the aforementioned studies examining either dendritic cell- or macrophage-specific FLIP deficiency, yet there is a link between reduced FLIP in circulating B cells and SLE, the impact of FLIP expression in dendritic cells and macrophages in the kidney merits investigation in both murine models of and patients with LN.

3.1.4. Caspase-8—Following FasL binding to Fas, FADD recruits pro-caspase-8. The aggregation and homodimerization of pro-caspase-8 results in its autocatalysis and/or activation to induce the degradative phase of apoptosis through activation of caspase-3/7, coordinators of the degradative phase of apoptosis [105]. Although caspase-8 clearly functions in regulating programmed cell death, accumulating evidence implicates caspase-8 in activities independent of its role in programmed cell death, including motility [138], metastasis [139], suppression of inflammation [140, 141], NFκB activation [142] and IRF3 degradation [140, 143].

Human: Anti-caspase-8 autoantibodies are detected in the sera of patients with SLE [144]. Further, neutrophils isolated from peripheral blood of patients with juvenile onset SLE display increased expression of caspase-8 [145]. A study shows that while peripheral blood lymphocytes from healthy control patients predominantly express an isoform of caspase-8, caspase-8L, which lacks the proteolytic domain, these same cell populations in some SLE patients express a relatively decreased amount of this isoform compared to intact caspase-8 [146].

Mice: Dendritic cell-specific deletion of caspase-8 (*CD11c*^{cre}*Casp8*$^{flox/flox}$) induces an aggressive SLE-like disease [147, 148]. This SLE-like disease in *CD11c*^{cre}*Casp8*$^{flox/flox}$ mice is characterized by splenomegaly, lymphadenopathy, elevated serum cytokine levels, hypergammaglobulinemia, proteinuria, autoantibodies, immune complex deposition in the kidney and severe glomerulonephritis [147]. *CD11c*^{cre}*Casp8*$^{flox/flox}$ dendritic cells do not display a survival advantage, indicating that defective dendritic cell apoptosis is not the underlying cause of the observed inflammation [147]. Caspase-8-deficient dendritic cells are hyper-responsive to TLR activation *in vitro* and *in vivo* [147]. As observed in patients with SLE, *Cre*^{CD11c}*Casp8*$^{fl/fl}$ mice develop an interferon signature, indicating that the loss of caspase-8 may increase the activity of interferon regulatory factors (IRFs), a family of transcription factors known to play a role in type 1 interferon production. Though caspase-8 is able to process IRF3 for degradation [143] and *CD11c*^{cre}*Casp8*$^{flox/flox}$ dendritic cells constitutively express elevated IRF3, deletion of IRF3 in *CD11c*^{cre}*Casp8*$^{flox/flox}$ mice does not inhibit, but rather exacerbates, SLE-like disease. Further, deletion of a redundant homolog of IRF3, IRF7, neither prevents nor exacerbates disease in *CD11c*^{cre}*Casp8*$^{flox/flox}$

mice [147]. As in *CD11c*^{cre}*FADD*$^{flox/flox}$ mice, deletion of MyD88 in *CD11c*^{cre}*Casp8*$^{flox/flox}$ mice prevents SLE-like disease, including immune complex deposition in the kidney and glomerulonephritis, though oral antibiotic treatment is ineffective at diminishing the observed inflammation [147]. Thus, caspase-8 in dendritic cells maintains tolerance in a manner that is independent of cell death and IRF3/7, but requires dampening of downstream MyD88 signaling [147]. Similar to *CD11c*^{cre}*Casp8*$^{flox/flox}$ mice, specific deletion of caspase-8 in myeloid cells (*LysM*$^{cre/cre}$*Casp8*$^{flox/flox}$) leads to the development of systemic inflammation. However, this inflammation is significantly milder and is characterized by splenomegaly, lymphadenopathy, elevated serum cytokine levels, hypergammaglobulinemia, proteinuria and immune complex deposition in the kidney without the development of glomerulonephritis [149]. *In vitro* studies reveal that caspase-8-deficient macrophages are prone to caspase-independent death in response to DR ligation, yet caspase-8-deficient myeloid populations are not predisposed to unchecked survival, as analysis of mixed bone marrow chimeric mice demonstrate that caspase-8 deficiency does not confer preferential expansion of myeloid populations [149]. Despite the mild inflammatory phenotype of *LysM*$^{cre/cre}$*Casp8*$^{flox/flox}$ mice, caspase-8-deficient macrophages are hyper-responsive to TLR activation *in vitro* and *in vivo*, and, in contrast to *Cre*^{CD11c}*Casp8*$^{fl/fl}$ mice, oral antibiotic treatment prevents inflammatory disease phenotypes in young *LysM*$^{cre/cre}$*Casp8*$^{flox/flox}$ mice [149]. These data suggest that the gut microbiota may contribute to the observed inflammation by providing a pool of endogenous TLR ligands. Moreover, caspase-8 controls the polarization of macrophages in response to M1-skewing media (IFNγ and LPS), as deletion of caspase-8 prevents formation of true M1 macrophages [149]. While it is clear that caspase-8 controls multiple functions within the dendritic cell and macrophage populations, future studies are required to determine the direct impact of these functions on development of kidney disease.

3.2. Intrinsic Pathway of Apoptosis in LN

In addition to the extrinsic pathway of apoptosis, there also exists an intrinsic pathway. The intrinsic pathway of apoptosis is regulated by the Bcl-2 protein family, which are divided into anti-apoptotic (Bcl-2, Bcl-x_L, Mcl-1) and pro-apoptotic (Bax, Bak, Bim) members [150]. The pro-apoptotic family is further categorized into the multi-Bcl-2 homology (BH) domain proteins, including Bax and Bak, and the BH3-only domain proteins, including Bad, Bok/Mtd, Bik/Blk/Nbk, Bid, Hrk/DP5, Bmf, Noxa, Puma/Bbc3 and Bim/Bod. The prevailing dogma is that the BH3-only proteins either activate the multi-BH pro-apoptotic proteins or sequester Bcl-2 anti-apoptotic proteins to induce apoptosis. Alternatively, the Bcl-2 pro-apoptotic proteins may bind and prevent the BH3-only domain proteins from activating the apoptotic cascade. Further, not all BH3-only domain proteins bind to all Bcl-2 anti-apoptotic members. Bim, Bid and Puma are the most promiscuous as they are able to bind equally to all Bcl-2 anti-apoptotic protein family members, while Bad and Noxa display a high degree of specificity of binding to Bcl-2 anti-apoptotic members [151]. This specificity to Bcl-2 anti-apoptotic proteins also correlates with their ability to induce apoptosis. Peptides that correspond to Bim, Bid or Puma BH3 domains are sufficient to induce apoptosis in whole cells and disrupt the mitochondrial membrane potential of isolated mitochondria. In contrast, Bad, Bok/Mtd, Bik/Blk/Nbk, Hrk/DP5, Bmf and Noxa

BH3-only proteins are unable to induce apoptosis and require additional unknown signals to activate the apoptotic cascade, and are therefore referred to as sensitizers of apoptosis. Once the apoptotic signal is activated, Bak and Bax form homo and heterodimers at the mitochondria causing the release of inner mitochondrial proteins, including cytochrome C. Cytochrome C binds to both APAF1 and pro-caspase-9 to form the apoptosome. This complex then activates downstream caspases, pro-caspase-3 and 7, to cleave numerous proteins induce DNA degradation by DNAse [151, 152].

3.3.1. The Bcl-2 family in LN—Studies implicate the intrinsic apoptotic pathway in the pathogenesis of LN [153–157]. Here, we examine members of the intrinsic apoptotic pathway in phagocytic cell populations of the innate immune system in the context of LN (TABLE 1).

Human: The release of nucleosomal antigens from dying cells plays a pivotal role in the evolution of LN. The nucleosome can be degraded by caspase-activated DNAse, which is decreased in SLE patients with nephropathy [153]; further, polymorphisms in the DNASE1 gene are linked to LN [154]. Examination of renal biopsies from LN patients shows that BCL-2 is up-regulated in T and B cells that have infiltrated the tubulointerstitium, but not the glomeruli [157].

Mouse: Activated caspase-3-positive cells are found in the tubules, interstitium and glomeruli of nephritic NZB/W (F1) mice [155]. There is also increased transcription of cytochrome C in proteinuric NZB/W (F1) mice compared to healthy control BALB/c [155]. Treatment with the Bcl-2 antagonist, ABT-737, results in potent inhibition of kidney disease, as NZB/W (F1) mice treated with IFN-α, to promote accelerated onset of disease, showed significantly decreased glomerulonephritis [158]. ABT-737 actively and selectively kills plasmacytoid dendritic cells and reduced the production of IFN-α by NZB/W (F1) mice [159]. In addition, treatment with the oral Bcl-2 specific inhibitor ABT-199, also attenuates glomerulonephritis in NZB/W (F1) mice and diminishes the frequency of infiltrating adaptive and innate immune cells [157]. To understand the role that the Bcl-2 family plays in the development of disease, genetically modified mice are utilized. The contribution of Bcl-2 family members to development of autoimmune disease is controversial [160–162]. Mcl-1 transgenic mice and mice overexpressing Bcl-2 in all hematopoietic cells do not develop a full-blown SLE-like disease [160, 162]. However, transgenic mice overexpressing Bcl-2 in multiple hematopoietic linages (VavP-Bcl-2) show the propensity for development of autoimmune kidney disease [161].

