arthritis research&therapy

REVIEW

Mechanisms of tissue injury in lupus nephritis

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Abstract

Systemic lupus erythematosus is a prototypic autoimmune disease characterized by autoantibody production and immune complex formation/deposition in target organs such as the kidney. Resultant local inflammation then leads to organ damage. Nephritis, a major cause of morbidity and mortality in patients with lupus, occurs in approximately 50% of lupus patients. In the present review, we provide an overview of the current research and knowledge concerning mechanisms of renal injury in both lupus-prone mouse models and human lupus patients.

Introduction

Nephritis is a major cause of morbidity and mortality in patients with lupus. Nephritis occurs in approximately 50% of lupus patients, but rates vary significantly between genders (men more than women) and ethnicities (more common in people of color). Men and minorities with lupus nephritis are also more likely to progress to end-stage renal disease than women or people of European ancestry. The multiple factors underlying these demographic differences are unclear at this time [1].

The International Society of Nephrology revised the World Health Organization classification of lupus nephritis recently, although maintaining six classes [2]. The pathologic classes vary from mild mesangial involvement (Class I) to diffuse proliferative disease (Class IV) to membranous disease (Class V) to end-stage fibrosis (Class VI). Although most attention in lupus nephritis is focused on glomerular disease, there is also significant tubular disease that impacts prognosis and renal function [3]. For the purposes of the present review, we will primarily focus on the proliferative forms of lupus nephritis (focal proliferative, Class III disease; and diffuse proliferative, Class IV disease), highlighting several contributors to tissue injury.

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Much of what is known about pathogenic factors in tissue damage in lupus nephritis was derived from studies of murine models of lupus, with confirmation as possible in humans. These studies utilize multigenic models of lupus (that is, MRL/lpr, NZB/NZW, and NZM congenic strains) as well as single gene mutants (that is, DNAse 1, Nrf2, or Fcγ receptor (FCγR) knockouts) [4,5]. These models share common features of human disease such as anti-double-stranded DNA (anti-dsDNA) antibodies and proliferative nephritis, but differ in their renal cytokine/chemokine profile, cellular infiltration and acuity/chronicity of disease [5]. Thus, as in human disease, there is heterogeneity of pathogenic mechanisms in murine lupus nephritis.

Autoantibodies and renal immune complex deposition

The presence of autoantibodies is a requirement for development of lupus nephritis [6]. Antibodies to dsDNA/nucleosomes are most closely linked with development of nephritis [7], although what separates pathogenic from nonpathogenic anti-dsDNA antibodies is not clear [8]. Pathogenic anti-dsDNA antibodies deposit as immune complexes (IC) [6]. When anti-C1q antibodies are present along with anti-dsDNA antibodies, development of renal disease is accelerated [9,10].

There are three postulated mechanisms for formation of glomerular ICs, all of which probably contribute to disease in some patients, given the heterogeneity of disease [11]. The first mechanism is deposition of preformed serum ICs [12]. This mechanism is hard to confirm, as ICs are difficult to isolate or quantify in lupus patient sera and thus are not felt to play a major role in the pathogenesis of lupus nephritis. Binding of autoantibodies to *in situ* glomerular antigens such as laminin, annexin II or heparin is a second mechanism postulated for IC deposition. This crossreactivity is demonstrated via the elution of antibodies from glomeruli that bind these antigens in addition to dsDNA/chromatin [13,14].

A recent series of investigations implicates a third mechanism, anti-dsDNA/chromatin antibodies binding to nucleosomes/DNA present in the glomerular matrix, as the most compelling [13]. Due to charge/charge interactions, circulating DNA/nucleosomes can deposit in the glomerular basement membrane and serve as antigen for autoantibodies. Another source of glomerular DNA/

nucleosomes is retention of nucleosomes from necrotic intrinsic glomerular cells [7]. Indeed, recent electron microscopic co-localization experiments in human and mouse lupus kidneys indicated that antibodies present in the glomerulus are bound to electron-dense deposits that were identified to be nucleosomal material [15]. Following the formation of these ICs, there is downregulation of DNAse I in the kidney, which allows for enhanced amounts of nucleosomal material in the glomerulus [16]. These complexes can then lead to further activation of immune pathways by co-stimulation of FcγRs and endosomal Toll-like receptors (TLRs) and/or by activating the complement cascade [7]. Although the latter mechanism of antibodies binding nucleosomal material from necrotic glomerular cells provides a compelling story, it is likely that any of these mechanisms may be present in a given patient [11].

