

Pathogenic cellular and molecular mediators in lupus nephritis

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Abstract

Kidney involvement in patients with systemic lupus erythematosus – lupus nephritis (LN) – is one of the most important and common clinical manifestations of this disease and occurs in 40–60% of patients. Current treatment regimens achieve a complete kidney response in only a minority of affected individuals, and 10–15% of patients with LN develop kidney failure, with its attendant morbidity and considerable prognostic implications. Moreover, the medications most often used to treat LN – corticosteroids in combination with immunosuppressive or cytotoxic drugs – are associated with substantial side effects. Advances in proteomics, flow cytometry and RNA sequencing have led to important new insights into immune cells, molecules and mechanistic pathways that are instrumental in the pathogenesis of LN. These insights, together with a renewed focus on the study of human LN kidney tissue, suggest new therapeutic targets that are already being tested in lupus animal models and early-phase clinical trials and, as such, are hoped to eventually lead to meaningful improvements in the care of patients with systemic lupus erythematosus-associated kidney disease.

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Key points

- Understanding of the cellular and molecular mechanisms underlying lupus nephritis (LN) is progressing rapidly, facilitated by new tools for advanced 'omic' analyses.
- Increasingly fine immune cell profiling based on patterns of expression of cell surface markers and genes is defining T cell and macrophage subsets that are important in disease mechanisms.
- Chromatin release and/or its ineffective clearance stimulate adaptive and innate immunity in LN.
- Resident kidney cells, including podocytes, mesangial cells and tubular epithelial cells, participate actively in the pathology of LN.
- Closer attention to technical aspects in trial design is driving successes in clinical trials in systemic lupus erythematosus and stimulating much additional interest in the rational design and application of novel LN therapies.

Introduction

Lupus nephritis (LN) occurs in ~50% of patients with systemic lupus erythematosus (SLE) and is a major contributor to morbidity and mortality¹. Despite current management, the newest population-based SLE registry – the Lupus Midwest Network (LUMEN) – revealed that 13% of patients with LN developed kidney failure; only 61% were alive and without kidney failure or a kidney transplant at 10 years of follow-up². LN pathogenesis is characterized by the deposition of autoantibodies and immune complexes (ICs), activation and/or proliferation of infiltrating immune cells and kidney resident cells, and the presence of several pathogenic molecules at the site of injury, namely the inflamed kidneys³. The most severe disease is associated with 'proliferative' LN, where increased numbers of cells are observed within the glomeruli, representing infiltrating immune cells. By contrast, membranous LN (which is characterized by sub-epithelial IC deposits in the glomeruli), is generally associated with better outcomes. The presence of mixed features of proliferative and membranous histopathology is not an uncommon finding in LN.

Systemic disease involves impaired clearance of autoantigens, aberrant lymphocyte activation, and overproduction of autoantibodies and pro-inflammatory mediators, all of which contribute to the pathogenesis of LN. However, the precise cells, molecules and mechanisms within the kidney that contribute to local pathology continue to be a hotbed of intense investigation^{4–6}.

Numerous advances in the past decade, powered by new platforms and technologies, have greatly advanced our understanding of LN (Table 1). The application of intravital imaging has enabled the visualization of immune cell dynamics in the kidney over time⁷. Single-cell RNA sequencing (scRNA-seq) has allowed the identification of gene signatures and cell clusters within the kidneys of patients with LN^{8–12}. Moreover, comprehensive 'omics' screens, including transcriptomics and proteomics, have accelerated the understanding of molecular pathogenesis of LN considerably^{8,13–16}. Of note, some cutting-edge techniques, such as mass cytometry and multiplexed tissue imaging, have been used in studies pertaining to SLE or the kidneys but their application in LN is yet to be explored¹⁷.

In this Review, we examine the evidence supporting the involvement of different adaptive and innate immune cells in the pathogenesis of LN, as well as the role of non-immune resident kidney cells. Further, we discuss the molecular mechanisms and mediators that drive SLE and promote LN, taking stock of insights gained from studies conducted over the past decade, including the therapeutic potential of new molecular targets.

Cellular pathogenesis of lupus nephritis

The presence of prominent immune infiltrates in the glomerular or peri-glomerular regions of the kidney, as well as the tubulointerstitium, represent a hallmark of LN. These manifestations are referred to as glomerulonephritis (GN) and tubulointerstitial nephritis (TIN), respectively. Almost all patients with LN have GN, whereas TIN almost always develops after the initial GN^{18,19}. TIN might result from the same immune mechanisms that elicit the initial GN, including ICs, serum-derived cytokines and damage caused by infiltrating innate and adaptive immune cells. Alternatively, TIN might be driven by mechanisms common to any GN, including tubular injury and death due to the presence of proteins in the urine (for example, albumin or transferrin), hypoxia, ischaemia or oxidative stress^{18,19}. Although current LN classification is based primarily on glomerular pathology, with less attention accorded to the tubulointerstitial compartment, TIN is an important component in LN pathology and disease outcome²⁰. Below, we interrogate each major leukocyte type in LN, with respect to their prevalence in the glomerular and tubulointerstitial compartments, as well as their potential pathogenic role.

T cells

T cells comprise the majority of kidney-infiltrating immune cells in patients with LN and in lupus-prone mice²¹ (Table 2). Infiltrating CD4⁺ and CD8⁺ T cells in LN kidneys mediate injury and are relevant to the development of progressive kidney failure^{22,23}. Interestingly, most CD4⁺ and CD8⁺ kidney-infiltrating T cells (KITs) in murine lupus might not be effector cells, as their cytokine production and proliferative capacity are reduced compared with that of peripheral blood T cells, and they have an 'exhausted' transcriptional signature²¹. CD8⁺ KITs existed first in a transitional state, before clonally expanding and evolving towards exhaustion, based on trajectory analysis, whereas CD4⁺ KITs included both helper and cytotoxic subsets with a highly prevalent exhaustion signature, indicating that the kidney microenvironment suppresses T cells by progressively inducing exhausted states²⁴. In contrast to data from murine models, scRNA-seq analysis of LN biopsy samples has not revealed features of exhausted T cells, as the observed CD8⁺ T cells (and natural killer (NK) cells) express high levels of granzymes B and K⁸. These seemingly discrepant data highlight the complex nature of LN, the heterogeneity of KITs, and possibly reflect species differences²⁵.

CD8⁺ T cells. CD8⁺ T cells predominate in periglomerular infiltrates, and their numbers not only correlate positively with the kidney pathology activity index and serum creatinine, but also predict poor outcome in Class III and IV LN²⁶. Tubulointerstitial CD8⁺ T cells also correlate with clinical and histological impairment in LN, and are associated with an unfavourable long-term kidney outcome²⁷. Several subsets of CD8⁺ T cells have been described. A substantial number of CD107a⁺ cytotoxic CD8⁺ T cells have been reported in LN peritubular infiltrates, where intrarenal expression of CD107a⁺ correlates with proteinuria²⁸. The proportion of CD8⁺ tissue-resident memory T (T_{RM}) cells was significantly increased in the kidneys of patients with LN and MRL/lpr mice

Table 1 | Emerging methods advancing the study and understanding of lupus nephritis

Methods	Patients	Controls	Findings	Refs.
scRNA-seq	16 kidney samples and 12 skin samples from patients with LN	5 skin samples from healthy individuals	Chronicity index, IgG deposition and proteinuria correlated with a transcriptomic-based score composed of IFN-inducible genes in kidney tubular cells scRNA-seq analysis of skin biopsy samples might be used as a biomarker of kidney disease	12
scRNA-seq	24 kidney biopsy samples	10 kidney biopsy samples	21 subsets of immune cells detected, including multiple populations of myeloid cells, T cells, NK cells and B cells A continuum of intermediate states spanning patrolling, phagocytic and alternatively activated monocytes was identified The kidney and systemic IFN responses correlated highly	8
scRNA-seq	21 kidney tissue samples, with 17 concurrent skin biopsy samples	3 pairs of skin and kidney biopsy tissue from healthy individuals	IFN response signatures in tubular cells and in keratinocytes distinguished patients with LN from healthy individuals A high IFN response signature and fibrotic signature in tubular cells were associated with failure to respond to treatment	9
scRNA-seq	Kidney sample from 1 patient with LN	Kidney sample from 1 healthy individual	IFN α and IFN β signalling pathway was enriched in B cells and NKT cells of patients with LN	11
Mass cytometry	Urine and peripheral blood of 13 patients with LN (6-month follow-up)	6 patients with different acute inflammatory kidney diseases	The urine signature of activated T cells and macrophages seems to reflect leukocytic infiltrates in the kidney	17
Aptamer-based screen (1,129 proteins)	Urine samples from 7 patients with active LN (and 8 with inactive SLE)	Urine samples from 8 healthy individuals	Urine proteins that best distinguish active LN from inactive disease included VCAM-1 across three ethnicities; CD166 (also known as ALCAM) and PF-4, in Black and Asian patients; properdin in Black patients; soluble E-selectin, BFL1 (also known as BCL2A1) and hemopexin in white patients; and TFPI in Asian patients. Most of these proteins correlated significantly with disease activity indices	14
Kiloplex Quantibody protein array (1,000 proteins)	Urine samples from 15 patients with SLE, of whom 12 had LN	Urine samples from 9 healthy individuals	Urine ANGPTL4, L-selectin and TGF β 1 are potential biomarker candidates for tracking disease activity in LN	13
Kiloplex Quantibody protein array (1,000 proteins)	Urine samples from 30 patients with LN (3-, 6-, and 12-month follow-ups after kidney biopsy)	Urine samples from 7 healthy individuals	Patients could be stratified over a urine chemokine gradient inducible by IFN γ , which correlated significantly with the number of kidney-infiltrating CD8 $^{+}$ cells; urinary IL-16 reflected histological activity	10,16

ANGPTL4, angiopoietin-related protein 4; IFN, interferon; IL, interleukin; LN, lupus nephritis; NK, natural killer; PF-4, platelet factor 4; scRNA-seq, single-cell RNA sequencing; SLE, systemic lupus erythematosus; TFPI, tissue factor pathway inhibitor; TGF β 1, transforming growth factor- β 1; VCAM-1, vascular cell adhesion protein 1.

compared with healthy controls, and was positively associated with podocyte injury and glomerulosclerosis^{29,30}. In mice with chronic graft-versus-host disease that develop a typical lupus-like syndrome, adoptive transfer of CD8 $^{+}$ CD103 $^{+}$ induced regulatory T (iT_{reg}) cells reduced systemic and kidney disease and improved survival³¹. Interestingly, frequencies of circulating and urinary CD8 T cells have been reported to reflect disease activity and treatment response in LN³², with higher frequencies associated with higher disease activity and a reduction being indicative of response to treatment.