Despite their involvement in cell death, the BH3-only proteins are reported to possess non-apoptotic functions [163]. BAD can regulate glucokinase activity, respiration and ATP production [164]. Bid not only possesses lipid transferase activity [165], but also regulates nucleotide-binding, oligomerization domain (NOD)-like signaling independent of its BH3 domain or association with Bax, as Bid-deficient macrophages show defective cytokine production in response to NOD-like signaling activation [166]. However, only deletion of Bim results in SLE-like systemic autoimmunity [167]. Approximately 50% of $Bim^{-/-}$ mice develop SLE-like nephritis characterized by the presence of IgG-immune complex depositions in the glomeruli, [167], thus highlighting novel functions for Bim in the control

of systemic autoimmunity. Histological examination of kidneys from *Bim*$^{-/-}$ mice reveal glomerular hypercellularity and increased mesangial matrix [167]. SLE-like nephritis is also found in *Bim*$^{-/-}$.*Fas*$^{lpr/lpr}$ mice, as indicated by increased mesangial expansion and interstitial infiltration [168]. *Bim*$^{-/-}$*Bmf*$^{-/-}$ mice develop glomerulonephritis, which leads to premature mortality [169]. The development of SLE-like nephritis in *Bim*$^{-/-}$ mice may be attributed to enhanced antigen presentation by dendritic cells and increased numbers of myeloid cells. Similar to results observed in mice that overexpress Bcl-2 in dendritic cells [170–172], *Bim*$^{-/-}$ dendritic cells are more efficient in inducing proliferation of OVA-specific OT-II-transgenic CD4 and OT-I-trangenic CD8 T cells *in vivo* [173]. In contrast to the dendritic cell-specific Bcl-2-overexpressing mice [170], only *Bim*$^{-/-}$ dendritic cells have an increased propensity for producing autoantibodies following adoptive transfer and LPS stimulation [173, 174]. Further, *Bim*$^{-/-}$ macrophages exhibit increased expression of inflammatory markers, including CD86 and MHCII, and secrete elevated levels of IL-1β following thioglycollate elicitation or TLR ligation [175]. Bim may also contribute to SLE-like nephritis through alteration of the renal microenvironment by impacting the functions of kidney endothelial and epithelial cells [176]. Bim is a critical regulator of ankios, a form of cell death resulting from matrix detachment, in epithelial cells, thus acting as a sensor of integrin and growth factor signals to the ERK pathway [177]. *Bim*$^{-/-}$ kidney epithelial cells demonstrate increased adhesion, sustained osteopontin and thrombopondin-1 (TSP1) [176]. Previous data show that lupus-prone NZB/W (F1) mice have increased extracellular matrix (ECM) components that may contribute to glomerular injury in SLE-like nephritis [178], suggesting that increased ECM in the kidney could be important LN pathogenesis [178]. Thus it is conceivable that aberrations in ECM composition in NZB/W (F1) mice are due to a decrease in the expression of Bim that is required for maintaining normal ankios of ECM, implicating Bim in the maintenance of renal homeostasis. Bcl-2 is at the forefront as a potential therapeutic target in SLE. However, as global deletion of Bim results in SLE-like systemic autoimmunity characterized by the development of glomerulonephritis, there is an unmet need of investigating dendritic cell- and macrophage-specific roles for Bim in LN.

3.3. Necroptotic pathway in LN

Other forms of ordered cell death pathways beyond apoptosis have been identified, including necroptosis [179]. Both the apoptotic (described above) and necroptotic pathways involve similar signaling components, yet the underlying mechanisms by which these orderly ends occur differ and depend on the cytosolic milieu. Necroptosis is carried out by the receptor interacting protein kinases 1 and 3 (RIPK1 and RIPK3) and the pseudokinase mixed lineage kinase domain-like (MLKL). Necroptosis is triggered by a number of proinflammatory factors linked to LN, including members of the TNF superfamily, TWEAK, TLRs and other DNA- and RNA-sensing receptors [66], or by other stimuli when apoptosis is blocked [77] and involves components of the extrinsic apoptotic pathway. Once the signal is initiated, FADD is recruited and this protein aggregation facilitates recruitment of pro-caspase-8, which upon dimerization becomes active. Active caspase-8 can initiate the degradative phase of apoptosis or can block necroptosis depending upon the availability of FLIP [180, 181]. Low levels of FLIP allow caspase-8 homodimers to form and apoptosis ensues as described above [180]. Conversely, when FLIP is present at sufficient levels, this catalytically inactive homolog of caspase-8 can be recruited by FADD to form a heterodimer with caspase-8 that

not only prevents apoptosis but also limits necroptosis by suppressing RIPK1-RIPK3 signaling [180]. Further, in the absence of FADD or caspase-8, apoptosis may be prevented, but under these conditions RIPK1-RIPK3 signaling proceeds unchecked, also potentially leading to necroptosis [180]. Necroptosis results in rapid plasma membrane permabilization and the release of nucleosomes and other DAMPs that serve as SLE-associated antigens. Other caspase-8 death-independent functions have also been directly linked to RIPK activity. TLR engagement provokes RIPK signaling independent of death receptor activation, leading to ripoptosome formation, a complex containing similar proteins involved in necroptosis, or the necrosome (FADD, caspase-8, FLIP, RIPK1) [182]. Ripoptosome/RIPK3 activity induces IL-1β production [183], and caspase-8/RIPK signaling can regulate the Nlrp3 inflammasome [148, 184, 185].

Human—In PBMCs isolated from patients with SLE, expression of RIPK1 is significantly decreased and negatively correlates with the SLE activity index [123]. Further, B cells isolated from PBMCs of SLE patients also show decreased expression of both RIPK1 and RIPK3.

Mouse—While *RIPK1*$^{-/-}$ mice die perinatally [186], *RIPK3*$^{-/-}$ mice develop normally (TABLE 1) [187]. Deletion of either RIPK1 or RIPK3 can rescue the embryonic lethality that occurs with global knockout of either FADD or caspase-8, but not FLIP [180, 188, 189], and deletion of RIPK3 in *CD11c*^{cre}*FADD*$^{flox/flox}$ and *LysM*$^{cre/cre}$*FADD*$^{flox/flox}$ mice also rescues the phenotypes associated with phagocyte-specific FADD deficiency [125, 126]. Similar to *CD11c*^{cre}*FADD*$^{flox/flox}$ and *LysM*$^{cre/cre}$*FADD*$^{flox/flox}$ mice, deletion of RIPK3 prevents disease symptoms in *LysM*$^{cre/cre}$*Casp8*$^{flox/flox}$ mice resulting from caspase-8 deficiency in myeloid cells [149]. However, RIPK3 is not involved in the aggressive SLE-like disease in dendritic cell-specific caspase-8-deficient mice (*CD11c*^{cre}*Casp8*$^{flox/flox}$), as kidney damage persists [147, 148]. *In vitro* studies also implicate RIPK1 in the hyperactivation of dendritic cells and macrophages from *CD11c*^{cre}*Casp8*$^{flox/flox}$ and *LysM*$^{cre/cre}$*Casp8*$^{flox/flox}$ mice following TLR activation [147, 149], suggesting that uncontrolled RIPK1 activity may contribute to the SLE-like disease in *CD11c*^{cre}*Casp8*$^{flox/flox}$ mice and the inflammatory phenotypes in *LysM*$^{cre/cre}$*Casp8*$^{flox/flox}$ mice. Together, these data suggest that action of necroptotic mediators within the dendritic cell and macrophage populations merit further evaluation in the nephritic kidney.

3.4. Inhibitors of Apoptosis in LN

A group of proteins called the inhibitors of apoptosis proteins (IAPs) may provide another mechanism by which the programmed cell death machinery participate in LN. IAPs can regulate cell death. XIAP is a direct inhibitor of apoptosis, as it can bind to and prevent downstream effector functions of caspases -3, -7 and -9 [190–192]. In contrast, cellular IAP1 (cIAP1) and cellular IAP2 (cIAP2) are unable to directly inhibit caspases and instead promote prosurvival signaling from TNF receptor (TNFR)1 complex I and limit formation of the apoptosis-inducing TNFR1 complex II [193–195]. In response to pro-apoptotic stimuli, the second mitochondria-derived activator of caspases (Smac) can be liberated from the mitochondria into the cytoplasm to block the anti-apoptotic activity of IAPs [196, 197],

and a number of compounds designed as therapeutic targets imitate the structure of these molecules (Smac mimetics) [191].

Human—Patients with juvenile onset SLE show decreased expression of XIAP, cIAP1 and cIAP2 in their circulating neutrophil population [145].

Mouse—While IAPs have not been examined in the dendritic cells, murine studies show that elimination of IAPs in myeloid cells ($LysM^{cre/cre}cIAP1^{flox/flox}cIAP2^{-/-}$ and $LysM^{cre/cre}cIAP1^{flox/flox}cIAP2^{-/-}XIAP^{-/-}$) causes splenomegaly as well as a spontaneous inflammatory arthritis relating to myeloid cell dysfunction and mediated by TNF and IL-1β (TABLE 1) [198, 199]. However, despite the ensuing inflammation caused by myeloid-cell specific deletion of multiple IAPs, the effect of this deletion is not examined in the kidney [198, 199]. These data indicate that IAPs tightly control the apoptotic machinery, and although IAPs are linked to juvenile onset SLE, IAP activity in phagocytes in the kidney has yet to be examined in either humans or murine models of SLE.

4. Conclusions

The controlled removal of dying cells by professional phagocytes, such as dendritic cells and macrophages, is crucial for the maintenance of tissue integrity and homeostasis; however, when this process goes awry, inflammation and exposure to self-antigens can occur and autoimmunity may ensue, potentially within the kidney. The current standard-of-care treatment regimen for patients with class III/IV LN combines mycophenolate mofetil (MMF) and corticosteroids [200, 201]. Because of the acceptance of MMF as a first-line therapy and the limited predictive value of the diagnostic biopsy for long-term renal prognosis [55, 202], an argument exists against performing renal biopsies [203]. However, the rate of complete remission for the proliferative subtypes of LN is less than 50% despite the many advances in these immunosuppressive drug regimens [204–206]. Strikingly, permanent renal impairment still occurs in 40% of patients with class III-V LN [206, 207]. In light of the overall failure of the standard-of-care immunosuppressive treatments, it would argue that we currently have an incomplete comprehension of LN disease pathogenesis. Therefore, there is an emerging belief that emphasizes a new role for the renal biopsy that extends beyond its current use in histopathologic classification for diagnostic purposes [203]. Thus, renal biopsies, repeat biopsies in particular, have the potential to become valuable tools in understanding LN at the molecular, proteomic and lipidomic levels in a cell-specific context to predict treatment response and determine prognosis [10, 203]. It is evident, as examined here, that many cell-specific inflammatory pathways associated with the programmed cell death machinery contribute to the pathogenesis of LN. Should dendritic cells and macrophages themselves present with defects in signaling mediators and/or inhibitors of programmed cell death pathways, one can predict detrimental outcomes to the kidney. Early detection and treatment of LN are crucial in order to minimize the risk of irreversible renal impairment and to maintain proper kidney function. Therefore, analysis of cell-specific and pathway-specific immune dysregulation via utilization of the kidney biopsy has the potential to lead to personalized precision-based medicine for patients suffering from LN.

Acknowledgments

The authors declare they have no competing interests. This work was supported by grants from the National Institutes of Health to CMC (K01AR064313) and HP (AR064546, AR050250, AR054796, AI092490, HL108795) and the American Heart Association to FT (PRE21410010), as well as funds provided to HP by the Mabel Green Myers Chair of Medicine.