Complement and tissue injury in lupus nephritis

Complement has a dual role in lupus. Deposition of complement proteins in glomeruli is a key feature of lupus nephritis. There is strong evidence that complement activation is deleterious in lupus nephritis [17]. This is in contrast to the known association of early complement component deficiency with lupus. Individuals deficient in C1 components, C2 and C4, have a high prevalence of lupus due to impaired clearance of ICs/apoptotic bodies leading to breaking of tolerance. Activation of the classical pathway of complement activation thus appears protective against lupus due to enhanced clearance of ICs and cellular debris [18].

Recent findings implicate the alternative complement pathway as a key component of complement-mediated damage in lupus nephritis [19,20]. Activation of the alternative complement pathway triggers an amplification loop that accelerates cleavage of C3 to C3b, covalent binding to cellular surfaces, with release of the anaphylotoxin C3a and C5a, and formation of the complement membrane attack complex. It is currently unclear which of the outcomes of complement activation are most important in lupus nephritis: generation of C3a and C5a or formation of the membrane attack complex.

Blocking the alternative complement pathway either genetically or pharmacologically leads to significantly decreased severity of renal disease in murine lupus models [20-22]. Eliminating the natural inhibitor of the alternative pathway, Factor H, leads to acceleration of lupus-like renal disease [23]. Pharmacologic inhibition of the alternative pathway is effective in both MRL/lpr mice and NZM congenic mice [19,21]. These results suggest that the alternative complement pathway is a key mechanism for tissue injury in lupus nephritis. Genetic deletion of C3 has minimal effect on murine lupus nephritis, probably due to diminished clearance of ICs enhancing immune activation by noncomplement-mediated mechanisms [24]. Blocking the C3a receptor has minimal impact on disease [25], while blocking complement activation further downstream is effective, as studies of C5aR-deficient mice or using a C5aR blocking antibody also led to decreased severity of renal disease in murine models of lupus [26,27].

Complement may also play a role in tubular damage in lupus. Development of proteinuria leads to spilling of complement components into the urine. Complement C3 is activated in urine via pH and urea, resulting in formation of membrane attack complexes on the epithelial side of tubular cells [28]. There are no complement protective mechanisms present on the epithelial side of renal tubular epithelial cells, resulting in unchecked complement activation and tubular damage. These experiments were performed under adriamycin-induced proteinuria in mice, not in lupus, but similar mechanisms may explain some of the tubular damage that occurs in lupus.

Fcγ receptors and Toll-like receptors in lupus nephritis

Another mechanism by which ICs may lead to tissue damage is via activation of activating FcγRs, upon binding of immunoglobulin Fc regions by FcγR-expressing cells [29]. Although FcγRs are clearly implicated in the development of lupus in genetic studies of gain-of-function and loss-of-function mutations and copy numbers of FcγR genes, their role in predisposition to lupus nephritis and/or tissue injury is not as clear [29-32]. In mice, knockout of specific FcγR can lead to accentuation or diminution of disease; most of the effect, however, is on development of lupus rather than specific tissue injury [33,34]. Any impact of FcγR on disease is highly dependent on background strain [35]. Similarly, reports of associations of FcγR genetic changes with nephritis appear linked to specific ethnicities [29].

FcγR may be important in association with TLRs in mediating IC-induced inflammation in the kidney [36]. As noted above, dsDNA-containing ICs may activate kidney resident cells via a co-signaling mechanism of FcγR activation via the autoantibody and TLR9 activation via dsDNA. This type of two-step activation is known to activate B cells by ICs containing either TLR9 or TLR7 activators such as dsDNA or single-stranded RNA [37]. Inhibition of TLR7/9 is effective in treating murine lupus, although whether primarily at the level of systemic autoimmunity or via blocking specifically renal tissue damage is not clear [38].