CD4 $^{+}$ T_H1 and T_H17 T cells. CD4 $^{+}$ T cells have also been implicated in LN, although studies in human LN are sparse. In MRL/lpr mice, CD4 $^{+}$ T cells in inflamed kidneys contribute to nephritis progression^{6,33}. Dysregulated CD4 $^{+}$ T cell subsets in LN include T helper 1 (T_H1) cells, T_H17 cells, T follicular helper (T_{FH}) cells and T_{reg} cells.

A T_H1 cell-type response is predominant in both the peripheral and the kidney milieu of patients with diffuse proliferative LN³⁴. Studies also suggest that T_H1 cells might migrate from peripheral blood to the kidney and subsequently into the urine during active LN³⁵. IFN γ -expressing CD4 $^{+}$ T_H1 cells in the inflamed kidneys of MRL/lpr mice contribute to nephritis progression³³.

Compared with healthy individuals, patients with active proliferative LN have a significant increase in the frequency of T_H17 cells in

peripheral blood^{36–39}. The frequency of these cells correlates positively with SLE disease activity index (SLEDAI), renal SLEDAI, histological activity index, and the degree of cellular crescent and endocapillary proliferation, but decrease in responders following therapy^{38,39}. In addition to T_H17 cells, CD3 $^{+}$ CD4 $^{-}$ CD8 $^{-}$ double-negative T cells also infiltrate the kidneys of patients with LN and represent a major source of IL-17 (ref. 40). The T_H17–IL-17 axis stimulates the synthesis of inflammatory cytokines by resident non-immune cells and immune cells, drives epithelial-to-mesenchymal transition, and promotes the recruitment of immune cells to the kidney, based on multiple in vitro and animal studies³⁷. *Fcgr2b*^{−/−} mice lacking IL-17, and especially those lacking the adaptor protein E3 ubiquitin ligase TRAF3IP2 (also known as CIKS or ACT1), which is essential in IL-17A-induced signalling, had less GN and greatly improved survival compared with wild type controls, which highlights the therapeutic potential of this axis in LN⁴¹.

However, in a scRNA-seq study of human LN kidneys, CD4 $^{+}$ T cell clusters are not clearly associated with T_H1 or T_H17 signatures, suggesting that T cell polarization might not be a major feature in human LN⁸. Of note, the T_H17–IL-17A immune axis has no major role in the pathogenesis of LN in MRL/lpr and NZB/W F1 mice⁴².

CD4 $^{+}$ T_{reg} cells. T_{reg} cells are immunosuppressive and are crucial to the regulation of immune tolerance. Although multiple early studies

Table 2 | Lymphoid cellular infiltrates within LN kidneys

Cell type	Marker	Mouse studies	Human studies	Refs.
T cells (CD45⁺CD3⁺CD19⁻)				
T _H 1 cells	CD4 ⁺ T-Bet ⁺ IFN γ ⁺ TNF ⁺	Infiltrating kidney CD4 ⁺ T cells have a T _H 1 cell phenotype in B6.Sle1.Yaa mice IFN γ -expressing CD4 ⁺ T _H 1 cells in the inflamed kidneys of MRL/lpr mice contribute to nephritis progression	A T _H 1 cell-type response was predominant in peripheral and kidney tissues of patients with diffuse proliferative LN Inverse correlation between T _H 1 cells in peripheral blood, and urinary and kidney tissue in LN	33–35,54
T _H 17 cells	CD4 ⁺ ROR γ t ⁺ IL-17 ⁺	The T _H 17 cell and IL-17A immune response has no major role in the immunopathogenesis of LN in MRL/lpr and NZB/W F1 mice	Circulating T _H 17 cells are dramatically elevated in patients with active proliferative LN compared with healthy individuals and correlate positively with SLEDAI, kidney SLEDAI, histological activity index, and the degree of cellular crescent and endocapillary proliferation; T _H 17 cells reduced following response to therapy	38,39,42
T _{FF} cells	CD4 ⁺ CXCR5 ⁺ PD-1 ⁺ ICOS ⁺ Bcl-6 ⁺ IL-21 ⁺	IL-21 blockade blocks accumulation of IL-21 ⁺ IFN γ ⁺ T _{FF} cells in B6.Sle1.Yaa mice	The presence of T _{FF} cells in kidney biopsy samples is associated with severe tubulointerstitial inflammation, high serum creatinine and low estimated glomerular filtration rate	49,54
T _{reg} cells	FOXP3 ⁺ CD25 ⁺ CD127 ^{low}	IL-2 therapy rectifies T _{reg} cell versus non-T _{reg} cell imbalances, and ameliorates LN in both NZB/W F1 and MRL/lpr mice	Most studies found that T _{reg} cells in peripheral blood are lower in patients with LN than in healthy individuals	43–46
T _{FR} cells	CXCR5 ⁺ FOXP3 ⁺	Co-treatment with soluble OX40L and Jagged-1 proteins increased T _{reg} cells, T _{FR} cells and the T _{FR} -to-T _{FF} cell ratio, and suppressed LN in NZB/W F1 mice Long treatment regimen of low-dose IL-2 therapy increased T _{FR} -to-T _{FF} ratio and ameliorated kidney pathology	NA	57,58
CD8 ⁺ T cells	CD3 ⁺ CD8 ⁺ CD4 ⁻	CD8 ⁺ T cell number elevated in the inflamed kidney in MRL/lpr and in pristane-induced LN models; cells predominantly localized in the tubulointerstitium Proximal tubular epithelial cells induce a cytotoxic and inflammatory phenotype in CD8 ⁺ T cells	Total number of kidney CD8 ⁺ T cells correlates positively with kidney activity index and serum creatinine, and predicts poor outcome in Class III and IV LN	26,155
B cells (CD45⁺ CD19⁺ CD3⁻)				
Plasma cells	CD38 ⁺ CD138 ⁺ IgD ⁻	In NZB/W mice, inflamed kidneys are a major reservoir of autoreactive plasma cells, which are observed mainly in the tubulointerstitium	Plasma cell infiltration in the kidney medulla is associated with increased disease severity in patients with LN	67
ABCs	CD21 ⁺ CD11c ⁺ T-bet ⁺ IgD ⁻ CD27 ⁻	In B6.SLE1,2,3 mice, T-bet ⁺ B cells promote the rapid appearance of autoantibodies and germinal centres Conditional deletion of T-bet from B cells impaired the formation of germinal centres and mitigated the development of kidney damage and rapid mortality.	Peripheral blood ABCs are increased in patients with LN compared with individuals without LN and correlate positively with the severity of kidney damage in patients with LN CD20 ⁺ CD11c ⁺ B cells present in kidney biopsy samples from patients with active LN	59–61,66
ILCs (Lineage⁻ CD127⁺)				
ILC1/NK cells	CD56 ⁺ CRTH2 ⁺ T-bet ⁺ IFN γ ⁺ TNF ⁺	Infiltrating NK cells in kidneys of MRL/lpr mice had a more mature, activated phenotype compared with kidney and peripheral NK cells from prediseased mice	Circulating NK cells are diminished, with impaired cytotoxicity in patients with SLE, particularly in those with LN, compared with healthy individuals Increased frequencies of Ki67 ⁺ NK cells correlated strongly with clinical severity and active nephritis CD56 expression identifies NK cells or NK-like T-cells, which are present in the kidney interstitium and peri-glomerular areas but only rarely in glomeruli in LN	71–74
ILC2	CRTH2 ⁺ GATA3 ⁺ IL-4 ⁺ IL-5 ⁺ IL-13 ⁺	In MRL/lpr mice, progression of LN is accompanied by a reduction of ILC2 abundance in inflamed kidney tissue ILC2 restoration via IL-33 administration ameliorates LN and mortality	NA	75

ABCs, age-associated B cells; BCMA, B cell maturation protein (also known as TNFRSF17); CCR, CC-chemokine receptor; CXCR, CX-chemokine receptor; ILC, innate lymphoid cells; LN, lupus nephritis; NA, not available; NK, natural killer; SLE, systemic lupus erythematosus; SLEDAI, SLE disease activity index; T_{FF}, T follicular helper; T_{FR}, follicular regulatory T; T_H, T helper; TLR4, Toll-like receptor 4; T_{FF}, T peripheral helper; T_{reg}, regulatory T.

measuring the numbers of T_{reg} cells and their function in patients with SLE and LN yielded conflicting results, most reports indicate that patients with LN have fewer T_{reg} cells in peripheral blood than healthy individuals, with a considerable increase in T_H17 cell-to-T_{reg} cell ratios⁴³.

Different T_{reg} cell subtypes, including T_{reg}1 and T_{reg}17 cells, which have transcriptional signatures that resemble those of T_H1 and T_H17 cells, respectively, have been identified, which might underlie discrepancies between study findings. In human LN, these data need further scrutiny.

Several therapeutic strategies that target T_{reg} cells have been proposed in LN⁴³. Short-term IL-2 therapy rectifies T_{reg} cell versus non- T_{reg} T cell imbalances, and ameliorates LN in both NZB/W F1 and MRL/lpr mice^{44–46}. Erythropoietin, which has newly recognized immunoregulatory functions, ameliorates LN by reducing T_H17 cell frequencies and increasing T_{reg} cell frequencies in mice with pristane-induced GN and MRL/lpr mice⁴⁷. Given the heterogeneity of T_{reg} cells and the paucity of adoptive transfer studies in human SLE and LN, our understanding of these cells will continue to evolve in the coming years.

CD4⁺ T_{FH} cells. T_{FH} cells have a crucial role in orchestrating germinal centres (GCs), affinity maturation, class switch recombination, and generation of plasma cells and memory B cells⁴⁸. scRNA-seq analysis of kidney samples from patients with LN identified a distinct cluster of T_{FH} -like cells⁸. T_{FH} cells are commonly detected in kidney biopsy samples and their presence is associated with severe tubulointerstitial inflammation, high serum creatinine, and a low estimated glomerular filtration rate⁴⁹. T_{FH} -like cells are distributed diffusely throughout the tubulointerstitium, usually in the proximity of CD20⁺ B cells. Nevertheless, studies examining T_{FH} cells within the kidney milieu in LN have been sparse, and the potential role of these cells in human LN needs to be substantiated further. Of note, *TNFSF4*, which encodes OX40L, is a susceptibility locus for SLE, and OX40L signalling through OX40 on activated CD4⁺T cells promotes the differentiation of T_{FH} cells, plasma-blast accumulation, and nephritis^{50,51}. However, a potential mechanistic link between OX40L polymorphisms and the differentiation of T_{FH} cells in LN kidneys remains to be established.