References

1. Borchers AT, Leibushor N, Naguwa SM, Cheema GS, Shoenfeld Y, Gershwin ME. Lupus nephritis: a critical review. Autoimmun Rev. 2012; 12:174–194. [PubMed: 22982174]
2. Madaio MP. The role of autoantibodies in the pathogenesis of lupus nephritis. Semin Nephrol. 1999; 19:48–56. [PubMed: 9952280]
3. Kalaaji M, Sturfelt G, Mjelle JE, Nossent H, Rekvig OP. Critical comparative analyses of anti-alpha-actinin and glomerulus-bound antibodies in human and murine lupus nephritis. Arthritis Rheum. 2006; 54:914–926. [PubMed: 16508974]
4. Trouw LA, Groeneveld TW, Seelen MA, Duijs JM, Bajema IM, Prins FA, Kishore U, Salant DJ, Verbeek JS, van Kooten C, Daha MR. Anti-C1q autoantibodies deposit in glomeruli but are only pathogenic in combination with glomerular C1q-containing immune complexes. J Clin Invest. 2004; 114:679–688. [PubMed: 15343386]
5. Ullal AJ, Reich CF 3rd, Clowse M, Criscione-Schreiber LG, Tochacek M, Monestier M, Pisetsky DS. Microparticles as antigenic targets of antibodies to DNA and nucleosomes in systemic lupus erythematosus. J Autoimmun. 2011; 36:173–180. [PubMed: 21376534]
6. Hakkim A, Furnrohr BG, Amann K, Laube B, Abed UA, Brinkmann V, Herrmann M, Voll RE, Zychlinsky A. Impairment of neutrophil extracellular trap degradation is associated with lupus nephritis. Proc Natl Acad Sci U S A. 2010; 107:9813–9818. [PubMed: 20439745]
7. Vlahakos DV, Foster MH, Adams S, Katz M, Ucci AA, Barrett KJ, Datta SK, Madaio MP. Anti-DNA antibodies form immune deposits at distinct glomerular and vascular sites. Kidney Int. 1992; 41:1690–1700. [PubMed: 1501424]
8. Liang Z, Xie C, Chen C, Kreska D, Hsu K, Li L, Zhou XJ, Mohan C. Pathogenic profiles and molecular signatures of antinuclear autoantibodies rescued from NZM2410 lupus mice. J Exp Med. 2004; 199:381–398. [PubMed: 14757744]
9. Clark MR, Trotter K, Chang A. The Pathogenesis and Therapeutic Implications of Tubulointerstitial Inflammation in Human Lupus Nephritis. Semin Nephrol. 2015; 35:455–464. [PubMed: 26573548]
10. Davidson A. What is damaging the kidney in lupus nephritis? Nat Rev Rheumatol. 2016; 12:143–153. [PubMed: 26581344]
11. Austin HA 3rd, Muenz LR, Joyce KM, Antonovych TT, Balow JE. Diffuse proliferative lupus nephritis: identification of specific pathologic features affecting renal outcome. Kidney Int. 1984; 25:689–695. [PubMed: 6482173]
12. Bergtold A, Gavhane A, D'Agati V, Madaio M, Clynes R. FcR-bearing myeloid cells are responsible for triggering murine lupus nephritis. J Immunol. 2006; 177:7287–7295. [PubMed: 17082647]
13. Kinloch AJ, Chang A, Ko K, Henry Dunand CJ, Henderson S, Maienschein-Cline M, Kaverina N, Rovin BH, Salgado Ferrer M, Wolfgeher D, Liarski V, Haddon DJ, Utz PJ, Wilson PC, Clark MR. Vimentin is a dominant target of in situ humoral immunity in human lupus tubulointerstitial nephritis. Arthritis & rheumatology. 2014; 66:3359–3370. [PubMed: 25306868]
14. Winchester R, Wiesendanger M, Zhang HZ, Steshenko V, Peterson K, Geraldino-Pardilla L, Ruiz-Vazquez E, D'Agati V. Immunologic characteristics of intrarenal T cells: trafficking of expanded CD8+ T cell beta-chain clonotypes in progressive lupus nephritis. Arthritis Rheum. 2012; 64:1589–1600. [PubMed: 22130908]
15. Condon MB, Ashby D, Pepper RJ, Cook HT, Levy JB, Griffith M, Cairns TD, Lightstone L. Prospective observational single-centre cohort study to evaluate the effectiveness of treating lupus nephritis with rituximab and mycophenolate mofetil but no oral steroids. Ann Rheum Dis. 2013; 72:1280–1286. [PubMed: 23740227]

16. Diaz-Lagares C, Croca S, Sangle S, Vital EM, Catapano F, Martinez-Berriotxoa A, Garcia-Hernandez F, Callejas-Rubio JL, Rascon J, D'Cruz D, Jayne D, Ruiz-Irastorza G, Emery P, Isenberg D, Ramos-Casals M, Khamashta MA, Registry U-B. Efficacy of rituximab in 164 patients with biopsy-proven lupus nephritis: pooled data from European cohorts. Autoimmun Rev. 2012; 11:357–364. [PubMed: 22032879]
17. Rovin BH, Furie R, Latinis K, Looney RJ, Fervenza FC, Sanchez-Guerrero J, Maciuca R, Zhang D, Garg JP, Brunetta P, Appel G, Group LI. Efficacy and safety of rituximab in patients with active proliferative lupus nephritis: the Lupus Nephritis Assessment with Rituximab study. Arthritis Rheum. 2012; 64:1215–1226. [PubMed: 22231479]
18. Lightstone L. The landscape after LUNAR: rituximab's crater-filled path. Arthritis Rheum. 2012; 64:962–965. [PubMed: 22231618]
19. Leadbetter EA, Rifkin IR, Hohlbaum AM, Beaudette BC, Shlomchik MJ, Marshak-Rothstein A. Chromatin-IgG complexes activate B cells by dual engagement of IgM and Toll-like receptors. Nature. 2002; 416:603–607. [PubMed: 11948342]
20. Ravetch JV, Kinet JP. Fc receptors. Annu Rev Immunol. 1991; 9:457–492. [PubMed: 1910686]
21. Ivashkiv LB. Cross-regulation of signaling by ITAM-associated receptors. Nat Immunol. 2009; 10:340–347. [PubMed: 19295630]
22. Nimmerjahn F, Ravetch JV. Fcgamma receptors as regulators of immune responses. Nat Rev Immunol. 2008; 8:34–47. [PubMed: 18064051]
23. Jonsen A, Gunnarsson I, Gullstrand B, Svenungsson E, Bengtsson AA, Nived O, Lundberg IE, Truedsson L, Sturfelt G. Association between SLE nephritis and polymorphic variants of the CRP and FcgammaRIIIa genes. Rheumatology (Oxford). 2007; 46:1417–1421. [PubMed: 17596285]
24. Floto RA, Clatworthy MR, Heilbronn KR, Rosner DR, MacAry PA, Rankin A, Lehner PJ, Ouwehand WH, Allen JM, Watkins NA, Smith KG. Loss of function of a lupus-associated FcgammaRIIb polymorphism through exclusion from lipid rafts. Nat Med. 2005; 11:1056–1058. [PubMed: 16170323]
25. Karassa FB, Trikalinos TA, Ioannidis JP. R-SLEm-ai Fc gamma, The Fc gamma RIIIA-F158 allele is a risk factor for the development of lupus nephritis: a meta-analysis. Kidney Int. 2003; 63:1475–1482. [PubMed: 12631364]
26. Karassa FB, Trikalinos TA, Ioannidis JP, Fcgamma R-SLEM-AI. Role of the Fcgamma receptor IIa polymorphism in susceptibility to systemic lupus erythematosus and lupus nephritis: a meta-analysis. Arthritis Rheum. 2002; 46:1563–1571. [PubMed: 12115187]
27. Gelmetti AP, Freitas AC, Woronik V, Barros RT, Bonfa E, Monteiro RC. Polymorphism of the FcgammaRIIalpha IgG receptor in patients with lupus nephritis and glomerulopathy. J Rheumatol. 2006; 33:523–530. [PubMed: 16511922]
28. Kang S, Rogers JL, Monteith AJ, Jiang C, Schmitz J, Clarke SH, Tarrant TK, Truong YK, Diaz M, Fedoriw Y, Vilen BJ. Apoptotic Debris Accumulates on Hematopoietic Cells and Promotes Disease in Murine and Human Systemic Lupus Erythematosus. J Immunol. 2016; 196:4030–4039. [PubMed: 27059595]
29. Bolland S, Ravetch JV. Spontaneous autoimmune disease in Fc(gamma)RIIB-deficient mice results from strain-specific epistasis. Immunity. 2000; 13:277–285. [PubMed: 10981970]
30. Madaio MP, Carlson J, Cataldo J, Ucci A, Migliorini P, Pankewycz O. Murine monoclonal anti-DNA antibodies bind directly to glomerular antigens and form immune deposits. J Immunol. 1987; 138:2883–2889. [PubMed: 3553329]
31. Segerer S, Schlondorff D. Role of chemokines for the localization of leukocyte subsets in the kidney. Semin Nephrol. 2007; 27:260–274. [PubMed: 17533005]
32. Barrat FJ, Meeker T, Gregorio J, Chan JH, Uematsu S, Akira S, Chang B, Duramad O, Coffman RL. Nucleic acids of mammalian origin can act as endogenous ligands for Toll-like receptors and may promote systemic lupus erythematosus. J Exp Med. 2005; 202:1131–1139. [PubMed: 16230478]
33. Geissmann F, Manz MG, Jung S, Sieweke MH, Merad M, Ley K. Development of monocytes, macrophages, and dendritic cells. Science. 2010; 327:656–661. [PubMed: 20133564]