Immune cells in lupus nephritis

Following the formation and/or deposition of ICs in the kidney, interactions between resident renal cells and infiltrating inflammatory cells promote tissue injury.

Local cytokine, chemokine and adhesion molecule production leads to further influx of inflammatory cells and production of proinflammatory cytokines, ultimately resulting in renal inflammation, tissue injury and fibrosis. T cells are important mediators in both mouse models and human patients in the progression of lupus nephritis. Lupus T cells express increased levels of molecules necessary for homing and/or demonstrate increased homing to the kidney [39-42]. Mechanisms by which T cells contribute to tissue injury include activating and providing help to nephritogenic antibody-producing B cells, recruiting macrophages and dendritic cells (DCs), and producing cytokines. Indeed, kidney-infiltrating T cells – including $CD4^+$, $CD8^+$ and IL17-producing $CD4^-CD8^-$ double-negative T cells – are activated and express a wide array of proinflammatory cytokines [43-46]. Depleting T cells or blocking T-cell activation reduces progression of nephritis in lupus mouse models [47,48].

Pathogenic B cells have a variety of functions that contribute to lupus nephritis. Namely they produce autoantibodies that can cause renal damage via disruption of cellular functions, cytotoxicity mediated by interactions with complement and release of inflammatory mediators. Studies in lupus mouse models demonstrated that infiltrating B cells in the kidney secrete antibodies with various Ag specificities, contributing to increased *in situ* ICs [49-51]. Similarly, germinal center-like structures and T-cell–B-cell aggregates present in the kidney suggest *in situ* secretion of pathogenic antibodies, including nephritogenic antibodies, and ICs in human lupus patients [52-54]. Depleting B cells either prior to or after disease onset prevented and/or delayed the onset of nephritis in several different lupus mouse models [55-58] and resulted in complete or partial clinical remission in patients [59]. MRL/lpr lupus-prone mice that have B cells unable to secrete antibodies still develop nephritis, however, although less severely [60] – indicating that additional B-cell functions, such as antigen presentation and activation of pathogenic T cells and proinflammatory cytokine production (IL-6 and TNFα), contribute significantly to kidney injury.

Neutrophils, macrophages and DCs, present in nephritic kidneys, also are contributors to injury. Neutrophils are a source of neutrophil extracellular traps that contain self-antigens such as histones and DNA, and are present in ICs deposited in the kidney of systemic lupus erythematosus (SLE) patients [61-64]. The response to neutrophil extracellular traps contributes to kidney injury through the activation of plasmacytoid DCs and production of type I interferon [63,64]. DCs and macrophages produce T-helper type 1 proinflammatory cytokines (IL-12 and IFNγ), express chemokine receptors and interact with autoreactive T cells to recruit additional inflammatory cells. Reduction of $CD11c^+$ DCs in the MRL/lpr lupus-prone model resulted in improved kidney disease [65], and the presence of plasmacytoid DCs was correlated with high IL-18 expression in the glomeruli of patients with active nephritis [66]. An activated macrophage population with a type II phenotype (M2b) that expresses high amounts of proinflammatory cytokines and exhibits tissue degradation is associated with the onset of proteinuria in NZB/NZW F1 mice [67-69]. Similarly, in lupus patients with nephritis, macrophage infiltration in the kidney correlates with disease [70] (reviewed in [71]).