Cytokines have key roles in T_{FH} cell differentiation, including IL-2, IL-6, IL-21, IL-17, and IFN. IL-21 promotes T_{FH} cell responses and is also secreted by T_{FH} cells, which promote B cell differentiation^{52,53}. Anti-IL-21 blockade reduces GC B cells, titres of autoantibodies, T_{FH} and T_H1 cell infiltration in the kidneys, and improves disease and survival in lupus-prone B6.Sle1.Yaa mice⁵⁴.

Follicular regulatory T (T_{FR}) cells, which suppress T_{FH} cell function, are reported to be reduced in patients with SLE⁵⁵ compared with healthy individuals, but this reduction is corrected after standard-of-care treatment⁵⁶. Co-treatment with soluble OX40L and Jagged-1 proteins increased T_{reg} cells, T_{FR} cells and the T_{FR} -to- T_{FH} ratio, and suppressed LN in NZB/W F1 mice⁵⁷. Low-dose IL-2 consistently increased the T_{FR} -to- T_{FH} cell ratio, restoring the function of T_{FR} cells in mice and patients with SLE⁵⁸. This intricate balance between T_{reg} and T_{FH} cells that is constantly modulated by the cytokine milieu, in the context of genetic polymorphisms, is an exciting area for future exploration in LN.

B cells and plasma cells

A range of B cell activation states have been observed in the kidneys of patients with LN⁸. Over the past decade, a novel, distinct, mature, autoantibody-producing subset of B cells that accumulates with age has been described; these cells have been termed 'age-associated B cells' (ABCs)⁵⁹. In patients with SLE, peripheral blood ABCs are increased compared with healthy controls, strongly correlate with anti-chromatin antibody levels⁶⁰ and track with disease activity^{61,62}. scRNA-seq analysis of kidney samples from patients with LN suggested local activation of B cells with an ABC signature⁸.

T-bet is a key ABC transcription factor and, as potent antigen-presenting cells, CD11c⁺T-bet⁺ ABCs affect T_{FH} cell differentiation and disrupt affinity-based GC selection, which contributes to autoantibody production⁶³. Deletion of the gene encoding T-bet in B cells reduced the formation of GCs, lymphocyte activation, kidney damage and rapid

mortality in B6.SLE1,2,3 lupus mice⁵⁹. Of note, T-bet⁺ ABCs have also been reported⁶⁴. In terms of their functional potential, ABCs phenocopy IgD⁺CD27⁺ double-negative B cells⁶⁵, whose frequencies correlate with the severity of kidney damage in patients with LN⁶⁶.

Inflamed kidneys in NZB/W F1 mice have a reservoir of autoreactive plasma cells, mainly located in the tubulointerstitium of the cortex and outer medulla, with some being observed in periglomerular infiltrates^{67,68}. Plasma cell infiltration in the kidney medulla is associated with increased disease severity in patients with LN, but not with tubulointerstitial IC deposition, arguing against a direct contribution of local antibody production to medullary inflammation⁶⁷. Multiplexed confocal microscopy of human LN kidneys showed that B cells often organized into large periglomerular neighbourhoods with T_{FH} cells⁶⁹; interestingly, high B cell densities were associated with protection from kidney failure, whereas high densities of CD8⁺, $\gamma\delta$ or CD4⁺CD8⁺ T cells were associated with both acute kidney failure and progression to kidney failure. Collectively, the prevalence of B cells, ABCs and plasma cells within LN kidneys and their precise pathogenic role warrants further examination.

Innate lymphoid cells

Innate lymphoid cells (ILCs) are subdivided into cytotoxic NKs and four groups of 'helper' ILCs – ILC1, ILC2, ILC3 (analogous to T_H1 , T_H2 , and T_H17 cells, respectively) and lymphoid tissue inducer cells⁷⁰. In patients with SLE, especially those with LN, circulating NK cells are diminished and their cytotoxicity is impaired⁷¹. Increased frequencies of Ki67⁺ NK cells (that is, proliferating NK cells) correlate strongly with clinical severity and active nephritis⁷². CD56 expression identifies NK cells or NK-like T cells, which are present in the kidney interstitium and peri-glomerular areas but only rarely in glomeruli in LN⁷³ (Table 2). scRNA-seq of whole human LN kidney tissue identified two NK cell populations: CD56^{dim}CD16⁺ NK cells and CD56^{bright}CD16⁺ NK cells⁸. In MRL/lpr mice, kidney infiltrating NK cells were also identified, with a more mature, activated phenotype compared with that observed in peripheral NK cells from mice prior to disease development⁷⁴. Among the other ILCs, ILC2s are reduced in MRL/lpr mice, but the restoration of ILC2s through IL-33 administration ameliorates LN and mortality⁷⁵. Additional studies are clearly warranted to elucidate the prevalence and pathogenic significance of ILCs in LN.

Neutrophils

The blood neutrophil signature is strongly associated with progression to LN and disease severity in patients with SLE, and could potentially be a biomarker for monitoring treatment responses^{76,77} (Table 3). The recruitment of circulating neutrophils in glomerular capillaries following IC deposition might be mediated by neutrophil fragment crystallizable γ receptors (Fc γ Rs) that bind the Fc-portion of deposited ICs⁷⁸, and Abl or Src kinases⁷⁹. Another study suggests that acute skin exposure to UV light might trigger neutrophil migration and kidney inflammation⁸⁰. However, data suggesting a prominent presence of neutrophils within LN kidneys, either in spontaneous murine models or in human LN, are lacking.

Neutrophil extracellular traps (NETs), which are net-like extracellular structures comprising modified chromatin decorated with cytoplasmic and granular proteins, are extruded by neutrophils during a form of neutrophil cell death termed NETosis⁸¹. NETs are elevated in the circulation of patients with SLE, particularly in those with LN, and their abundance correlates with circulating levels of anti-double-stranded DNA (dsDNA), C3 and C4, and proteinuria^{82,83}. Low-density

Table 3 | Myeloid cellular infiltrates within LN kidneys

Cell type	Marker	Mouse studies	Human studies	Refs.
Neutrophils	CD66b ⁺ Elastase ⁺	Deletion or inhibition of NOX2, peptidylarginine deiminase or neutrophil elastase reduces NET formation but does not ameliorate murine LN	Blood neutrophil signature is strongly associated with progression to LN and disease severity, and could potentially be a biomarker for monitoring treatment responses	76,77, 91–93
DCs	HLA-DR ⁺ CD123 ⁺	Kidney-infiltrating CD11c ⁺ cells in lupus-prone mice promote LN by enhancing kidney-infiltrating T cell responses; kidney DCs are responsible for the local synthesis of C1q in LN and are associated with progressive tubulointerstitial inflammation	Lower numbers of pDCs in patients with severe LN and increased mDCs are associated with early, mild LN Plasmacytoid DCs accumulate within glomeruli in LN.	126–129
Monocytes	MCSFR ⁺ CD11b ⁺ CD14 ⁺ HLA-DR ⁺	Glomerular fractalkine expression and CD16 ⁺ monocyte accumulation were prominently increased in MRL/lpr mice Intracapillary immune complexes also induced direct recruitment of 6-sulfo LacNAc-expressing monocytes (slanMo) from the microcirculation via interaction with CD16	Trajectory analysis of scRNA-seq data from LN kidney biopsy samples identifies a continuum of intermediate states of monocytes in the kidney, suggesting the differentiation of peripheral inflammatory CD16 ⁺ monocytes into a phagocytic phenotype and then into alternatively activated macrophages within the kidney Patients with severe LN have a higher grade of CD14 ⁺ CD16 ⁺ infiltration in the kidneys and lower peripheral levels of non-classical (CD14 ⁺ CD16 ⁺) monocytes, potentially reflecting recruitment to kidney tissues	8,100, 101,103
Macrophages	CD68 ⁺ (humans) F4/80 ^{hi} (mouse)	Activated kidney macrophages are markers of disease onset and disease remission in LN and NZB/W F1 mice	Kidney expression of CD68 is associated with progression to chronic kidney disease in patients with proliferative LN	105,108
M1-like macrophages	CD80 ⁺ CD86 ⁺	Kidney macrophages are skewed towards an M1, rather than an M2, phenotype during spontaneous LN in MRL/lpr mice	NA	112
M2-like macrophages	CD163 ⁺ CD206 ⁺	Polarizing macrophages towards M2a in various LN mouse models results in less kidney damage and prolongs survival The number of M2b macrophages is associated with kidney damage	CD163 ⁺ M2c-like macrophages are the dominant subpopulation in kidney biopsy samples The number of glomerular M2-like macrophages correlate with the degree of proteinuria in patients with LN	113,115

DCs, dendritic cells; iNOS, inducible nitric oxide synthase; LN, lupus nephritis; mDCs, myeloid DCs; pDCs, plasmacytoid DCs; scRNA-seq, single-cell RNA sequencing.

granulocytes, which are the main group of neutrophils that produce NETs, are elevated in SLE⁸⁴ compared with healthy individuals. High NET levels identify patients with active and severe disease, including nephritis⁸⁵. NETs have been observed in skin lesions and in the glomeruli and tubulointerstitium of biopsy samples from patients with proliferative LN, and their presence was associated with a higher disease activity index^{86–89}.

However, some studies have challenged the notion that NETs are nephritogenic. NOX2[−] deficiency in lupus-prone mice reduced NET formation, but markedly exacerbated GN^{90,91}. Accordingly, treatment with NOX2 activators induced NET formation and ameliorated nephritis⁹¹. Similarly, deletion or inhibition of peptidylarginine deiminase activity reduces NET formation but does not ameliorate murine LN⁹². Neutrophil elastase (NE) or NE-dependent NETs have no effect on nephritis, dermatitis, or immune system composition in MRL/lpr mice⁹³. Further studies are needed to define the true prevalence of neutrophils and NETs within LN kidneys, and to clarify the conditions under which they might be pathogenic.