34. Farache J, Zigmond E, Shakhar G, Jung S. Contributions of dendritic cells and macrophages to intestinal homeostasis and immune defense. Immunol Cell Biol. 2013; 91:232–239. [PubMed: 23399695]
35. Galli SJ, Borregaard N, Wynn TA. Phenotypic and functional plasticity of cells of innate immunity: macrophages, mast cells and neutrophils. Nat Immunol. 2011; 12:1035–1044. [PubMed: 22012443]
36. Teteris SA, Engel DR, Kurts C. Homeostatic and pathogenic role of renal dendritic cells. Kidney Int. 2011; 80:139–145. [PubMed: 21613986]
37. Sahu R, Bethunaickan R, Singh S, Davidson A. Structure and function of renal macrophages and dendritic cells from lupus-prone mice. Arthritis & rheumatology. 2014; 66:1596–1607. [PubMed: 24866269]
38. Heymann F, Meyer-Schwesinger C, Hamilton-Williams EE, Hammerich L, Panzer U, Kaden S, Quaggin SE, Floege J, Grone HJ, Kurts C. Kidney dendritic cell activation is required for progression of renal disease in a mouse model of glomerular injury. J Clin Invest. 2009; 119:1286–1297. [PubMed: 19381017]
39. Kassianos AJ, Wang X, Sampangi S, Muczynski K, Healy H, Wilkinson R. Increased tubulointerstitial recruitment of human CD141(hi) CLEC9A(+) and CD1c(+) myeloid dendritic cell subsets in renal fibrosis and chronic kidney disease. Am J Physiol Renal Physiol. 2013; 305:F1391–1401. [PubMed: 24049150]
40. Cheng M, Gu X, Herrera GA. Dendritic cells in renal biopsies of patients with acute tubulointerstitial nephritis. Hum Pathol. 2016; 54:113–120. [PubMed: 27085555]
41. Fiore N, Castellano G, Blasi A, Capobianco C, Loverre A, Montinaro V, Netti S, Torres D, Manno C, Grandaliano G, Ranieri E, Schena FP, Gesualdo L. Immature myeloid and plasmacytoid dendritic cells infiltrate renal tubulointerstitium in patients with lupus nephritis. Mol Immunol. 2008; 45:259–265. [PubMed: 17570528]
42. Tucci M, Quatraro C, Lombardi L, Pellegrino C, Dammacco F, Silvestris F. Glomerular accumulation of plasmacytoid dendritic cells in active lupus nephritis: role of interleukin-18. Arthritis Rheum. 2008; 58:251–262. [PubMed: 18163476]
43. Liu J, Karypis G, Hippen KL, Vegoe AL, Ruiz P, Gilkeson GS, Behrens TW. Genomic view of systemic autoimmunity in MRLlpr mice. Genes Immun. 2006; 7:156–168. [PubMed: 16508641]
44. Berthier CC, Bethunaickan R, Gonzalez-Rivera T, Nair V, Ramanujam M, Zhang W, Bottinger EP, Segerer S, Lindenmeyer M, Cohen CD, Davidson A, Kretzler M. Cross-species transcriptional network analysis defines shared inflammatory responses in murine and human lupus nephritis. J Immunol. 2012; 189:988–1001. [PubMed: 22723521]
45. Ronnblom L, Alm GV. The natural interferon-alpha producing cells in systemic lupus erythematosus. Hum Immunol. 2002; 63:1181–1193. [PubMed: 12480262]
46. van der Pouw Kraan TC, Wijbrandts CA, van Baarsen LG, Voskuyl AE, Rustenburg F, Baggen JM, Ibrahim SM, Fero M, Dijkmans BA, Tak PP, Verweij CL. Rheumatoid arthritis subtypes identified by genomic profiling of peripheral blood cells: assignment of a type I interferon signature in a subpopulation of patients. Ann Rheum Dis. 2007; 66:1008–1014. [PubMed: 17223656]
47. Fairhurst AM, Xie C, Fu Y, Wang A, Boudreaux C, Zhou XJ, Cibotti R, Coyle A, Connolly JE, Wakeland EK, Mohan C. Type I interferons produced by resident renal cells may promote end-organ disease in autoantibody-mediated glomerulonephritis. J Immunol. 2009; 183:6831–6838. [PubMed: 19864599]
48. Hashimoto D, Miller J, Merad M. Dendritic cell and macrophage heterogeneity in vivo. Immunity. 2011; 35:323–335. [PubMed: 21943488]
49. Roszer T. Understanding the Mysterious M2 Macrophage through Activation Markers and Effector Mechanisms. Mediators Inflamm. 2015; 2015:816460. [PubMed: 26089604]
50. Gordon S, Martinez FO. Alternative activation of macrophages: mechanism and functions. Immunity. 2010; 32:593–604. [PubMed: 20510870]
51. Odegaard JI, Chawla A. Alternative macrophage activation and metabolism. Annu Rev Pathol. 2011; 6:275–297. [PubMed: 21034223]
52. Martinez FO, Gordon S. The M1 and M2 paradigm of macrophage activation: time for reassessment. F1000Prime Rep. 2014; 6:13. [PubMed: 24669294]

53. Murray PJ, Allen JE, Biswas SK, Fisher EA, Gilroy DW, Goerdt S, Gordon S, Hamilton JA, Ivashkiv LB, Lawrence T, Locati M, Mantovani A, Martinez FO, Mege JL, Mosser DM, Natoli G, Saeij JP, Schultze JL, Shirey KA, Sica A, Suttles J, Udalova I, van Ginderachter JA, Vogel SN, Wynn TA. Macrophage Activation and Polarization: Nomenclature and Experimental Guidelines. Immunity. 2014; 41:14–20. [PubMed: 25035950]

54. Xue J, Schmidt SV, Sander J, Draffehn A, Krebs W, Quester I, De Nardo D, Gohel TD, Emde M, Schmidleithner L, Ganesan H, Nino-Castro A, Mallmann MR, Labzin L, Theis H, Kraut M, Beyer M, Latz E, Freeman TC, Ulas T, Schultze JL. Transcriptome-based network analysis reveals a spectrum model of human macrophage activation. Immunity. 2014; 40:274–288. [PubMed: 24530056]

55. Hill GS, Delahousse M, Nochy D, Remy P, Mignon F, Mery JP, Bariety J. Predictive power of the second renal biopsy in lupus nephritis: significance of macrophages. Kidney Int. 2001; 59:304–316. [PubMed: 11135084]

56. Duffield JS. Macrophages in kidney repair and regeneration. J Am Soc Nephrol. 2011; 22:199–201. [PubMed: 21289208]

57. Lech M, Anders HJ. Macrophages and fibrosis: How resident and infiltrating mononuclear phagocytes orchestrate all phases of tissue injury and repair. Biochim Biophys Acta. 2013; 1832:989–997. [PubMed: 23246690]

58. Bethunaickan R, Berthier CC, Ramanujam M, Sahu R, Zhang W, Sun Y, Bottinger EP, Ivashkiv L, Kretzler M, Davidson A. A unique hybrid renal mononuclear phagocyte activation phenotype in murine systemic lupus erythematosus nephritis. J Immunol. 2011; 186:4994–5003. [PubMed: 21411733]

59. Ginhoux F, Jung S. Monocytes and macrophages: developmental pathways and tissue homeostasis. Nat Rev Immunol. 2014; 14:392–404. [PubMed: 24854589]

60. Bethunaickan R, Berthier CC, Zhang W, Eksi R, Li HD, Guan Y, Kretzler M, Davidson A. Identification of stage-specific genes associated with lupus nephritis and response to remission induction in (NZB x NZW)F1 and NZM2410 mice. Arthritis & rheumatology. 2014; 66:2246–2258. [PubMed: 24757019]

61. Lin SL, Castano AP, Nowlin BT, Lupher ML Jr, Duffield JS. Bone marrow Ly6Chigh monocytes are selectively recruited to injured kidney and differentiate into functionally distinct populations. J Immunol. 2009; 183:6733–6743. [PubMed: 19864592]

62. Nathan C, Ding A. Nonresolving inflammation. Cell. 2010; 140:871–882. [PubMed: 20303877]

63. Triantafyllopoulou A, Franzke CW, Seshan SV, Perino G, Kalliolias GD, Ramanujam M, van Rooijen N, Davidson A, Ivashkiv LB. Proliferative lesions and metalloproteinase activity in murine lupus nephritis mediated by type I interferons and macrophages. Proc Natl Acad Sci U S A. 2010; 107:3012–3017. [PubMed: 20133703]

64. Chalmers SA, Chitu V, Ramanujam M, Putterman C. Therapeutic targeting of macrophages in lupus nephritis. Discov Med. 2015; 20:43–49. [PubMed: 26321086]

65. Denny MF, Chandaroy P, Killen PD, Caricchio R, Lewis EE, Richardson BC, Lee KD, Gavalchin J, Kaplan MJ. Accelerated macrophage apoptosis induces autoantibody formation and organ damage in systemic lupus erythematosus. J Immunol. 2006; 176:2095–2104. [PubMed: 16455965]

66. Fenton K. The effect of cell death in the initiation of lupus nephritis. Clin Exp Immunol. 2015; 179:11–16. [PubMed: 25041590]

67. Klaas M, Oetke C, Lewis LE, Erwig LP, Heikema AP, Easton A, Willison HJ, Crocker PR. Sialoadhesin promotes rapid proinflammatory and type I IFN responses to a sialylated pathogen, Campylobacter jejuni. J Immunol. 2012; 189:2414–2422. [PubMed: 22851711]

68. Ip CW, Kroner A, Crocker PR, Nave KA, Martini R. Sialoadhesin deficiency ameliorates myelin degeneration and axonopathic changes in the CNS of PLP overexpressing mice. Neurobiol Dis. 2007; 25:105–111. [PubMed: 17064921]

69. Kidder D, Richards HE, Lyons PA, Crocker PR. Sialoadhesin deficiency does not influence the severity of lupus nephritis in New Zealand black x New Zealand white F1 mice. Arthritis Res Ther. 2013; 15:R175. [PubMed: 24286366]

70. Biesen R, Demir C, Barkhudarova F, Grun JR, Steinbrich-Zollner M, Backhaus M, Haupl T, Rudwaleit M, Riemekasten G, Radbruch A, Hiepe F, Burmester GR, Grutzkau A. Sialic acid-

binding Ig-like lectin 1 expression in inflammatory and resident monocytes is a potential biomarker for monitoring disease activity and success of therapy in systemic lupus erythematosus. Arthritis Rheum. 2008; 58:1136–1145. [PubMed: 18383365]