Cytokines and chemokines

Production of cytokines and chemokines in glomeruli early during lupus nephritis precedes inflammatory cell infiltration and proteinuria [72,73]. T-helper type 1 cytokines are predominantly present in nephritic kidneys in SLE patients [74,75]. T-helper type 1 proinflammatory cytokines that contribute to tissue damage include IL-12, IL-18 and IFNγ. High IL-18 and/or IL-12 production is observed in glomeruli of human and mouse lupus nephritis. IL-18 overexpression in kidneys of predisease MRL/lpr lupus-prone mice resulted in accumulation of leukocytes in the kidney and increased renal pathology and proteinuria [76]. Similarly, MRL/lpr mice in which IL-12 was overexpressed presented increased T-cell infiltration, specifically IFNγ-producing T cells, and accelerated nephritis [77], while MRL/lpr $IL12^{-/-}$ mice showed reduced IFNγ levels and delayed nephritis [78]. Higher IL-18, IL-12 and IFNγ levels were demonstrated in SLE patients compared with healthy controls, and specifically in SLE patients with nephritis compared with patients without nephritis. Urinary IL-12 levels correlated with onset and severity of nephritis in these patients [66,79]. The major mechanism of renal injury by IL-18 and IL-12 is probably through their upregulation of IFNγ. The levels of IFNγ in nephritic MRL/lpr mice are increased compared with controls, and kidney pathology in mice overexpressing IL-12 requires IFNγ [77]. Importantly, IFNγ signaling was demonstrated to directly induce cell death of tubular epithelial cells in MRL/lpr kidneys [80].

Chemokines contribute to renal damage by recruiting inflammatory cells to the kidney. Proinflammatory chemokines/growth factors including monocyte chemoattractant protein-1 (MCP-1, CCL2), macrophage inflammatory protein-1β (CCL4), RANTES (CCL5), macrophage colony-stimulating factor and IFNγ-induced protein-10 (CXCL10) were demonstrated to be upregulated in the kidney of lupus-prone mice prior to proteinuria and renal damage [81]. Their expression was followed by mononuclear infiltration and increased expression of their respective receptors (CCR1, CCR2 and CCR5). Increased levels of macrophage inflammatory protein-1α (CCL3), MCP-1, RANTES and IFNγ-induced protein-10

were also observed in the serum of lupus patients [82,83]. Of these chemokines, MCP-1 was demonstrated to be associated with kidney damage in lupus. MCP-1 levels increase in the kidney as nephritis progresses in the MRL/lpr lupus model [84]. A knockout of MCP-1 on the MRL/lpr background resulted in reduced macrophage and T-cell infiltration in the kidney, reduced proteinuria and renal pathology and prolonged survival [84]. Blockade of MCP-1 after disease onset improved renal disease and prolonged survival, characterized by decreased renal infiltration by macrophages and T cells [85,86]. In lupus nephritis patients, tubulointerstitial expression of MCP-1 was demonstrated to be associated with chronic renal damage [75] and urinary MCP-1 levels were associated with renal disease activity [87,88].

Transcription factors

The signal transducers and activators of transcription (STAT) factor family is part of the Jak/STAT signaling pathway activated by cytokines and contains several members identified as playing roles in lupus nephritis, including STAT1 and STAT4.

STAT1, when activated, binds to IFNγ-activated sequences in the promoters of IFNγ-inducible genes, and IFNγ induced the activation of STAT1 in mesangial cells of MRL/lpr mice [89]. Elevated STAT1 expression, both total and activated forms, is present in kidneys of nephritic lupus mice with predominant expression in glomeruli [89]. In SLE patients, STAT1 expression is present in renal biopsies of lupus nephritis patients and expression levels correlated with disease activity [90].

STAT4 was identified as a lupus risk gene. A polymorphism identified in STAT4 is associated with dsDNA antibodies and severe nephritis in human SLE [91]. In NZM2410 and NZM2328 lupus-prone mouse strains, loss of STAT4 results in lower levels of IgG anti-dsDNA antibodies, but development of more severe renal disease [92,93].

Transcription factors such as STAT factors influence the expression of an array of genes that play a role in the cellular function of immune cells and/or the response of cells in target tissues to inflammation, influencing the extent of tissue injury. Dysregulation of transcription in lupus nephritis is further indicated by the profound effect of alterations in Ets factor/Fli-1 expression and the impact of histone deacetylase inhibitors, which diminish gene transcription, on development and severity of renal disease.