Monocytes and macrophages

Glomerular macrophages can be derived from circulating monocytes recruited by endothelial cells that are activated via nucleic acid-sensing Toll-like receptors (TLRs)⁹⁴. Monocyte CC-chemokine receptor 2 (CCR2)

and endothelial tumour necrosis factor receptor 2 (TNFR2) can promote the differentiation of monocytes into macrophages within the inflamed kidney vasculature⁹⁵. Along with infiltrating macrophages, the kidneys also have a network of tissue-resident macrophages located around glomeruli and tubulointerstitium. Resident kidney macrophages derive from embryonic progenitors, are long-lived and self-renewing, and can also be replenished from bone marrow progenitors with age⁹⁴. The tissue-resident macrophage population increases in mouse models of LN, and has a mixed pro-inflammatory and anti-inflammatory phenotype that might reflect a failure to resolve inflammation^{96,97}. Kidney-resident macrophages take up circulating ICs that are ‘pumped’ into the interstitium via vesicular trans-endothelial transport, triggering an FcγRIV-dependent inflammatory response and the recruitment of monocytes and neutrophils⁹⁸. The pathogenic roles of tissue-resident macrophages and monocyte-derived macrophages have been suggested to be distinct, with resident cells orchestrating leukocyte recruitment and infiltrating cells taking up and presenting IC antigens⁹⁹.

Trajectory analysis using scRNA-seq data from LN kidney biopsy samples identified a continuum of intermediate states of monocytes in the kidney, suggesting that peripheral inflammatory CD16⁺ (classical) monocytes differentiate into a phagocytic phenotype and then into alternatively activated macrophages within the kidney⁸. Patients with more severe LN have a higher grade of CD14⁺CD16⁺ infiltration in the

kidneys and lower peripheral levels of non-classical (CD14⁺CD16⁺⁺) monocytes, potentially reflecting recruitment to the kidney¹⁰⁰. Fractalkine is expressed on injured endothelial cells and is a membrane-bound chemokine that attracts cells expressing its receptor, CX-chemokine 3 receptor 1 (CX3CR1), including CD16⁺ monocytes¹⁰¹. Glomerular fractalkine expression and CD16⁺ monocyte accumulation were prominently increased in MRL/lpr mice and in patients with active LN^{101,102}. Intracapillary ICs also induced a direct recruitment of 6-sulfo LacNAc-expressing monocytes (slanMo) from the microcirculation via interaction with CD16 (ref. 103). Infiltration of kidneys with mononuclear phagocytes is associated with more severe disease and worse prognosis^{104,105}, possibly because of local inflammation and excessive tissue remodelling¹⁰⁶. Non-classical patrolling monocytes (CD43⁺) accumulate in glomerular vessels in murine lupus kidneys and in patients with SLE, with a potential pathogenic role¹⁰⁷; CD16 surface expression in these cells is similar to that of non-classical monocytes.

Kidney expression of CD68 is associated with progression to chronic kidney disease in patients with proliferative LN¹⁰⁸. Macrophages have been traditionally described as classically activated M1 pro-inflammatory cells at one extreme and alternatively activated M2 anti-inflammatory cells at the other extreme of this spectrum¹⁰⁹. M2 macrophages can be further categorized as M2a, M2b and M2c – M2a macrophages are referred to as alternatively activated or profibrotic, M2b as regulator or T_H2-related, and M2c as deactivated, remodelling, or anti-inflammatory^{110,111}. Kidney macrophages are skewed towards an M1, rather than M2, phenotype during spontaneous LN in MRL/lpr mice¹¹². Polarizing macrophages towards M2a in various LN mouse models result in less kidney damage and prolonged survival¹¹³. In patients with LN, CD163⁺ M2c-like macrophages are the dominant subpopulation in kidney biopsy samples and M2a macrophages are associated with disease progression¹¹⁴. The number of glomerular M2-like macrophages correlate with the degree of proteinuria in patients with LN¹¹⁵. Importantly, urinary levels of CD163 (a marker of M2c-like macrophages) are elevated in active LN and correlate well with serial disease activity, long-term outcome and concurrent renal pathology in LN^{116,117}; CD163⁺ cells have also been implicated in kidney fibrosis and progression to kidney failure¹¹⁸.

Macrophage depletion ameliorates nephritis induced by antibodies against the glomerular basement membrane¹¹⁹. Macrophage depletion using a colony-stimulating factor-1 receptor (CSF-1R) kinase inhibitor in MRL/lpr mice significantly ameliorated kidney disease, and improved kidney histopathology, without affecting IgG and C3 deposition¹²⁰. Similarly, inhibiting nuclear factor-κB (NF-κB) signalling in myeloid cells reduced infiltrating classically activated macrophages in the kidneys significantly, decreased kidney inflammatory cytokines levels and attenuated kidney disease¹²¹. Interestingly, IL-22 from ILC3 aggravated LN by promoting macrophage infiltration, whereas deletion of IL-22 or IL-22R reduced disease and kidney macrophage infiltration significantly in MRL/lpr mice¹²².

Notably, the universal myeloid cell marker, integrin αM (also known as CD11b), and several other molecules that are crucial to macrophage activation, including components of the type I interferon (IFN-I) pathway and NF-κB signalling pathway, are well replicated SLE susceptibility genes⁵. How genetic variants in these susceptibility genes impact the recruitment and functional phenotype of macrophages in the kidney remains to be elucidated.

Several of the cellular changes described above have been verified by scRNA-seq studies supported by the NIH Accelerating Medicines Partnership (AMP) 1.0 studies^{8,9,12}. Preliminary findings from

AMP 2.0, which is a much larger effort than AMP1.0 and used a more advanced sequencing technology applied to kidney biopsy tissue from >150 patients with LN^{123,124} (>70,000 cells comprising 134 distinct cell subsets) suggest that different leukocyte populations are associated with specific histopathological features. Importantly, macrophage differentiation states seem to distinguish between proliferative and membranous disease. Furthermore, macrophage populations analogous to those associated with acute kidney injury – similar in their expression of genes involved in lipid processing and phagocytosis – are found in human LN and in mouse models of the disease.

Dendritic cells

Dendritic cells (DCs) are sentinels that constantly survey the kidney microenvironment to serve their antigen-presenting function¹²⁵. Distinctive features of peripheral blood DC subpopulations are associated with different degrees of severity of LN – patients with severe LN have low numbers of plasmacytoid DCs (pDCs) whereas early-stage or mild LN is associated with the presence of myeloid DCs with increased expression of co-stimulatory molecules^{126,127}. pDCs are distinct from other DC populations that are mainly involved in antigen presentation to T cells; a main function of pDCs is the production of IFN-I during viral infections (discussed below)¹²⁵.

In LN, DCs infiltrate the kidneys and are involved not only in antigen presentation but also in the formation of tertiary lymphoid structures (TLS) that amplify inflammation⁹⁴. DC-like CD11c⁺ cells were detected in the kidneys of lupus-prone mice as LN progressed, where they promoted LN by enhancing KIT responses¹²⁸. CD11c⁺ DC infiltrates in the tubulointerstitium of MRL/lpr mice were associated with progressive tubulointerstitial inflammation¹²⁹. These kidney DCs have also been implicated in local production of C1q in LN, thus contributing to local complement activation¹²⁹. A 2021 study reported the presence of an inflammatory DC with shared monocyte surface markers (including CD14, CD16, CD64, CD68, CD163) in human LN kidneys, suggesting that these inflammatory DCs may be derived from circulating pro-inflammatory monocytes¹³⁰. Although systemic DC activation and antigen presentation to T cells are vital to the systemic origins of LN, data supporting an essential pathogenic role for DCs within the kidneys or draining lymph nodes in human LN is lacking.

Tertiary lymphoid structures

TLS are ectopic lymphoid structures that develop in non-lymphoid organs following chronic inflammation and have been reported in LN^{131–133}. In 32 patients with LN, 18 kidney biopsy samples contained areas of scattered B cell distribution, 10 had nodular aggregates without separate T or B cell zones, 3 had distinct B and T cell regions but no follicular DCs, and 4 had clearly separate B and T cell zones with a central follicular DC network, which were reminiscent of organized lymphoid structures¹³⁴. The presence of either T cell and B cell aggregates or GCs is associated with the presence of ICs in the tubular basement membrane¹³¹. TLS in LN and other chronic kidney disease models have been linked to worse disease prognosis¹³⁵. Kidney TLS in NZB/W F1 murine LN mice form large, interconnected networks that resemble lymph nodes in cell composition, structure and gene signature¹³². High B cell-activating factor (BAFF) levels are required to induce or maintain TLS compartments and to recruit T cells to glomeruli during LN; reducing BAFF levels reduces TLS formation and attenuates LN¹³⁶. Mesenchymal stromal-like cells reported within TLS in kidneys of lupus-prone mice might act as lymphoid tissue organizer cells by accelerating inflammation and orchestrating TLS formation¹³⁷.

Resident kidney cells

Emerging evidence indicates that kidney-resident cells in LN are not innocent bystanders, but can also have an active pathological role¹³⁸.

Podocytes. Podocytes express many molecules of the innate and adaptive immune system, suggesting that they are actively involved in the immune-mediated injury of the kidney¹³⁹. Podocytes can contribute to LN pathogenesis through several mechanisms, including secretion of cytokines and chemokines, and crosstalk with parietal epithelial cells and immune cells^{140,141}. Podocytes can also function as non-haematopoietic professional antigen-presenting cells in the kidney. T cell–podocyte contact has been reported in murine and human LN kidney tissue¹⁴².

Importantly, podocyte damage is common in LN, including dysregulation of the podocyte actin cytoskeleton and foot process effacement, which are associated with loss of the filtration barrier¹⁴³. Structural podocyte damage and/or loss is reported to be more common in proliferative than membranous LN and associated with worse prognosis¹⁴⁴. Understanding what causes damage to podocytes in LN is crucial. The presence of autoantibodies against podocyte antigens (for example, α -enolase and annexin A1) in the glomeruli of patients with LN suggests a potential role of autoantibodies in podocyte injury¹⁴⁵. Activation of NOD-, LRR- and pyrin domain-containing protein (NLRP3) and calcium/calmodulin-dependent protein kinases IV (CaMK4) have also been implicated^{146,147}, with other mediators likely still to be identified.