71. Schwartz N, Goilav B, Putterman C. The pathogenesis, diagnosis and treatment of lupus nephritis. Curr Opin Rheumatol. 2014; 26:502–509. [PubMed: 25014039]
72. Martin F, Kearney JF. Marginal-zone B cells. Nat Rev Immunol. 2002; 2:323–335. [PubMed: 12033738]
73. Cinamon G, Zachariah MA, Lam OM, Foss FW Jr, Cyster JG. Follicular shuttling of marginal zone B cells facilitates antigen transport. Nat Immunol. 2008; 9:54–62. [PubMed: 18037889]
74. Kraal G. Cells in the marginal zone of the spleen. Int Rev Cytol. 1992; 132:31–74. [PubMed: 1555921]
75. You Y, Zhao H, Wang Y, Carter RH. Cutting edge: Primary and secondary effects of CD19 deficiency on cells of the marginal zone. J Immunol. 2009; 182:7343–7347. [PubMed: 19494255]
76. McGaha TL, Karlsson MC. Apoptotic cell responses in the splenic marginal zone: a paradigm for immunologic reactions to apoptotic antigens with implications for autoimmunity. Immunol Rev. 2016; 269:26–43. [PubMed: 26683143]
77. Arandjelovic S, Ravichandran KS. Phagocytosis of apoptotic cells in homeostasis. Nat Immunol. 2015; 16:907–917. [PubMed: 26287597]
78. Leventis PA, Grinstein S. The distribution and function of phosphatidylserine in cellular membranes. Annu Rev Biophys. 2010; 39:407–427. [PubMed: 20192774]
79. Wermeling F, Chen Y, Pikkarainen T, Scheynius A, Winqvist O, Izui S, Ravetch JV, Tryggvason K, Karlsson MC. Class A scavenger receptors regulate tolerance against apoptotic cells, and autoantibodies against these receptors are predictive of systemic lupus. J Exp Med. 2007; 204:2259–2265. [PubMed: 17893199]
80. Greenberg ME, Sun M, Zhang R, Febbraio M, Silverstein R, Hazen SL. Oxidized phosphatidylserine-CD36 interactions play an essential role in macrophage-dependent phagocytosis of apoptotic cells. J Exp Med. 2006; 203:2613–2625. [PubMed: 17101731]
81. Elomaa O, Kangas M, Sahlberg C, Tuukkanen J, Sormunen R, Liakka A, Thesleff I, Kraal G, Tryggvason K. Cloning of a novel bacteria-binding receptor structurally related to scavenger receptors and expressed in a subset of macrophages. Cell. 1995; 80:603–609. [PubMed: 7867067]
82. Boullier A, Friedman P, Harkewicz R, Hartvigsen K, Green SR, Almazan F, Dennis EA, Steinberg D, Witztum JL, Quehenberger O. Phosphocholine as a pattern recognition ligand for CD36. J Lipid Res. 2005; 46:969–976. [PubMed: 15722561]
83. Cohen PL, Caricchio R, Abraham V, Camenisch TD, Jennette JC, Roubey RA, Earp HS, Matsushima G, Reap EA. Delayed apoptotic cell clearance and lupus-like autoimmunity in mice lacking the c-mer membrane tyrosine kinase. J Exp Med. 2002; 196:135–140. [PubMed: 12093878]
84. Walport MJ, Davies KA, Botto M. C1q and systemic lupus erythematosus. Immunobiology. 1998; 199:265–285. [PubMed: 9777411]
85. Bijl M, Reefman E, Horst G, Limburg PC, Kallenberg CG. Reduced uptake of apoptotic cells by macrophages in systemic lupus erythematosus: correlates with decreased serum levels of complement. Ann Rheum Dis. 2006; 65:57–63. [PubMed: 15919679]
86. Botto M, Dell'Agnola C, Bygrave AE, Thompson EM, Cook HT, Petry F, Loos M, Pandolfi PP, Walport MJ. Homozygous C1q deficiency causes glomerulonephritis associated with multiple apoptotic bodies. Nat Genet. 1998; 19:56–59. [PubMed: 9590289]
87. Crocker PR, Paulson JC, Varki A. Siglecs and their roles in the immune system. Nat Rev Immunol. 2007; 7:255–266. [PubMed: 17380156]
88. Miyake Y, Asano K, Kaise H, Uemura M, Nakayama M, Tanaka M. Critical role of macrophages in the marginal zone in the suppression of immune responses to apoptotic cell-associated antigens. J Clin Invest. 2007; 117:2268–2278. [PubMed: 17657313]
89. Bratton DL, Henson PM. Apoptotic cell recognition: will the real phosphatidylserine receptor(s) please stand up? Curr Biol. 2008; 18:R76–79. [PubMed: 18211846]
90. Prabagar MG, Do Y, Ryu S, Park JY, Choi HJ, Choi WS, Yun TJ, Moon J, Choi IS, Ko K, Ko K, Young Shin C, Cheong C, Kang YS. SIGN-R1, a C-type lectin, enhances apoptotic cell clearance

through the complement deposition pathway by interacting with C1q in the spleen. Cell Death Differ. 2013; 20:535–545. [PubMed: 23238564]

91. Li H, Fu YX, Wu Q, Zhou Y, Crossman DK, Yang P, Li J, Luo B, Morel LM, Kabarowski JH, Yagita H, Ware CF, Hsu HC, Mountz JD. Interferon-induced mechanosensing defects impede apoptotic cell clearance in lupus. J Clin Invest. 2015; 125:2877–2890. [PubMed: 26098211]
92. Mountz JD, Yang P, Wu Q, Zhou J, Tousson A, Fitzgerald A, Allen J, Wang X, Cartner S, Grizzle WE, Yi N, Lu L, Williams RW, Hsu HC. Genetic segregation of spontaneous erosive arthritis and generalized autoimmune disease in the BXD2 recombinant inbred strain of mice. Scand J Immunol. 2005; 61:128–138. [PubMed: 15683449]
93. Li H, Wu Q, Li J, Yang P, Zhu Z, Luo B, Hsu HC, Mountz JD. Cutting Edge: defective follicular exclusion of apoptotic antigens due to marginal zone macrophage defects in autoimmune BXD2 mice. J Immunol. 2013; 190:4465–4469. [PubMed: 23543760]
94. Hsu HC, Yang P, Wang J, Wu Q, Myers R, Chen J, Yi J, Guentert T, Tousson A, Stanus AL, Le TV, Lorenz RG, Xu H, Kolls JK, Carter RH, Chaplin DD, Williams RW, Mountz JD. Interleukin 17-producing T helper cells and interleukin 17 orchestrate autoreactive germinal center development in autoimmune BXD2 mice. Nat Immunol. 2008; 9:166–175. [PubMed: 18157131]
95. Zhou Z, Niu H, Zheng YY, Morel L. Autoreactive marginal zone B cells enter the follicles and interact with CD4+ T cells in lupus-prone mice. BMC Immunol. 2011; 12:7. [PubMed: 21251257]
96. Artinger K, Kirsch AH, Aringer I, Schabhuttl C, Rosenkranz AR, Eller P, Rho E, Eller K. The Spleen Plays No Role in Nephrotoxic Serum Nephritis, but Constitutes a Place of Compensatory Haematopoiesis. PLoS One. 2015; 10:e0135087. [PubMed: 26247770]
97. Fletcher CA, Groom JR, Woehl B, Leung H, Mackay C, Mackay F. Development of autoimmune nephritis in genetically asplenic and splenectomized BAFF transgenic mice. J Autoimmun. 2011; 36:125–134. [PubMed: 21216131]
98. Smathers PA, Santoro TJ, Chused TM, Reeves JP, Steinberg AD. Studies of lymphoproliferation in MRL-lpr/lpr mice. J Immunol. 1984; 133:1955–1961. [PubMed: 6332142]
99. Ubara Y, Hara S, Katori H, Tagami T, Kitamura A, Yokota M, Matsushita Y, Takemoto F, Yamada A, Nagahama K, Hara M, Chayama K. Splenectomy may improve the glomerulopathy of type II mixed cryoglobulinemia. Am J Kidney Dis. 2000; 35:1186–1192. [PubMed: 10845834]
100. Hsu CY, Chen HJ, Hsu CY, Kao CH. Splenectomy increases the subsequent risk of systemic lupus erythematosus. Rheumatol Int. 2016; 36:271–276. [PubMed: 26527220]
101. Misra DP, Jain VK, Negi VS. Splenectomy increases the subsequent risk of systemic lupus erythematosus: a word of caution. Rheumatol Int. 2016; 36:277–278. [PubMed: 26661402]
102. Radic M, Marion T, Monestier M. Nucleosomes are exposed at the cell surface in apoptosis. J Immunol. 2004; 172:6692–6700. [PubMed: 15153485]
103. Munoz LE, Lauber K, Schiller M, Manfredi AA, Herrmann M. The role of defective clearance of apoptotic cells in systemic autoimmunity. Nat Rev Rheumatol. 2010; 6:280–289. [PubMed: 20431553]
104. Peter ME, Budd RC, Desbarats J, Hedrick SM, Hueber AO, Newell MK, Owen LB, Pope RM, Tschopp J, Wajant H, Wallach D, Wiltrout RH, Zornig M, Lynch DH. The CD95 receptor: apoptosis revisited. Cell. 2007; 129:447–450. [PubMed: 17482535]
105. Green DR. Apoptotic pathways: The roads to ruin. Cell. 1998; 94:695–698. [PubMed: 9753316]
106. Boatright KM, Deis C, Denault JB, Sutherlin DP, Salvesen GS. Activation of caspases-8 and -10 by FLIP(L). Biochem J. 2004; 382:651–657. [PubMed: 15209560]
107. Micheau O, Thome M, Schneider P, Holler N, Tschopp J, Nicholson DW, Briand C, Grutter MG. The long form of FLIP is an activator of caspase-8 at the Fas death-inducing signaling complex. J Biol Chem. 2002; 277:45162–45171. [PubMed: 12215447]
108. Luo X, Budihardjo I, Zou H, Slaughter C, Wang X. Bid, a Bcl-2 interacting protein mediates cytochrome c release from mitochondria in response to activation of cell surface death receptors. Cell. 1998; 94:481–490. [PubMed: 9727491]
109. Li P, Nijhawan D, Budihardjo I, Srinivasula SM, Ahmad M, Alnemri ES, Wang X. Cytochrome c and dATP-dependent formation of Apaf-1/caspase-9 complex initiates an apoptotic protease cascade. Cell. 1997; 91:479–489. [PubMed: 9390557]