Reactive intermediates in tissue injury

Several studies utilizing competitive inhibitors of inducible nitric oxide synthase (iNOS) suggest that iNOS activity is pathogenic in murine lupus [94,95]. Inhibiting iNOS activity in MRL/lpr mice, before disease onset, with the nonspecific arginine analog L-N^G-monomethyl-L-arginine reduced 3-nitrotyrosine formation in the kidney, partially restored renal catalase activity, and inhibited cellular proliferation and necrosis within the glomerulus [94,95]. The partially selective iNOS inhibitor L-N^6-(1-iminoethyl)lysine had a similar effect when used to treat these mice prior to disease onset [96]. L-N^G-monomethyl-L-arginine therapy in NZB/W mice that were already suffering from nephritis had a similar but less profound effect on proteinuria and renal histopathology than did preventative therapy [97]. However, L-N^G-monomethyl-L-arginine as monotherapy for the treatment of active disease was less effective in the rapidly progressive MRL/lpr model [97]. These findings suggest that overproduction of nitric oxide is deleterious and mediates tissue damage in lupus nephritis.

The mechanisms through which iNOS activity may be pathogenic in SLE were studied in animal models and *in vitro*. Peroxynitrite ($ONOO^-$), a byproduct of iNOS activity, can nitrate amino acids and change the catalytic activity of enzymes [97]. One such enzyme, catalase, serves to protect host tissues from free radical attack [98]. In vascular tissue, prostacyclin synthase and endothelial nitric oxide synthase are inactivated by peroxynitrite, leading to vasoconstriction [99]. These observations suggest that one mechanism through which iNOS activity is pathogenic is via deactivation of tissue protective enzymes. Nitrosylation is also being increasingly recognized as a mechanism for impacting gene regulation similar to methylation and acetylation. Nitrosylation of NF-κB modulates its function, altering resultant inflammatory gene transcription. Such nitrosylation does not appear to impact the nuclear migration of NF-κB, but rather modulates its transcriptional activity once inside the nucleus [100]. Such nitrosylation can be achieved *in vivo* by administering *S*-nitrosoglutathione, providing a potential therapeutic pathway via modulation of reactive intermediates [100].

Markers of systemic nitric oxide production are elevated in patients with SLE in a manner that parallels disease activity [101]. Those patients with lupus nephritis had the most elevated markers of systemic nitric oxide production among SLE subjects [102]. This observation spawned the hypothesis that glomerular proliferative lesions were a source of increased nitric oxide production, as well as a potential result of inappropriate nitric oxide production. Several reports supported this hypothesis, with renal biopsy studies showing increased iNOS expression in the glomeruli of lupus nephritis subjects [101,103] – particularly in mesangial cells, glomerular epithelial cells, and infiltrating inflammatory cells [101]. When 3-nitrotyrosine was used as a surrogate for iNOS activity, the association with disease activity was greater in African Americans [104], suggesting a possible