Mesangial cells. Mesangial cells proliferate and express a wide array of pro-inflammatory and profibrotic factors in response to a variety of lupus-relevant pathological stimuli, and contribute to inflammation and fibrosis in LN by promoting leukocyte recruitment, activation and maturation, and remodelling of the extracellular matrix^{6,148}. Mesangial cells are of myeloid origin and can present antigen and modulate CD4⁺ T lymphocyte proliferation and differentiation¹⁴⁹. Kidney mesangial cells also express TLRs and produce IFNs when stimulated¹⁵⁰. In addition to regulating the production of IL-2 and IL-17 by T cells, CaMK4 controls mesangial cell proliferation and promotes their production of IL-6 (ref. 151); inhibition or genetic ablation of CaMK4 suppressed LN in MRL/lpr mice^{147,152}. Of note, most information about mesangial cells in LN is derived from *in vitro* studies and murine models; thus, their pathogenic relevance to human LN remains to be confirmed.

Tubular epithelial cells. Tubular epithelial cells (TECs) participate actively in the tubulointerstitial pathology of LN through the expression of cytokines, chemokines and fibrogenic molecules, and via interactions with infiltrating immune cells¹⁵³. Proximal TECs express proteins associated with antigen presentation, and induce CD4⁺ T cell activation and proliferation¹⁵⁴. In murine LN, CD8⁺ T cells localize close to proximal tubules, and promote enhanced apoptosis of tubular cells¹⁵⁵. Murine and human TECs might exert immunosuppression through a mechanism that involves IL-23 receptor, CaMK4, and competitive uptake of arginine. TEC-targeted delivery of a CaMK4 inhibitor efficiently suppressed kidney inflammation in lupus-prone MRL/lpr mice¹⁵⁶.

In contrast to infiltrating immune cells, our current knowledge of how resident kidney cells might contribute to LN is shaped by isolated studies that have not been independently validated. Moreover, the lack of human LN studies creates a substantial knowledge gap.

Emerging molecular mechanisms in lupus nephritis

Above, we have discussed several molecules implicated in the pathogenesis of LN, in the context of the cells that produce them, or the cells that are targeted by various pathogenic molecules. Below, we highlight the latest molecular pathways to be implicated in LN pathogenesis.

Heightened IFN signature in SLE and LN

IFNs, particularly IFN-I, have been well recognized as central mediators in the immunopathogenesis of SLE¹⁵⁷. An IFN signature (that is, the overexpression of hundreds of gene transcripts induced by IFN-I) is prevalent in 70–90% of patients with SLE^{77,158}. A high baseline IFN signature is also associated with earlier development of nephritis¹⁵⁹ and an increased rate of subsequent kidney disease activity in LN¹⁶⁰. Moreover, the prevalence of class III and IV LN is significantly increased in patients with high serum IFN¹⁶¹. Persistently high levels of IFN λ are also associated with an unfavourable histological response to treatment in LN¹⁶², whereas high circulating IFN γ is linked to high SLE disease activity such as active arthritis and nephritis, and the presence of anti-Ro60 antinuclear antibodies^{163,164}.

Although pDCs are professional IFN-I-producing cells, this function might be defective in patients with SLE¹⁶⁵. However, another study showed that neutrophils have the capacity to produce IFN α in response to circulating chromatin¹⁶⁶. Of note, although pDCs are 27 times more efficient in producing IFNs than neutrophils, blood neutrophils are 100 times more frequent than pDCs¹⁶⁶. Non-haematopoietic cells might also be responsible for IFN production prior to clinical autoimmunity¹⁶⁵.

In the kidneys, experimental models of immune nephritis implicated resident kidney cells as IFN-I producers¹⁶⁷ – kidney TECs have been suggested to be major IFN α producers, which might create an autocrine circuit within the tubulointerstitium¹⁶⁸. In LN, the intrarenal IFN response score correlates significantly with that of peripheral blood⁸. One study reported that the IFN signature was most prominent in glomerular areas, suggesting that resident glomerular cells are a major contributor¹⁶¹. Nonetheless, upregulated IFN-I response signature in tubular cells, particularly in proliferative LN, is associated with non-response to treatment⁹ and correlates with the kidney pathology chronicity index, IgG deposition, and proteinuria¹². Ongoing spatial transcriptomic and spatial proteomic studies might clarify the current discrepancies in the literature, which might arise owing to sampling error when renal sections are examined.

Multiple therapeutic strategies targeting IFNs or related pathways have been investigated, including those targeting IFNs or IFN receptors^{169–172}, upstream pDCs^{173,174}, and the downstream JAK–STAT pathway¹⁷⁵. Anifrolumab, which is a blocking human monoclonal antibody against the IFN-I receptor subunit 1 (ref. 176), has been approved by the US Federal and Drug Administration for adults with moderate-to-severe SLE who are receiving standard therapy¹⁷⁷. In patients with active LN, although the primary end point was not met, an anifrolumab-intensified regimen was associated with improved complete kidney response with sustained glucocorticoid reduction¹⁷⁸.

Activation of nucleic acid sensors

One potential mechanism for the enhanced IFN signature in SLE is heightened stimulation of nucleic acid sensors, which drive the production of IFN-I by sensing nucleic acids¹⁷⁹. Mounting evidence indicates that both endosomal and cytosolic nucleic sensors are activated in lupus (Fig. 1). Of note, genetic polymorphisms in several of these molecules, including TLRs and IRFs, have been documented in SLE⁵.

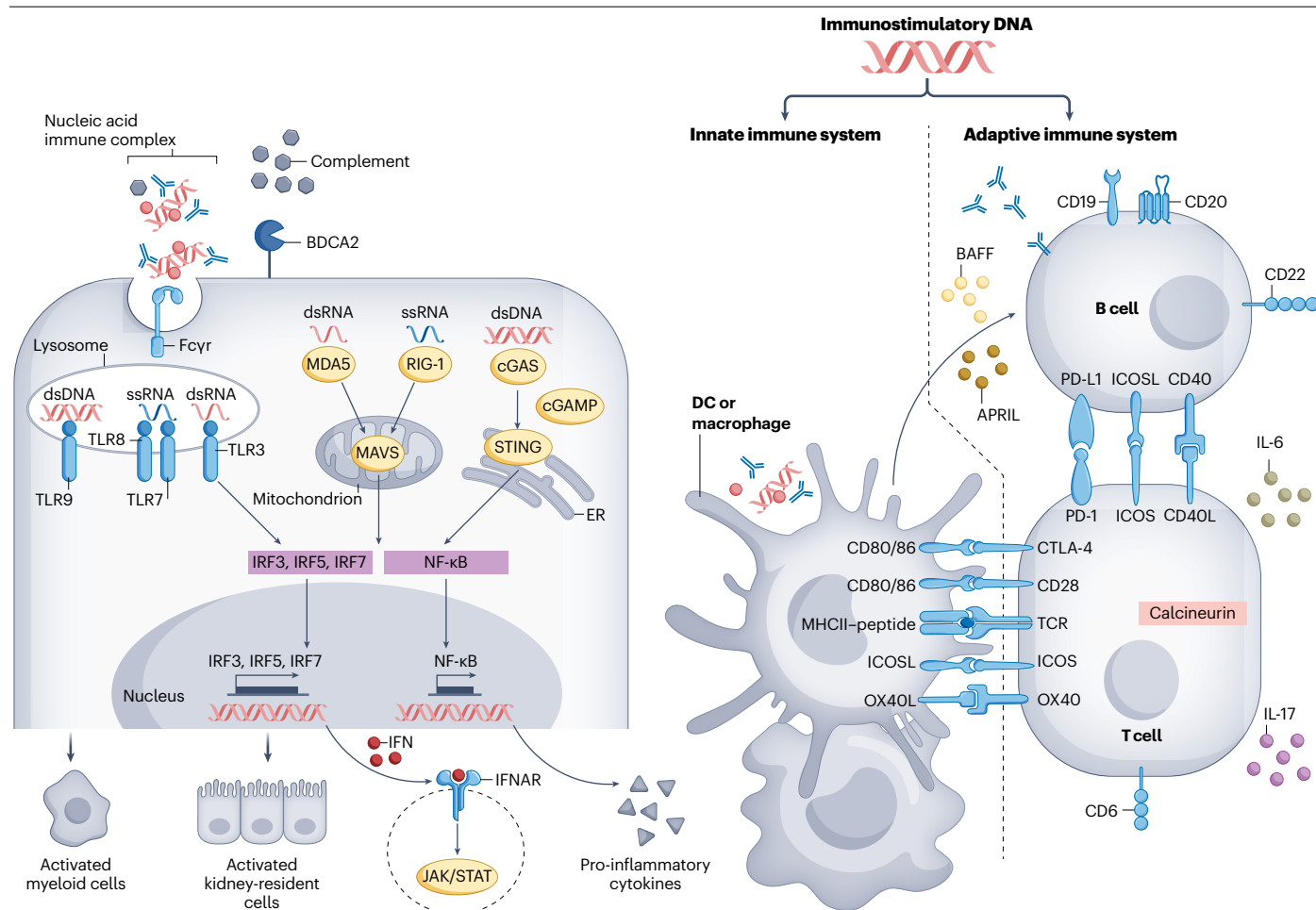


Fig. 1 | Pathogenic consequences of immunostimulatory DNA in systemic lupus erythematosus and lupus nephritis. Cytosolic RNA is sensed by cytosolic retinoic acid-inducible gene I (RIG-I) or melanoma differentiation-associated protein 5 (MDA5), which principally bind single-stranded RNA (ssRNA) and double-stranded RNA (dsRNA), respectively, and promote oligomerization of mitochondrial antiviral-signalling protein (MAVS) on the mitochondrial membrane. Cytosolic DNA is recognized by 2,3-cyclic GMP-AMP synthase (cGAS), which dimerizes to synthesize 2,3-cyclic GMP-AMP (cGAMP) and activates stimulator of interferon genes (STING) on the endoplasmic reticulum (ER) surface. MAVS and STING

subsequently activate transcription factors such as interferon regulatory factors (IRF) 3, 5 and 7 and nuclear factor- κ B (NF- κ B) to produce IFN β and cytokines, and activate infiltrating immune cells and resident kidney cells in lupus nephritis. Chromatin, processed by antigen-presenting cells can also activate T cells and cognate B cells in an antigen-specific manner, leading to the generation of autoreactive lymphocytes and the production of anti-nuclear autoantibodies. Thus, immunostimulatory chromatin has a vital role in activating both the adaptive and innate arms of immune system in lupus nephritis, collectively orchestrating disease pathogenesis. APRIL, a proliferating-inducing ligand; BAFF, B cell-activating factor.