110. Wang K, Yin XM, Chao DT, Milliman CL, Korsmeyer SJ. BID, a novel BH3 domain only death agonist. Genes Dev. 1996; 10:2859–2869. [PubMed: 8918887]
111. Moudi B, Salimi S, Farajian Mashhadi F, Sandoughi M, Zakeri Z. Association of FAS and FAS ligand genes polymorphism and risk of systemic lupus erythematosus. ScientificWorldJournal. 2013; 2013:176741. [PubMed: 24348139]
112. Bollain YGJJ, Arellano-Rodriguez M, de Torres-Del-Muro FJ, Daza-Benitez L, Munoz-Valle JF, Avalos-Diaz E, Herrera-Esparza R. Soluble fas and the -670 polymorphism of fas in lupus nephritis. Int J Nephrol. 2014; 2014:780406. [PubMed: 25505993]
113. Cohen PL, Eisenberg RA. Lpr and gld: single gene models of systemic autoimmunity and lymphoproliferative disease. Annu Rev Immunol. 1991; 9:243–269. [PubMed: 1910678]
114. Ito MR, Terasaki S, Itoh J, Katoh H, Yonehara S, Nose M. Rheumatic diseases in an MRL strain of mice with a deficit in the functional Fas ligand. Arthritis Rheum. 1997; 40:1054–1063. [PubMed: 9182916]
115. Teichmann LL, Ols ML, Kashgarian M, Reizis B, Kaplan DH, Shlomchik MJ. Dendritic cells in lupus are not required for activation of T and B cells but promote their expansion, resulting in tissue damage. Immunity. 2010; 33:967–978. [PubMed: 21167752]
116. Lenda DM, Kikawada E, Stanley ER, Kelley VR. Reduced macrophage recruitment, proliferation, and activation in colony-stimulating factor-1-deficient mice results in decreased tubular apoptosis during renal inflammation. J Immunol. 2003; 170:3254–3262. [PubMed: 12626584]
117. Tesch GH, Maifert S, Schwarting A, Rollins BJ, Kelley VR. Monocyte chemoattractant protein 1-dependent leukocytic infiltrates are responsible for autoimmune disease in MRL-Fas(lpr) mice. J Exp Med. 1999; 190:1813–1824. [PubMed: 10601356]
118. Perez de Lema G, Maier H, Franz TJ, Escribese M, Chilla S, Segerer S, Camarasa N, Schmid H, Banas B, Kalaydjiev S, Busch DH, Pfeffer K, Mampaso F, Schlondorff D, Luckow B. Chemokine receptor Ccr2 deficiency reduces renal disease and prolongs survival in MRL/lpr lupus-prone mice. J Am Soc Nephrol. 2005; 16:3592–3601. [PubMed: 16267157]
119. Inoue A, Hasegawa H, Kohno M, Ito MR, Terada M, Imai T, Yoshie O, Nose M, Fujita S. Antagonist of fractalkine (CX3CL1) delays the initiation and ameliorates the progression of lupus nephritis in MRL/lpr mice. Arthritis Rheum. 2005; 52:1522–1533. [PubMed: 15880599]
120. Stranges PB, Watson J, Cooper CJ, Choisy-Rossi CM, Stonebraker AC, Beighton RA, Hartig H, Sundberg JP, Servick S, Kaufmann G, Fink PJ, Chervonsky AV. Elimination of antigen-presenting cells and autoreactive T cells by Fas contributes to prevention of autoimmunity. Immunity. 2007; 26:629–641. [PubMed: 17509906]
121. Cuda CM, Agrawal H, Misharin AV, Haines GK 3rd, Hutcheson J, Weber E, Schoenfeldt JA, Mohan C, Pope RM, Perlman H. Requirement of myeloid cell-specific Fas expression for prevention of systemic autoimmunity in mice. Arthritis Rheum. 2012; 64:808–820. [PubMed: 22143975]
122. Richez C, Blanco P, Rifkin I, Moreau JF, Schaeverbeke T. Role for toll-like receptors in autoimmune disease: the example of systemic lupus erythematosus. Joint Bone Spine. 2010; 78:124–130. [PubMed: 20961794]
123. Zhu L, Yang X, Chen W, Li X, Ji Y, Mao H, Nie J, Yu X. Decreased expressions of the TNF-alpha signaling adapters in peripheral blood mononuclear cells (PBMCs) are correlated with disease activity in patients with systemic lupus erythematosus. Clin Rheumatol. 2007; 26:1481–1489. [PubMed: 17235653]
124. Parikh SV, Malvar A, Song H, Alberton V, Lococo B, Vance J, Zhang J, Yu L, Rovin BH. Characterising the immune profile of the kidney biopsy at lupus nephritis flare differentiates early treatment responders from non-responders. Lupus Sci Med. 2015; 2:e000112. [PubMed: 26629350]
125. Young JA, He TH, Reizis B, Winoto A. Commensal microbiota are required for systemic inflammation triggered by necrotic dendritic cells. Cell Rep. 2013; 3:1932–1944. [PubMed: 23727238]
126. Schock SN, Young JA, He TH, Sun Y, Winoto A. Deletion of FADD in Macrophages and Granulocytes Results in RIP3- and MyD88-Dependent Systemic Inflammation. PLoS One. 2015; 10:e0124391. [PubMed: 25874713]

127. Ma Y, Liu H, Tu-Rapp H, Thiesen HJ, Ibrahim SM, Cole SM, Pope RM. Fas ligation on macrophages enhances IL-1R1-Toll-like receptor 4 signaling and promotes chronic inflammation. Nat Immunol. 2004

128. Espinosa A, Zhou W, Ek M, Hedlund M, Brauner S, Popovic K, Horvath L, Wallerskog T, Oukka M, Nyberg F, Kuchroo VK, Wahren-Herlenius M. The Sjogren's syndrome-associated autoantigen Ro52 is an E3 ligase that regulates proliferation and cell death. J Immunol. 2006; 176:6277–6285. [PubMed: 16670339]

129. Zhang J, Fang L, Zhu X, Qiao Y, Yu M, Wang L, Chen Y, Yin W, Hua ZC. Ro52/SSA sensitizes cells to death receptor-induced apoptosis by down-regulating c-FLIP(L). Cell Biol Int. 2012; 36:463–468. [PubMed: 22288650]

130. Tao J, Dong J, Li Y, Liu YQ, Yang J, Wu Y, Li L, Shen GX, Tan ZJ, Tu YT. Up-regulation of cellular FLICE-inhibitory protein in peripheral blood B lymphocytes in patients with systemic lupus erythematosus is associated with clinical characteristics. J Eur Acad Dermatol Venereol. 2009; 23:433–437. [PubMed: 19335730]

131. Huang QQ, Perlman H, Birkett R, Doyle R, Fang D, Haines GK, Robinson W, Datta S, Huang Z, Li QZ, Phee H, Pope RM. CD11c-mediated deletion of Flip promotes autoreactivity and inflammatory arthritis. Nat Commun. 2015; 6:7086. [PubMed: 25963626]

132. Wu YJ, Wu YH, Mo ST, Hsiao HW, He YW, Lai MZ. Cellular FLIP Inhibits Myeloid Cell Activation by Suppressing Selective Innate Signaling. J Immunol. 2015; 195:2612–2623. [PubMed: 26238491]

133. Kamada N, Nunez G. Regulation of the immune system by the resident intestinal bacteria. Gastroenterology. 2014; 146:1477–1488. [PubMed: 24503128]

134. Kabat AM, Srinivasan N, Maloy KJ. Modulation of immune development and function by intestinal microbiota. Trends Immunol. 2014; 35:507–517. [PubMed: 25172617]

135. Lukens JR, Gurung P, Vogel P, Johnson GR, Carter RA, McGoldrick DJ, Bandi SR, Calabrese CR, Vande Walle L, Lamkanfi M, Kanneganti TD. Dietary modulation of the microbiome affects autoinflammatory disease. Nature. 2014; 516:246–249. [PubMed: 25274309]

136. Huang QQ, Perlman H, Huang Z, Birkett R, Kan L, Agrawal H, Misharin A, Gurbuxani S, Crispino JD, Pope RM. FLIP: a novel regulator of macrophage differentiation and granulocyte homeostasis. Blood. 2010; 116:4968–4977. [PubMed: 20724542]

137. Gordy C, Pua H, Sempowski GD, He YW. Regulation of steady-state neutrophil homeostasis by macrophages. Blood. 2011; 117:618–629. [PubMed: 20980680]

138. Helfer B, Boswell BC, Finlay D, Cipres A, Vuori K, Bong Kang T, Wallach D, Dorfleutner A, Lahti JM, Flynn DC, Frisch SM. Caspase-8 promotes cell motility and calpain activity under nonapoptotic conditions. Cancer Res. 2006; 66:4273–4278. [PubMed: 16618751]

139. Dohrman A, Kataoka T, Cuenin S, Russell JQ, Tschopp J, Budd RC. Cellular FLIP (long form) regulates CD8+ T cell activation through caspase-8-dependent NF-kappa B activation. J Immunol. 2005; 174:5270–5278. [PubMed: 15843523]

140. Rajput A, Kovalenko A, Bogdanov K, Yang SH, Kang TB, Kim JC, Du J, Wallach D. RIG-I RNA helicase activation of IRF3 transcription factor is negatively regulated by caspase-8-mediated cleavage of the RIP1 protein. Immunity. 2011; 34:340–351. [PubMed: 21419663]

141. Kovalenko A, Kim JC, Kang TB, Rajput A, Bogdanov K, Dittrich-Breiholz O, Kracht M, Brenner O, Wallach D. Caspase-8 deficiency in epidermal keratinocytes triggers an inflammatory skin disease. J Exp Med. 2009; 206:2161–2177. [PubMed: 19720838]

142. Hu WH, Johnson H, Shu HB. Activation of NF-kappaB by FADD, Casper, and caspase-8. J Biol Chem. 2000; 275:10838–10844. [PubMed: 10753878]

143. Sears N, Sen GC, Stark GR, Chattopadhyay S. Caspase-8-mediated cleavage inhibits IRF-3 protein by facilitating its proteasome-mediated degradation. J Biol Chem. 2011; 286:33037–33044. [PubMed: 21816816]

144. Ueki A, Isozaki Y, Tomokuni A, Hatayama T, Ueki H, Kusaka M, Shiwa M, Arikuni H, Takeshita T, Morimoto K. Intramolecular epitope spreading among anti-caspase-8 autoantibodies in patients with silicosis, systemic sclerosis and systemic lupus erythematosus, as well as in healthy individuals. Clin Exp Immunol. 2002; 129:556–561. [PubMed: 12197899]

145. Midgley A, Mayer K, Edwards SW, Beresford MW. Differential expression of factors involved in the intrinsic and extrinsic apoptotic pathways in juvenile systemic lupus erythematosus. Lupus. 2011; 20:71–79. [PubMed: 21078760]

146. Horiuchi T, Himeji D, Tsukamoto H, Harashima S, Hashimura C, Hayashi K. Dominant expression of a novel splice variant of caspase-8 in human peripheral blood lymphocytes. Biochem Biophys Res Commun. 2000; 272:877–881. [PubMed: 10860845]

147. Cuda CM, Misharin AV, Gierut AK, Saber R, Haines GK 3rd, Hutcheson J, Hedrick SM, Mohan C, Budinger GS, Stehlik C, Perlman H. Caspase-8 Acts as a Molecular Rheostat To Limit RIPK1- and MyD88-Mediated Dendritic Cell Activation. J Immunol. 2014; 192:5548–5560. [PubMed: 24808358]

148. Kang TB, Yang SH, Toth B, Kovalenko A, Wallach D. Caspase-8 blocks kinase RIPK3-mediated activation of the NLRP3 inflammasome. Immunity. 2013; 38:27–40. [PubMed: 23260196]