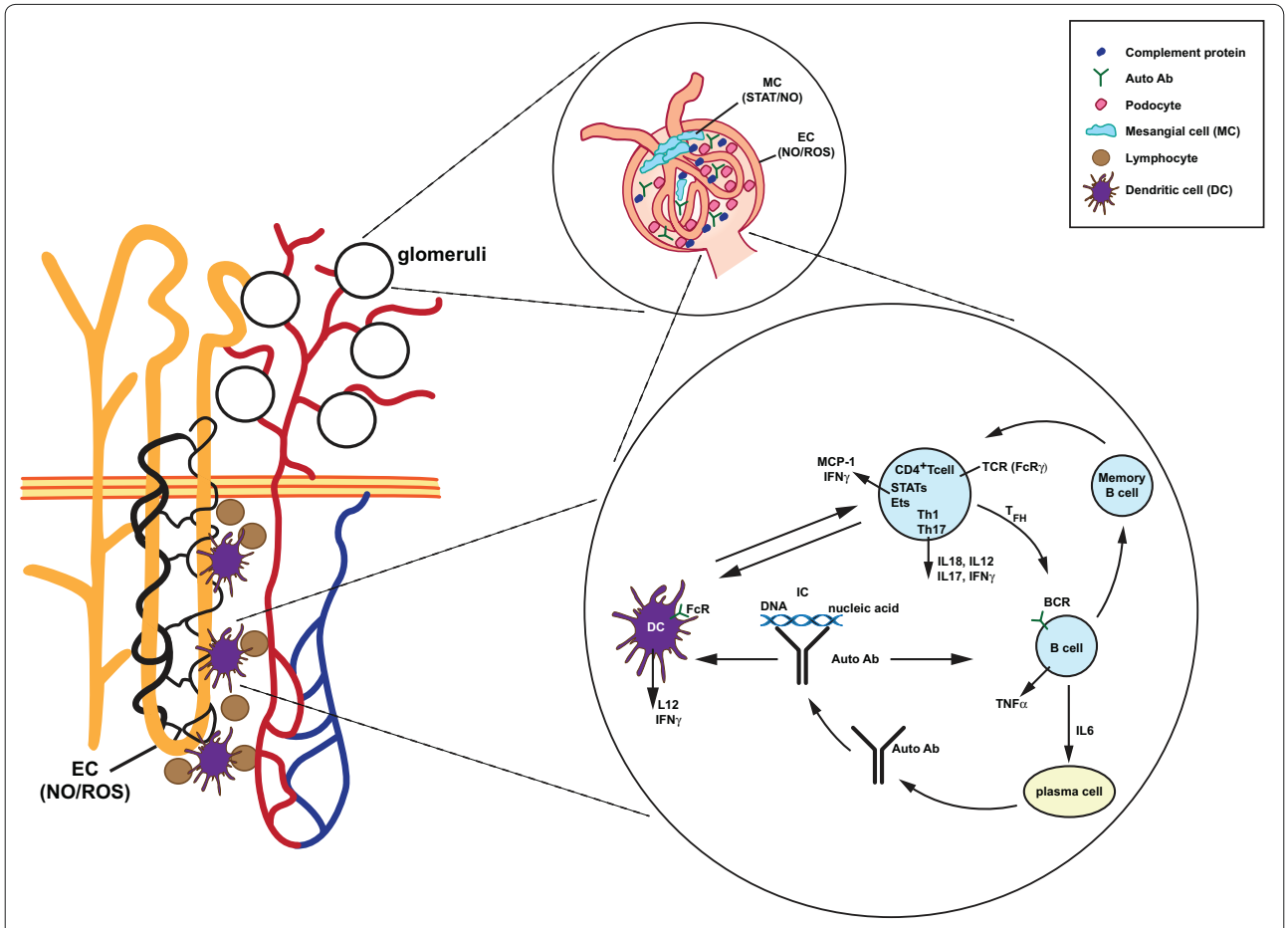

Figure 1. Summary of proposed pathogenic mechanisms in tissue injury in lupus nephritis. Top right: The first step leading to nephritis involves the production of autoantibodies to self-antigens followed by formation of immune complexes (ICs) in glomeruli. IC deposition leads to complement activation and intrinsic renal cell activation (mesangial cells (MC) and endothelial cells (EC)), both leading to local chemokine and cytokine inflammation. Chemokine expression leads to an influx of inflammatory cells such as lymphocytes and macrophages. Left: Influx of immune cells leads to interstitial as well as further glomeruli inflammation and EC activation. Activated renal cells (MC and podocytes) and infiltrating immune cells (macrophages and dendritic cells (DCs)) produce reactive nitrogen (nitric oxide (NO)) and reactive oxygen species (ROS). The combined expression of cytokines and ROS results in further renal inflammation and fibrosis, resulting in cumulative tissue destruction both at the glomerular level (top right) and the tubular level (left). Bottom right: Lymphocyte interactions and functions such as cytokine expression and antibody production contribute to inflammation and damage in the tubules and glomeruli. BCR, B-cell receptor; FcR, Fc receptor; MCP-1, monocyte chemoattractant protein-1; STAT, signal transducers and activators of transcription; TCR, T-cell receptor.

difference between Caucasians and African Americans in reactive oxygen intermediate production versus reactive nitrogen intermediate production that may impact outcome.