Endosomal DNA and RNA sensors. TLR7 and TLR9 are highly expressed in the endosomes of pDCs and B cells, and are activated by ICs that contain RNA or DNA, respectively¹⁷⁹. In addition to driving the production of IFN-I in pDCs, TLR7 also has a direct effect on B cells by promoting the development of spontaneous GCs, differentiation of plasmablasts, and production of autoantibodies^{180,181}. TLR7 activity is required for formation of anti-RNA autoantibodies, DC activation and severe GN in lupus mice^{180–183}, and TLR7 gain-of-function variants are associated with human lupus¹⁸⁴. High TLR7 expression in patients with SLE was associated with active disease, upregulation of IFN-responsive genes and autoantibody production¹⁸⁵. Given that TLR7 is encoded by an X chromosome locus, TLR7 might also contribute to the female bias in SLE by escaping X chromosome inactivation in women and leading to enhanced TLR7 expression¹⁸⁶. Similarly, the Y-linked

autoimmune accelerating (Yaa) locus associated with murine lupus leads to overexpression of TLR7 (ref. 187).

Despite having similar tissue expression and signalling pathways, TLR9 negatively regulates TLR7 (ref. 188). B cells from patients with SLE have defective *in vitro* TLR9 responses, which might contribute to a loss of B cell tolerance¹⁸⁹. Whereas B cell-intrinsic TLR7 deficiency prevents formation of autoantibodies against RNA and non-nuclear antigens, and limits systemic autoimmunity, B cell-specific TLR9 deletion results in decreased autoantibodies against dsDNA or nucleosomes, but increased autoantibodies targeting a broad range of systemic autoantigens, and exacerbates nephritis^{190,191}. TLR9 deficiency also leads to accelerated kidney disease in pristane-induced murine lupus¹⁹². Similarly, TLR7, but not TLR9, is responsible for the generation of anti-chromatin IgG antibodies in autoimmune-prone *Mer*^{-/-} mice¹⁹³.

In general, patients with SLE over-express TLRs 7, 8 and 9 (refs. 194,195), which might contribute to a heightened IFN signature.

Cytosolic DNA and RNA sensors. In addition to the endosomal TLR pathway, IFNs can also be produced through the newly described cytosolic nucleic acid sensing pathways¹⁹⁶. Cytosolic RNA from exogenous viruses or endogenous transcripts is sensed by cytosolic retinoic acid-inducible gene I (RIG-I) or melanoma differentiation-associated protein 5 (MDA5), which mainly bind ssRNA and dsRNA, respectively, and promote oligomerization of mitochondrial antiviral-signalling protein (MAVS) on the mitochondrial membrane. MAVS and STING subsequently activate IRF3 and NF- κ B to produce IFN- β and cytokines, respectively^{197,198} (Fig. 1).

Polymorphisms in *IFIH1*, which encodes MDA5, are associated with SLE, and constitutively activated MDA5 leads to a lupus-like disease in mice¹⁹⁸. Activation and oligomerization of the downstream molecule MAVS is observed in peripheral blood cells in over a third of patients with SLE and is associated with increased IFN- β production and autoantibodies to the small nuclear ribonucleoproteins Sm and U1RNP¹⁹⁹. MAVS also has a B cell-intrinsic role in autoreactive B cell activation that is independent of IFN-I expression²⁰⁰. MAVS polymorphisms have also been reported in SLE, and a MAVS loss-of-function variant is associated with decreased IFN-I and RNA-protein binding autoantibodies¹⁹⁹.

Cytosolic DNA from exogenous viruses, pieces of chromatin, mitochondrial DNA (mtDNA), or reverse-transcribed RNA is recognized by cyclic GMP-AMP synthase (cGAS), which dimerizes to synthesize 2,3-cyclic GMP-AMP (cGAMP) and activates stimulator of interferon genes (STING) on the endoplasmic reticulum (ER) (Fig. 1). Expression of cGAS in peripheral blood mononuclear cells is not only significantly elevated in SLE patients compared with healthy individuals but also correlates positively with the IFN score²⁰¹. Gain-of-function mutations in *TMEM173*, which encodes STING, lead to systemic inflammatory and autoimmune conditions, including lupus^{198,202,203}. However, the relevance of cGAS–STING signalling to the pathogenesis of SLE is variable and mouse model dependent, with conflicting results^{204–207}.

Excessive activation of endosomal and cytosolic nucleic acid sensors, partly driven by genetic polymorphisms, might contribute to the prominent IFN-I signature in lupus. In addition to potentially increasing the activation of systemic myeloid cells and B cells, these pathways might also promote kidney disease, although experimental evidence to support this hypothesis in the context of LN is scarce. Potential underlying mechanisms include kidney cell responses to systemic IFN, and amplification of local inflammation owing to excessive activation of endosomal and cytosolic nucleic acid sensors in kidney-infiltrating myeloid cells or kidney-resident cells. Of note, these nucleic sensors are expressed in multiple kidney-resident cells including mesangial cells, podocytes and TECs, and have been assigned pathogenic roles in other kidney diseases^{208–210}.

Novel sources of chromatin

Chromatin is a central autoantigen driving adaptive immune system activation in SLE²¹¹. The aforementioned cytosolic and endosomal nucleic acid sensors were first studied in the context of recognizing viral DNA and RNA but can also be activated by endogenous DNA or RNA. Early studies reported that ICs containing nucleic acids released by necrotic or late apoptotic cells and lupus IgG could induce IFN α production in pDCs²¹². Over the past decade, newer insights have emerged (Fig. 2). Below we consider several sources of DNA or chromatin that might drive anti-DNA autoantibody production – the diagnostic

hallmark of SLE – and activate the innate immune system by engaging nucleic acid sensors, systemically and locally within the kidneys.

NETosis. Various pathogens, antibodies, ICs and cytokines can trigger NETosis²¹³ (Fig. 2). In LN, autoantibodies, ICs, cytokines and IFN can all prime neutrophils for NETosis, and the DNA released in NETs can subsequently trigger IFN-I production by engaging TLR9 in pDCs, or by activating cGAS–STING in monocytes and/or macrophages^{88,173,214–216}, thus fuelling a vicious circle. This signalling is further augmented by DNA-bound immunostimulatory molecules such as IL-33, HMGB1 and LL37, which are released in NETs²¹⁷. This self-perpetrating loop is likely to be active systemically and in the kidney. For example, IL-33-decorated NETs have been detected in inflamed kidneys of patients with active lupus, especially in the tubulointerstitium, and shown to stimulate robust IFN- α synthesis by pDCs in a IL-33 receptor (ST2L)-dependent manner²¹⁸.

In addition to NETosis, ferroptosis, which is an iron-dependent form of non-apoptotic cell death, is associated with the release and activation of damage-associated molecular patterns such as HMGB1, and DNA or lipid oxidation products in immune cells²¹⁹. A 2021 report showed that autoantibodies and IFN-I cooperatively induce ferroptosis in neutrophils and this is pathogenically important in LN²²⁰. Likewise, a 2022 study linked TEC ferroptosis to glomerular injury and tubulointerstitial pathology in LN²²¹; these cells are also implicated in kidney fibrosis and progression to kidney failure¹¹⁸.

Mitochondrial DNA. Mitochondria are another important source of DNA (Fig. 2) and platelets represent a major reservoir of mitochondria in circulation and a key source of mitochondrial antigens in SLE^{222,223}. Moreover, defective programmed mitochondrial removal during erythropoiesis leads to the accumulation of red blood cells carrying mitochondria (Mito⁺ red blood cells) in patients with SLE²²⁴. Mitochondrial reactive oxygen species promote the release of oxidized mtDNA into the cytosol, which then oxidize the much more abundant NET genomic DNA. Oxidized DNA is more resilient to nuclease degradation and is more efficient than reduced DNA in activating the STING pathway and triggering IFN production^{185,225–227}. Antioxidants, which inhibit mitochondrial reactive oxygen species, dampen NET formation and improve clinical features and immune dysregulation in murine lupus^{87,88,228}. Given that oxidatively stressed mitochondria release short mtDNA fragments via pores formed by voltage-dependent anion channel (VDAC) oligomers in the mitochondrial outer membrane, inhibiting VDAC oligomerization decreased mtDNA and NET release, IFN signalling and disease severity in lupus mice²²⁹, again underscoring the pathogenic role of oxidized mtDNA in LN. Of relevance, mtDNA has also been observed in NETs in LN kidney biopsy samples.

Microparticles. Apoptotic microparticles derived from platelets, erythrocytes, endothelial cells and immune cells, and bearing alarmins, lipid mediators, cytokines, tissue factor, nucleic acids and multiple other autoantigens, have been documented in SLE^{230–233}. Certain subsets of microparticles are associated with kidney function (as assayed by GFR), disease activity and other clinical features of SLE^{230,231,233,234}. Microparticles prime neutrophils for NETosis in SLE²³², which might lead to subsequent glomerular deposition of NETs and NET-driven LN²³⁵. Notably, conflicting studies have reported that microparticle numbers are unchanged, or even significantly decreased in SLE^{232,234}, highlighting the need for further studies.