149. Cuda CM, Misharin AV, Khare S, Saber R, Tsai F, Archer AM, Homan PJ, Haines GK 3rd, Hutcheson J, Dorfleutner A, Budinger GR, Stehlik C, Perlman H. Conditional deletion of caspase-8 in macrophages alters macrophage activation in a RIPK-dependent manner. Arthritis Res Ther. 2015; 17:291. [PubMed: 26471282]

150. Adams JM, Cory S. The Bcl-2 protein family: arbiters of cell survival. Science. 1998; 281:1322–1326. [PubMed: 9735050]

151. Delbridge AR, Strasser A. The BCL-2 protein family, BH3-mimetics and cancer therapy. Cell Death Differ. 2015; 22:1071–1080. [PubMed: 25952548]

152. Opferman JT. Attacking cancer's Achilles heel: antagonism of anti-apoptotic BCL-2 family members. FEBS J. 2015

153. Martinez-Valle F, Balada E, Ordi-Ros J, Bujan-Rivas S, Sellas-Fernandez A, Vilardell-Tarres M. DNase1 activity in systemic lupus erythematosus patients with and without nephropathy. Rheumatol Int. 2010; 30:1601–1604. [PubMed: 19844716]

154. Panneer D, Antony PT, Negi VS. Q222R polymorphism in DNAse I gene is a risk factor for nephritis in South Indian SLE patients. Lupus. 2013; 22:996–1000. [PubMed: 23963431]

155. Seredkina N, Zykova SN, Rekvig OP. Progression of murine lupus nephritis is linked to acquired renal Dnase1 deficiency and not to up-regulated apoptosis. Am J Pathol. 2009; 175:97–106. [PubMed: 19528352]

156. Kalaaji M, Mortensen E, Jorgensen L, Olsen R, Rekvig OP. Nephritogenic lupus antibodies recognize glomerular basement membrane-associated chromatin fragments released from apoptotic intraglomerular cells. Am J Pathol. 2006; 168:1779–1792. [PubMed: 16723695]

157. Ko K, Wang J, Perper S, Jiang Y, Yanez D, Kaverina N, Ai J, Liarski VM, Chang A, Peng Y, Lan L, Westmoreland S, Olson L, Giger ML, Wang LC, Clark MR. BCL-2 as a Therapeutic Target in Human Tubulointerstitial Inflammation. Arthritis & rheumatology. 2016

158. Bardwell PD, Gu J, McCarthy D, Wallace C, Bryant S, Goess C, Mathieu S, Grinnell C, Erickson J, Rosenberg SH, Schwartz AJ, Hugunin M, Tarcsa E, Elmore SW, McRae B, Murtaza A, Wang LC, Ghayur T. The Bcl-2 family antagonist ABT-737 significantly inhibits multiple animal models of autoimmunity. J Immunol. 2009; 182:7482–7489. [PubMed: 19494271]

159. Zhan Y, Carrington EM, Ko HJ, Vikstrom IB, Oon S, Zhang JG, Vremec D, Brady JL, Bouillet P, Wu L, Huang DC, Wicks IP, Morand EF, Strasser A, Lew AM. Bcl-2 antagonists kill plasmacytoid dendritic cells from lupus-prone mice and dampen interferon-alpha production. Arthritis Rheumatol. 2015; 67:797–808. [PubMed: 25418983]

160. Zhou P, Levy NB, Xie H, Qian L, Lee CY, Gascoyne RD, Craig RW. MCL1 transgenic mice exhibit a high incidence of B-cell lymphoma manifested as a spectrum of histologic subtypes. Blood. 2001; 97:3902–3909. [PubMed: 11389033]

161. Egle A, Harris AW, Bath ML, O'Reilly L, Cory S. VavP-Bcl2 transgenic mice develop follicular lymphoma preceded by germinal center hyperplasia. Blood. 2004; 103:2276–2283. [PubMed: 14630790]

162. Ogilvy S, Metcalf D, Print CG, Bath ML, Harris AW, Adams JM. Constitutive Bcl-2 expression throughout the hematopoietic compartment affects multiple lineages and enhances progenitor cell survival. Proc Natl Acad Sci U S A. 1999; 96:14943–14948. [PubMed: 10611317]

163. Doerflinger M, Glab JA, Puthalakath H. BH3-only proteins: a 20-year stock-take. FEBS J. 2015; 282:1006–1016. [PubMed: 25565426]
164. Danial NN, Gramm CF, Scorrano L, Zhang CY, Krauss S, Ranger AM, Datta SR, Greenberg ME, Licklider LJ, Lowell BB, Gygi SP, Korsmeyer SJ. BAD and glucokinase reside in a mitochondrial complex that integrates glycolysis and apoptosis. Nature. 2003; 424:952–956. [PubMed: 12931191]
165. Esposti MD, Erler JT, Hickman JA, Dive C. Bid, a widely expressed proapoptotic protein of the Bcl-2 family, displays lipid transfer activity. Mol Cell Biol. 2001; 21:7268–7276. [PubMed: 11585909]
166. Yeretssian G, Correa RG, Doiron K, Fitzgerald P, Dillon CP, Green DR, Reed JC, Saleh M. Non-apoptotic role of BID in inflammation and innate immunity. Nature. 2011; 474:96–99. [PubMed: 21552281]
167. Bouillet P, Metcalf D, Huang DC, Tarlinton DM, Kay TW, Kontgen F, Adams JM, Strasser A. Proapoptotic Bcl-2 relative Bim required for certain apoptotic responses, leukocyte homeostasis, and to preclude autoimmunity. Science. 1999; 286:1735–1738. [PubMed: 10576740]
168. Hutcheson J, Scatizzi JC, Siddiqui AM, Haines GK 3rd, Wu T, Li QZ, Davis LS, Mohan C, Perlman H. Combined deficiency of proapoptotic regulators Bim and Fas results in the early onset of systemic autoimmunity. Immunity. 2008; 28:206–217. [PubMed: 18275831]
169. Labi V, Woess C, Tuzlak S, Erlacher M, Bouillet P, Strasser A, Tzankov A, Villunger A. Deregulated cell death and lymphocyte homeostasis cause premature lethality in mice lacking the BH3-only proteins Bim and Bmf. Blood. 2014; 123:2652–2662. [PubMed: 24632712]
170. Gautier EL, Huby T, Saint-Charles F, Ouzilleau B, Chapman MJ, Lesnik P. Enhanced dendritic cell survival attenuates lipopolysaccharide-induced immunosuppression and increases resistance to lethal endotoxic shock. J Immunol. 2008; 180:6941–6946. [PubMed: 18453615]
171. Nopora A, Brocker T. Bcl-2 controls dendritic cell longevity in vivo. J Immunol. 2002; 169:3006–3014. [PubMed: 12218115]
172. Hou WS, Van Parijs L. A Bcl-2-dependent molecular timer regulates the lifespan and immunogenicity of dendritic cells. Nat Immunol. 2004; 5:583–589. [PubMed: 15133508]
173. Chen M, Huang L, Wang J. Deficiency of Bim in dendritic cells contributes to overactivation of lymphocytes and autoimmunity. Blood. 2007; 109:4360–4367. [PubMed: 17227827]
174. Chen M, Huang L, Wang J. Deficiency of Bim in dendritic cells contributes to over-activation of lymphocytes and autoimmunity. Blood. 2007
175. Scatizzi JC, Hutcheson J, Pope RM, Firestein GS, Koch AE, Mavers M, Smason A, Agrawal H, Haines GK 3rd, Chandel NS, Hotchkiss RS, Perlman H. Bim-Bcl-2 homology 3 mimetic therapy is effective at suppressing inflammatory arthritis through the activation of myeloid cell apoptosis. Arthritis Rheum. 2010; 62:441–451. [PubMed: 20112357]
176. Sheibani N, Morrison ME, Gurel Z, Park S, Sorenson CM. BIM deficiency differentially impacts the function of kidney endothelial and epithelial cells through modulation of their local microenvironment. Am J Physiol Renal Physiol. 2012; 302:F809–819. [PubMed: 22169007]
177. Reginato MJ, Mills KR, Paulus JK, Lynch DK, Sgroi DC, Debnath J, Muthuswamy SK, Brugge JS. Integrins and EGFR coordinately regulate the pro-apoptotic protein Bim to prevent anoikis. Nat Cell Biol. 2003; 5:733–740. [PubMed: 12844146]
178. Nakamura T, Ebihara I, Tomino Y, Koide H. Effect of a specific endothelin A receptor antagonist on murine lupus nephritis. Kidney Int. 1995; 47:481–489. [PubMed: 7723234]
179. Pasparakis M, Vandenabeele P. Necroptosis and its role in inflammation. Nature. 2015; 517:311–320. [PubMed: 25592536]
180. Oberst A, Dillon CP, Weinlich R, McCormick LL, Fitzgerald P, Pop C, Hakem R, Salvesen GS, Green DR. Catalytic activity of the caspase-8-FLIP(L) complex inhibits RIPK3-dependent necrosis. Nature. 2011; 471:363–367. [PubMed: 21368763]
181. Hutcheson J, Perlman H. BH3-only proteins in rheumatoid arthritis: potential targets for therapeutic intervention. Oncogene. 2008; 27(Suppl 1):S168–175. [PubMed: 19641502]
182. Feoktistova M, Geserick P, Kellert B, Dimitrova DP, Langlais C, Hupe M, Cain K, MacFarlane M, Hacker G, Leverkus M. cIAPs block Ripoptosome formation, a RIP1/caspase-8 containing

intracellular cell death complex differentially regulated by cFLIP isoforms. Mol Cell. 2011; 43:449–463. [PubMed: 21737330]