To assess whether genes involved in reactive oxygen intermediate production are associated with lupus nephritis, polymorphisms in the gene for myeloperoxidase were assessed. There was a significant correlation between the low expressing myeloperoxidase 463A allele and the risk for developing nephritis in African Americans [105]. This association was subsequently confirmed in two other cohorts. This finding may seem paradoxical until one considers that reactive oxygen intermediates can sequester reactive nitrogen intermediates and that low myeloperoxidase activity can lead to increased OH radical stress. Polymorphisms of iNOS and endothelial nitric oxide synthase are also reported to be associated with genetic risk of developing lupus, although associations with renal disease are less clear [106,107]. A recent study demonstrated that inhibiting reactive intermediate production in diabetics improved renal function, suggesting that a similar strategy may also be effective in lupus [108].

Renal regeneration/fibrosis

End-stage renal disease in lupus is secondary to loss of glomerular and tubular function due to renal cell death and resultant fibrosis. The factors important in the inflammatory process are more clearly defined than the factors resulting in progressive glomerular/tubular loss

and fibrosis. As in other fibrotic processes, transforming growth factor beta expression is associated with renal fibrosis [109]. Co-factors such as hypertension, production of vasoactive substances such as kallikrein, ongoing proteinuria and nephrotoxic drugs play an important role in progression of renal disease in lupus. Genetic factors are probably also a major determinant of progression to end-stage renal disease. Factors involved in renal regeneration post injury are even less well defined. Recruitment of stromal cells to the kidney via chemokine receptors and C3a may result in repair of some tissue damage, but further research is needed in this area to define therapeutic strategies [110].

Conclusion

In summary, the pathogenesis of lupus nephritis and mechanisms of resultant renal injury remains an active field of investigation, with much knowledge gained but many questions still left to answer. The complexity and number of factors involved in disease make it difficult to derive a clear step-by-step pathogenic pathway. A summary of proposed pathogenic mechanisms is illustrated in Figure 1. Autoantibodies and ICs are important first mediators that are required for disease expression in human disease. Deposition of ICs, however, is not sufficient for disease expression, as numerous studies report lack of proliferative disease despite significant IgG/IC deposition in glomeruli. Downstream mediators are blocked in these pharmacologic/genetic studies, inhibiting disease activity without impacting IC deposition. Complement, TLRs and FcγRs play an amplification role in the initiation and propagation of disease. IC deposition with complement, TLR and/or FcγR activation stimulates intrinsic immune active glomerular cells to release inflammatory cytokines and chemoattractant chemokines, resulting in the influx of the spectrum of inflammatory cells. The end mediators of disease appear to be the reactive intermediates produced by both inflammatory cells and intrinsic glomerular cells. Although tissue repair post inflammatory injury is also probably a key prognostic process, very little is known regarding factors involved in tissue repair. These multiple mediators provide a host of targets for therapeutic intervention. Only 50% of patients respond to current standards of therapy. Clearly there is room for improvement, but no one therapy will probably be effective in most patients. Determining which pathway is key to a given patient is the challenge for the immediate future, as well as developing safe mechanisms for blocking these pathways.

Autoimmune Basis of Rheumatic Diseases

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Abbreviations

DC, dendritic cell; dsDNA, double-stranded DNA; FCγR, Fcγ receptor; IC, immune complex; IFN, interferon; IL, interleukin; iNOS, inducible nitric oxide synthase; MCP-1, monocyte chemoattractant protein-1; NF, nuclear factor; RANTES, regulated upon activation, normal T-cell expressed and secreted; SLE, systemic lupus erythematosus; STAT, signal transducers and activators of transcription; TLR, Toll-like receptor; TNF, tumor necrosis factor.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

TKN and GSG contributed equally to the drafting and editing of the final manuscript.

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