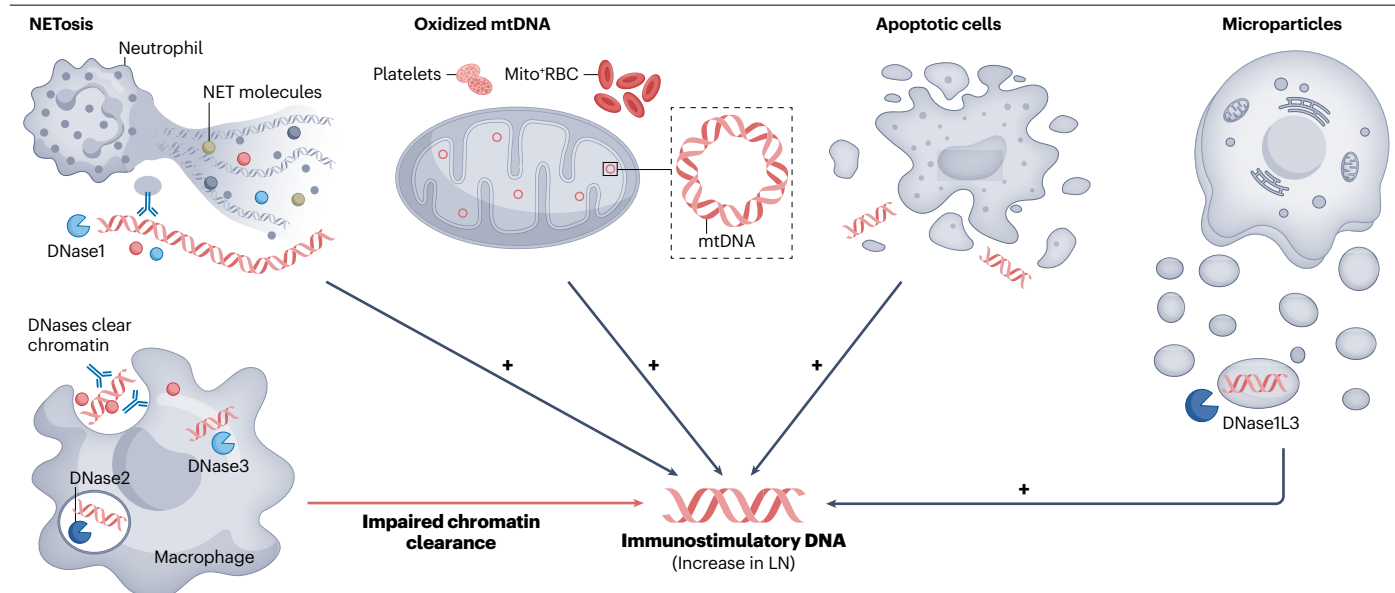


Fig. 2 | Sources of immunostimulatory DNA in systemic lupus erythematosus and lupus nephritis. Chromatin, in addition to being the key immunogen driving the adaptive immune response in systemic lupus erythematosus (SLE), has also emerged as a central driver of innate immunity owing to its ability to trigger cytosolic and endosomal nucleic acid sensors. In addition to nucleic acids released by necrotic or late apoptotic cells, novel sources of immunostimulatory DNA have been reported. Neutrophil extracellular traps (NETs) comprise modified chromatin and DNA decorated with cytoplasmic and granular proteins extruded during neutrophil cell death. Mitochondria provide another major source of immunostimulatory DNA (mtDNA). Platelets represent a major

reservoir of mitochondria in circulation and are a key source of mitochondrial antigens in SLE. Accumulation of red blood cells (RBCs) carrying mitochondria (Mito⁺ RBCs) has also been observed in patients with SLE. Apoptotic microparticles bearing nucleic acids have been documented in SLE. These diverse sources generate immunostimulatory DNA (grey arrows). By contrast, several DNases and RNases function to remove these DNA molecules, and their impaired function can also contribute to increased immunostimulatory DNA (red arrow). These factors, partly driven by polymorphisms in genes encoding key mediators of these pathways, contribute to the increased availability of immunostimulatory DNA in SLE and lupus nephritis (LN).

Defective chromatin clearance. Although the release of immunostimulatory or immunogenic DNA seems to be enhanced in SLE, the potential contribution of defective nucleic acid clearance in the development should not be overlooked²³⁶ (Fig. 2). Apoptotic remnants and ICs are typically engulfed by phagocytes, shuttled by phagosomes within these cells to lysosomal compartments, and processed in a non-inflammatory manner²³⁶. However, macrophages from patients with SLE have engulfment defects and impaired degradation of phagocytosed apoptotic cells and NETs^{94,237}. Macrophages from MRL/lpr mice have impaired lysosomal maturation, which enhances reactive oxygen species production and attenuates lysosomal acidification²³⁸. Lysosomal cathepsin K, which is involved in degrading biological macromolecules in lysosomes, contributes to disease in MRL/lpr mice, whereas its deficiency reduces kidney disease and autoantibodies²³⁹. Moreover, lysosomes are implicated in the deregulation of autophagy in SLE, both in mice and in patients²⁴⁰. Collectively, these events might promote the accumulation of uncleared nuclear antigens²³⁸.

Several nucleases have been implicated in the clearance of nucleic acids (Fig. 2). Most importantly, impaired function, genetic mutations, or deficiency of these nucleases are linked to SLE and LN. For example, DNASE1L3 is uniquely capable of digesting chromatin in microparticles released from apoptotic cells and DNASE1L3-deficient mice rapidly develop autoantibodies to DNA and chromatin, followed by an SLE-like disease²⁴¹. The therapeutic potential of DNases and RNases in SLE is an active area of investigation.

Overall, multiple processes can potentially enhance the release of immunostimulatory DNA in SLE, whereas genetic and non-genetic deficiencies in several nucleases might contribute to the accumulation of uncleared DNA. Both effects can promote the stimulation of cytosolic and endosomal nucleic sensors, resulting in increased release of IFN and other pro-inflammatory cytokines.

Autoantibodies and immune complexes

SLE is associated with >100 different circulating autoantibodies. Nevertheless, one of the most characteristic serological features of this disease is the presence of antibodies to native DNA (that is, dsDNA). Extrafollicular B cell differentiation into short-lived antibody-forming cells is the key mechanism of anti-DNA autoreactivity, which is facilitated by IFN-I signalling and IFN-I-producing pDCs²⁴². In addition to their close association with disease (>95% diagnostic specificity), anti-dsDNA antibodies (or at least cross-reactive antibodies that also bind dsDNA) seem to be instrumental in tissue injury, particularly in the kidney, but also in the skin and brain²⁴³. The unique specificity to dsDNA in SLE-associated antibodies intrigues researchers, and studies have continued to illuminate several quite novel aspects of their biology, including peculiar antigen–antibody binding features²⁴⁴, differential specificity for various types of DNA structures^{245,246}, capacity for penetration into live cells²⁴⁷, a role for the constant region in determining the fine specificity²⁴⁸, and the discovery of atypical non-canonical antibody functions including catalytic activity²⁴⁹.

Not all patients with clinically measured anti-DNA antibodies develop nephritis. Importantly, which antigens (nucleic acid or cross-reactive structural antigen) confer nephritogenic potential and why IC deposits or forms in the kidney remain contentious questions that are not yet resolved. Variation in DNA-binding antibody subgroups, which differ in their binding properties, pathogenic potential, and mechanism of disease induction, probably underlie the current discrepancies in study findings^{244,245,250}.

Although anti-dsDNA antibodies are most closely associated with LN, other autoantibodies, including related anti-nuclear antibodies (anti-nucleosomal or anti-histone), anti-ribosomal P antibodies, antibodies against soluble molecules involved in the disposal of apoptotic cells (for example, C1q), or local kidney antigens (for example, vimentin), might also be important^{251–253}. Newly discovered autoantibodies that have emerged from comprehensive omics studies²⁵⁴ also need to be validated in independent cohorts.

Complement

One of the main functions of the complement system is to safely remove ICs and apoptotic cells. Unsurprisingly, deficiency of early classical complement components such as C1q, C2 and C4 is an important (albeit quite rare) genetic susceptibility factor for the development of monogenic SLE or lupus-like conditions^{255,256}. However, complement activation and deposition, triggered by autoantibodies binding directly to kidney tissue or via ICs, are also a key feature of LN. All complement activation pathways have been implicated in the pathogenesis of SLE (reviewed in Satyam et al.²⁵⁷).

C3, C4 and other markers of complement activation are routinely monitored in clinical practice and are very useful indicators of disease activity and response to treatment, particularly in the kidney. The presence of complement cleavage products indicate complement activation, and technical advances such as their measurement through flow cytometry (for example, C4d deposited on erythrocytes), might be superior to measuring intact C3 and C4 in the serum²⁵⁸.

Complement inhibition has therapeutic potential and eculizumab, which is a fully humanized monoclonal antibody to C5 that prevents generation of C5a and the membrane attack complex, is now being explored in other conditions associated with complement activation after being approved to treat paroxysmal nocturnal haemoglobinuria and atypical haemolytic uraemic syndrome²⁵⁹. Interestingly, a systematic review provided some preliminary support for the use of eculizumab in a particular form of LN that is associated with thrombotic microangiopathy²⁵⁹. Similarly, avacopan, which is a small molecule inhibitor of the C5a receptor that is administered orally and has been approved for selected patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated nephritis, is now being studied for the treatment of LN²⁶⁰. Of note, understanding the dual protective and inflammatory roles of complement in LN is crucial to guiding the potential application of increasingly available complement-targeted therapies²⁶¹.

Cytokines and chemokines

Several cytokines and chemokines have been extensively studied in the context of LN pathogenesis, and here we highlight key mediators with demonstrated therapeutic potential in LN. For example, belimumab is an anti-BAFF monoclonal antibody that was recently approved (in combination with mycophenolate) for the treatment of LN²⁶², whereas anifrolumab, an anti-IFN α antibody, is indicated for moderate to severe SLE and is now being tested as an add-on to standard of care for LN (ClinicalTrials.gov Identifier: NCT05138133)^{263,264} (Fig. 3).

TNF-like weak inducer of apoptosis (TWEAK) is a member of the TNF cytokine superfamily, which binds to the Fn14 receptor that is expressed on multiple cell types including resident kidney cells. TWEAK–Fn14 interactions promote inflammation, kidney cell proliferation and/or cell death, vascular activation and fibrosis, through which they might contribute to the pathogenesis of LN. The importance of TWEAK–Fn14 signalling has been demonstrated in several murine models of SLE and LN^{265–268}. Moreover, serum and especially urinary TWEAK levels in patients correlate with nephritis and disease severity, and might help to monitor disease flares^{269,270}. Other key cytokines and chemokines with emerging therapeutic potential in LN include IL-17 (discussed above), TNF, transforming growth factor- β (TGF β), IL-6, IL-10, CCL-2, and CXC-chemokine ligand 10 (CXCL-10)^{270–273}. Notably, TGF β is also a key driver of fibrosis in LN¹¹⁸.

Studies combining large-scale urine proteomics with kidney single-cell transcriptomics have revealed a potential role for IFN γ and IL-16 in LN^{10,16}. Patients could be stratified over an IFN γ -inducible chemokine gradient and high chemokine levels identified patients with proliferative LN¹⁰. IL-16 was expressed by myeloid, NK and CD8⁺ T cells in LN kidneys. Response to treatment was associated with a reduction in urinary IL-16 (ref. 16), which also differentiates patients with proliferative LN from those with less severe LN subtypes or active SLE without kidney involvement²⁷⁴. IL-16 might also have pathogenic relevance in end-organs in SLE other than the kidney²⁷⁵.

Dozens of additional cytokines and chemokines, growth factors and other soluble mediators are emerging from recent large-scale proteomic screens of urine from patients with LN; several of these biomarkers are also elevated in LN kidneys^{13–15,269,276}. The feasibility of tracking urine biomarkers of active LN using patient-friendly point of care tests has also been reported²⁷⁷.