183. Vince JE, Wong WW, Gentle I, Lawlor KE, Allam R, O'Reilly L, Mason K, Gross O, Ma S, Guarda G, Anderton H, Castillo R, Hacker G, Silke J, Tschopp J. Inhibitor of apoptosis proteins limit RIP3 kinase-dependent interleukin-1 activation. Immunity. 2012; 36:215–227. [PubMed: 22365665]
184. Gurung P, Anand PK, Malireddi RK, Vande Walle L, Van Opdenbosch N, Dillon CP, Weinlich R, Green DR, Lamkanfi M, Kanneganti TD. FADD and Caspase-8 Mediate Priming and Activation of the Canonical and Noncanonical Nlrp3 Inflammasomes. J Immunol. 2014; 192:1835–1846. [PubMed: 24453255]
185. Shenderov K, Riteau N, Yip R, Mayer-Barber KD, Oland S, Hieny S, Fitzgerald P, Oberst A, Dillon CP, Green DR, Cerundolo V, Sher A. Cutting Edge: Endoplasmic Reticulum Stress Licenses Macrophages To Produce Mature IL-1beta in Response to TLR4 Stimulation through a Caspase-8- and TRIF-Dependent Pathway. J Immunol. 2014; 192:2029–2033. [PubMed: 24489101]
186. Zhang H, Zhou X, McQuade T, Li J, Chan FK, Zhang J. Functional complementation between FADD and RIP1 in embryos and lymphocytes. Nature. 2011; 471:373–376. [PubMed: 21368761]
187. Newton K, Sun X, Dixit VM. Kinase RIP3 is dispensable for normal NF-kappa Bs, signaling by the B-cell and T-cell receptors, tumor necrosis factor receptor 1, and Toll-like receptors 2 and 4. Mol Cell Biol. 2004; 24:1464–1469. [PubMed: 14749364]
188. Kaiser WJ, Upton JW, Long AB, Livingston-Rosanoff D, Daley-Bauer LP, Hakem R, Caspary T, Mocarski ES. RIP3 mediates the embryonic lethality of caspase-8-deficient mice. Nature. 2011; 471:368–372. [PubMed: 21368762]
189. Dillon CP, Oberst A, Weinlich R, Janke LJ, Kang TB, Ben-Moshe T, Mak TW, Wallach D, Green DR. Survival function of the FADD-CASPASE-8-cFLIP(L) complex. Cell Rep. 2012; 1:401–407. [PubMed: 22675671]
190. Deveraux QL, Takahashi R, Salvesen GS, Reed JC. X-linked IAP is a direct inhibitor of cell-death proteases. Nature. 1997; 388:300–304. [PubMed: 9230442]
191. Lattuada D, Casnici C, Crotta K, Seneci PF, Corradini C, Truzzi M, Ingegnoli F, Marelli O. Proapoptotic activity of a monomeric smac mimetic on human fibroblast-like synoviocytes from patients with rheumatoid arthritis. Inflammation. 2015; 38:102–109. [PubMed: 25212046]
192. Deveraux QL, Roy N, Stennicke HR, Van Arsdale T, Zhou Q, Srinivasula SM, Alnemri ES, Salvesen GS, Reed JC. IAPs block apoptotic events induced by caspase-8 and cytochrome c by direct inhibition of distinct caspases. EMBO J. 1998; 17:2215–2223. [PubMed: 9545235]
193. Wang L, Du F, Wang X. TNF-alpha induces two distinct caspase-8 activation pathways. Cell. 2008; 133:693–703. [PubMed: 18485876]
194. Eckelman BP, Salvesen GS. The human anti-apoptotic proteins cIAP1 and cIAP2 bind but do not inhibit caspases. J Biol Chem. 2006; 281:3254–3260. [PubMed: 16339151]
195. Mahoney DJ, Cheung HH, Mrad RL, Plenchette S, Simard C, Enwere E, Arora V, Mak TW, Lacasse EC, Waring J, Korneluk RG. Both cIAP1 and cIAP2 regulate TNFalpha-mediated NF-kappaB activation. Proc Natl Acad Sci U S A. 2008; 105:11778–11783. [PubMed: 18697935]
196. Du C, Fang M, Li Y, Li L, Wang X. Smac, a mitochondrial protein that promotes cytochrome c-dependent caspase activation by eliminating IAP inhibition. Cell. 2000; 102:33–42. [PubMed: 10929711]
197. Verhagen AM, Ekert PG, Pakusch M, Silke J, Connolly LM, Reid GE, Moritz RL, Simpson RJ, Vaux DL. Identification of DIABLO, a mammalian protein that promotes apoptosis by binding to and antagonizing IAP proteins. Cell. 2000; 102:43–53. [PubMed: 10929712]
198. Lawlor KE, Khan N, Mildenhall A, Gerlic M, Croker BA, D'Cruz AA, Hall C, Kaur Spall S, Anderton H, Masters SL, Rashidi M, Wicks IP, Alexander WS, Mitsuuchi Y, Benetatos CA, Condon SM, Wong WW, Silke J, Vaux DL, Vince JE. RIPK3 promotes cell death and NLRP3 inflammasome activation in the absence of MLKL. Nat Commun. 2015; 6:6282. [PubMed: 25693118]
199. Wong WW, Vince JE, Lalaoui N, Lawlor KE, Chau D, Bankovacki A, Anderton H, Metcalf D, O'Reilly L, Jost PJ, Murphy JM, Alexander WS, Strasser A, Vaux DL, Silke J. cIAPs and XIAP

regulate myelopoiesis through cytokine production in an RIPK1- and RIPK3-dependent manner. Blood. 2014; 123:2562–2572. [PubMed: 24497535]

200. Henderson L, Masson P, Craig JC, Flanc RS, Roberts MA, Strippoli GF, Webster AC. Treatment for lupus nephritis. Cochrane Database Syst Rev. 2012; 12:CD002922. [PubMed: 23235592]
201. Holdsworth SR, Gan PY, Kitching AR. Biologics for the treatment of autoimmune renal diseases. Nat Rev Nephrol. 2016; 12:217–231. [PubMed: 26949177]
202. Askenazi D, Myones B, Kamdar A, Warren R, Perez M, De Guzman M, Minta A, Hicks MJ, Kale A. Outcomes of children with proliferative lupus nephritis: the role of protocol renal biopsy. Pediatr Nephrol. 2007; 22:981–986. [PubMed: 17334789]
203. Parikh SV, Alvarado A, Malvar A, Rovin BH. The Kidney Biopsy in Lupus Nephritis: Past, Present, and Future. Semin Nephrol. 2015; 35:465–477. [PubMed: 26573549]
204. Dooley MA, Jayne D, Ginzler EM, Isenberg D, Olsen NJ, Wofsy D, Eitner F, Appel GB, Contreras G, Lisk L, Solomons N, Group A. Mycophenolate versus azathioprine as maintenance therapy for lupus nephritis. N Engl J Med. 2011; 365:1886–1895. [PubMed: 22087680]
205. Ginzler EM, Wax S, Rajeswaran A, Copt S, Hillson J, Ramos E, Singer NG. Atacicept in combination with MMF and corticosteroids in lupus nephritis: results of a prematurely terminated trial. Arthritis Res Ther. 2012; 14:R33. [PubMed: 22325903]
206. Houssiau FA, Lauwerys BR. Current management of lupus nephritis. Best Pract Res Clin Rheumatol. 2013; 27:319–328. [PubMed: 24238689]
207. Contreras G, Pardo V, Cely C, Borja E, Hurtado A, De La Cuesta C, Iqbal K, Lenz O, Asif A, Nahar N, Leclerq B, Leon C, Schulman I, Ramirez-Seijas F, Paredes A, Cepero A, Khan T, Pachon F, Tozman E, Barreto G, Hoffman D, Almeida Suarez M, Busse JC, Esquenazi M, Esquenazi A, Garcia Mayol L, Garcia Estrada H. Factors associated with poor outcomes in patients with lupus nephritis. Lupus. 2005; 14:890–895. [PubMed: 16335581]

Highlights

- As damage to the kidney as a consequence of lupus nephritis (LN) is one of the most prevalent and severe outcomes, understanding the underlying immunologic mechanisms by which this injury occurs could be critical for the prevention of permanent renal impairment.
- Phagocyte populations of the innate immune system, including dendritic cells and macrophages, have gained considerable traction as critical mediators of LN-associated damage.
- Examination of both human SLE and murine models of SLE reveals that disruptions in the normal function of programmed cell death machinery, with emphasis on their functions within dendritic cells and macrophages, can contribute to LN pathogenesis.
- Further analysis of the kidney biopsy at cell-specific molecular, proteomic and lipidomic levels may provide the vital information we currently lack for the optimization of personalized precision-based therpies for patients suffering from LN.

Table 1

SLE-like disease and LN in murine models with defects in cell death pathways

Protein	Mouse model	Cell types affected	Presence of SLE-like disease	Presence of Lupus Nephritis
Extrinsic apoptotic pathway				
Fas	MRL.*Fas*^{lpr}	all cells	++++ [114]	++++ [114]
	CD11c^{cre}*Fas*$^{flox/flox}$	dendritic cells	++ [120]	?
	LysM$^{cre/cre}$*Fas*$^{flox/flox}$	monocytes/ macrophages/ neutrophils	++ [121]	++ [121]
FADD	*CD11c*^{cre}*FADD*$^{flox/flox}$	dendritic cells	++ [125]	?
	LysM$^{cre/cre}$*FADD*$^{lox/flox}$	monocytes/ macrophages/ neutrophils	++ [126]	?
FLIP	*CD11c*^{cre}*Flip*$^{flox/flox}$	dendritic cells	- [131]	?
	LysM$^{cre/cre}$*Flip*$^{del/flox}$	monocytes/ macrophages/ neutrophils	NA [136]	NA [136]
	LysM$^{cre/+}$*Flip*$^{del/flox}$	monocytes/ macrophages/ neutrophils	- [136]	?
Caspase-8	*CD11c*^{cre}*Casp8*$^{flox/flox}$	dendritic cells	+++ [147, 148]	+++ [147, 148]
	LysM$^{cre/cre}$*Casp8*$^{flox/flox}$	monocytes/ macrophages/ neutrophils	++ [149]	- [149]
Intrinsic apoptotic pathway				
Mcl-1	Mcl-1	all hematopoietic cells	- [160]	?
Bcl2	Vav(P)-Bcl2	all hematopoietic cells	+ [162]	++ [161]
Bim	*Bim*$^{-/-}$	all cells	+++ [167, 168]	+++ [167, 168]
	Bim$^{-/-}$.*Fas*^{lpr}	all cells	+++ [168]	+++ [168]
	Bim$^{-/-}$*Bmf*$^{-/-}$	all cells	+++ [169]	+++ [169]
Necroptotic pathway				
RIPK3	*RIPK3*$^{-/-}$	all cells	- [187]	- [187]
Inhibitors of apoptosis				
IAPs	*CD11c*^{cre}*cIAP1*$^{flox/flox}$*cIAP2*$^{-/-}$	dendritic cells	?	?
	CD11c^{cre}*cIAP1*$^{flox/flox}$*cIAP2*$^{-/-}$*XIAP*$^{-/-}$	dendritic cells	?	?
	LysM$^{cre/cre}$*cIAP1*$^{flox/flox}$*cIAP2*$^{-/-}$	monocytes/ macrophages/ neutrophils	+ [198]	?
	LysM$^{cre/cre}$*cIAP1*$^{flox/flox}$*cIAP2*$^{-/-}$*XIAP*$^{-/-}$	monocytes/ macrophages/ neutrophils	+ [198]	?