These exciting studies further support possible integration of non-invasive longitudinal follow-up of patients with SLE into clinical practice and predict that more accurate and personalized diagnosis and intervention in LN is on the horizon, instead of the current more uniform (“cookie-cutter”) approach of renal histology assessment by microscopy and protocol-driven initiation of standard-of-care treatment.

Genetics of lupus nephritis

Polymorphisms in several genes that impact lymphocyte signalling and activation (for example, *BANK1*, *BLK*, *LYN*, *CSK*, *PTPN22*, *TNFSF4*, *PRKCB*, *RASGRP3*, *PP2CA*, *CD44*, *ETS1*, *PRDM1* and *HLA-DR*), inflammation (such as, *TNFAIP3*, *TNIP3*, *UBE2L3*, *IRAK1* and *ITGAM*), IFN production (for example, *IRF5*, *IRF7*, *TLR7*, *TLR8*, *TLR9* and *STAT4*), DNA clearance (such as *DNASE1*, *DNASE1L3* and *TREX1*) and the complement pathway (such as C1q and C4) confer susceptibility to SLE and/or LN^{4,5,278}. Hundreds of single-cohort studies have documented and validated several genes that are specifically associated with LN, including *APOL1*, *ACE*, *ITGAM*, *HLA-DR* and multiple FCR genes²⁷⁸. Interestingly, an unbiased meta-analysis of genome-wide association screens comparing patients with SLE and LN with those without LN, identified a comprehensive list of LN-associated genes, including *PDGFRA*, *HLA-DR2*, *HLA-DR3*, *SLCSA11*, *ID4*, *HAS2* and *SNTB1* (ref. 278). Active research is underway to elucidate how these genes contribute to disease at a mechanistic level.

Therapeutic advances in lupus nephritis

The remarkable strides made in the mechanistic understanding of the mediators and pathways involved in LN, together with successful drug therapies for other rheumatological indications, have stimulated much clinical trial activity in SLE and LN over the past decade and led

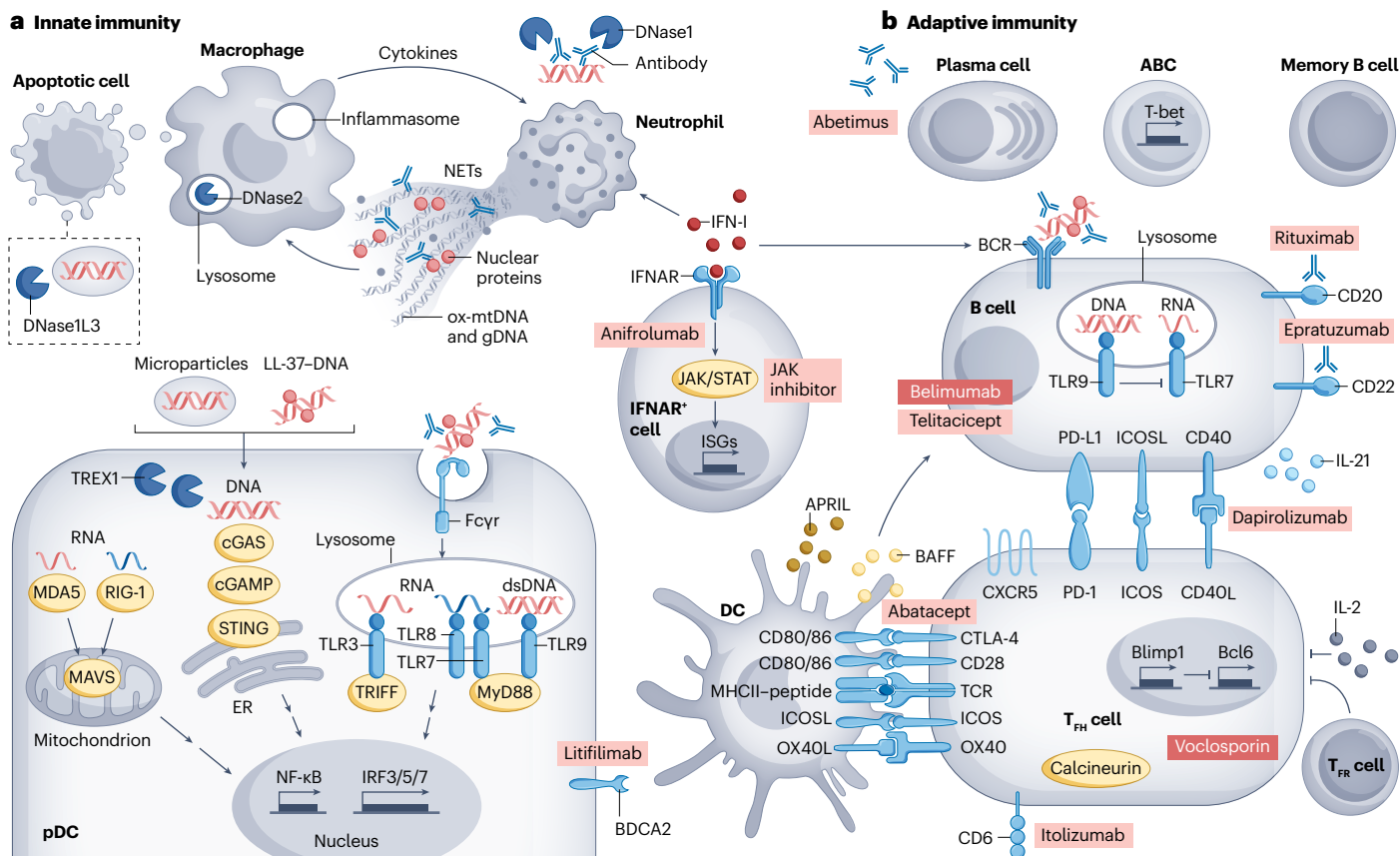


Fig. 3 | Overview of pathogenic mechanisms in LN and potential therapeutic targets. This figure highlights potential biological therapy targets in systemic lupus erythematosus (SLE) and lupus nephritis (LN) based on the underlying pathogenic node. **a**, Targets related to the generation of immunostimulatory DNA and pathways that can activate the innate immune system in SLE and LN. **b**, Targeting adaptive immune cells with a pathogenic role in disease and their associated pathways. Drugs highlighted in dark pink have been approved for

the treatment of LN. Abatacept, cytotoxic T lymphocyte-associated antigen 4 immunoglobulin fusion protein (CTLA4); anifrolumab, anti-IFN α receptor monoclonal antibody; belimumab, B cell-activating factor (BAFF)-specific monoclonal antibody; dapirolizumab, CD40 ligand antagonist; rituximab, CD20-specific monoclonal antibody; telitacept, TACI-Fc fusion protein targeting BAFF and a proliferating-inducing ligand (APRIL).

to the approval of belimumab and voclosporin, in combination with standard of care, for the treatment of LN. However, several unanticipated failures in phase III lupus clinical trials have also been reported, even of medications that exhibited very promising results in phase II²⁷. These medications (including rituximab, abatacept and baricitinib (a JAK inhibitor)) targeted key pathogenic mechanisms (Fig. 3), but primary endpoints were not met. Important variables such as sample size, choice of outcome measures, trial design and duration, length of follow-up, high placebo response rates, and high baseline use of corticosteroids or other immunosuppressants might complicate discernment of a positive signal. Moreover, SLE is a heterogeneous disorder involving many different cells and tissues, and positive results in a subset of patients might be difficult to ascertain. Even within LN, patients vary in pathological subtypes (for example, proliferative versus membranous histology) and phase of disease (incident LN versus disease relapse after a period of remission). A single biologic drug will unlikely successfully target all the mechanisms involved in the pathogenesis of LN. Targeting groups of patients stratified according to biomarker analyses or pharmacogenomics might improve trial success. Moreover,

systematic testing of combinations of drugs that target different pathways (a common approach in oncology therapy) might be more effective in LN^{280,281}.

The lack of success in clinical trials does not invalidate the underlying rationale for treatments. For example, although rituximab (an anti-CD20 mAb that depletes B cells) did not meet endpoints for LN²⁸², it remains widely used for this indication and there is strong real-world experience supporting its use, as endorsed by the American College of Rheumatology and European Alliance of Associations for Rheumatology. Moreover, a next-generation B cell-depleting agent that is more potent than rituximab – obinutuzumab – yielded promising results in a phase II randomized clinical trial in patients with active proliferative LN^{262,283}. Profound B cell depletion with anti-CD19 CAR T cell therapy also showed potential benefit in refractory SLE²⁸⁴.

Therefore, in LN, therapy development with a strong immunopathogenic rationale, together with close attention to patient selection and other aspects of trial design, is highly likely to identify newer and improved forms of treatment that will translate into better disease outcomes.

Conclusions

The past decade has witnessed tremendous growth in our understanding of the cellular and molecular basis of LN. In terms of renal infiltrating leukocytes, we have gained a better resolution of the subtypes of macrophages and T cells at the sites of injury. Insights have also emerged regarding neutrophil-released mediators in disease pathogenesis. Chromatin, in addition to being a key immunogen driving the adaptive immune response in this disease, has also emerged as a central driver of innate immunity owing to its ability to trigger cytosolic and endosomal nucleic acid sensors (Fig. 1). Collectively, current evidence suggests that increased generation and inefficient clearance of immunostimulatory chromatin drives both adaptive and innate immunity in LN, particularly in genetically susceptible individuals (Fig. 3). However, several aspects remain unclear, including the relative contribution of each of these chromatin-related mechanisms to the generation of immunostimulatory DNA in SLE and LN, the impact of genetic polymorphisms in generating immunostimulatory DNA and the relative contribution of systemic versus local immunostimulatory DNA in initiating and driving LN. Importantly, which of these processes can be targeted therapeutically remains a crucial question. Active research in all of these areas is likely to broaden our understanding of the origins, characteristics and impacts of the central autoantigen in SLE and LN, namely chromatin.

Emerging data also suggest that resident renal cells are not innocent bystanders in LN but can actively contribute to disease. The next decade could significantly expand these preliminary observations thanks to an explosion of transcriptomic and proteomic studies with spatial coordinates, taking the field one step closer to delivering personalized medicine in LN.

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Author contributions

All authors researched data for the article, made substantial contributions to discussions of the content and wrote, reviewed or edited the manuscript before submission.

Competing interests

C.P. is one of the holders of a patent describing the diagnostic use of urinary TWEAK in lupus nephritis (Method of treating lupus nephritis; Grant US-9730947-B2). C.M. and C.P. serve as scientific consultants to Equilibrium, which is developing anti-CD6 as a therapy for lupus nephritis. The other author declares no competing interests.

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