What is damaging the kidney in lupus nephritis?

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Summary

Despite marked improvements in the survival of patients with severe lupus nephritis over the last 50 years the rate of complete clinical remission following immune suppression is less than 50% and renal impairment still occurs in 40% of affected patients. An appreciation of factors leading to the development of chronic kidney disease (CKD) following acute or subacute renal injury in lupus patients is beginning to emerge. Processes that contribute to endstage renal injury include continuing inflammation, activation of intrinsic renal cells, cell stress and hypoxia, metabolic abnormalities, aberrant tissue repair and tissue fibrosis. This understanding is leading to the development of novel or adjunctive therapies that may protect from the secondary non-immune consequences of acute injury. Approaches based on a molecular/proteomic/lipidomic classification of disease should yield new information about the functional basis of disease heterogeneity so that the most effective and least toxic treatment regimens can be formulated for individual patients.

Introduction

Lupus nephritis (LN) affects 30–60% of adults and up to 70% of children with systemic lupus erythematosus (SLE) and is characterized by the glomerular deposition of immune complexes followed by recruitment of an inflammatory response. Glomerular disease is classified by light microscopy into five histologic subtypes of which classes III–V have the potential for long term damage. Further histologic classification uses composite scores for active inflammation and chronic scarring (1–5). Although classification drives therapeutic decision-making, the current scheme does not adequately predict which patients will respond to therapy (3, 6–7), indicating that additional phenotyping based on mechanisms of tissue injury is required. In addition, patients in clinical remission may exhibit progressive inflammation and fibrosis in repeat biopsies suggesting that improved disease monitoring could prevent undertreatment of subclinical disease (8–9).

While advances in immunosuppressive regimens and general medical care have erased most of the differences in long-term outcomes between proliferative and membranous LN (7, 10–11), the rate of complete remission for proliferative disease remains below 50% (12–14), and

Competing Interests
None

up to 40% of LN patients still develop some degree of renal impairment (11, 14). This failure of immunosuppressive agents to adequately treat LN, even in the setting of well-monitored clinical trials, reflects an incomplete understanding of disease pathogenesis. Either immune cell proliferation is not the only relevant cause of renal injury, or there is a therapeutic time window after which this type of intervention is no longer effective.

In the first section of this review I will discuss current knowledge of LN pathogenesis including disease initiation by immune complexes, immune activation in the kidney, and the responses of renal parenchymal cells to this insult. In the second part I will discuss approaches to identifying new pathogenic mechanisms, and review alternate ways to classify and monitor disease that include molecular and proteomic analyses. Finally I will address how these concepts may lead to improved therapies.

Mechanisms of renal damage

Initiation of inflammation by immune complexes

LN is initiated in most cases by the glomerular deposition of IgG and complement. Rarely, LN occurs in the absence of immune complexes, presumably due to direct damage by soluble inflammatory mediators (15). Sources of immune complexes include circulating anti-nuclear, anti-C1q, and crossreactive anti-glomerular autoantibodies (16–20), opsonized apoptotic particles, microparticles, and neutrophil NETs (21–22). Particulate DNA such as that within neutrophil NETs can be resistant to digestion by DNAse (22), and downregulation of renal DNAse I can be a late feature of disease (23). Although antibodies eluted from LN kidneys are enriched for anti-DNA activity, not all anti-DNA antibodies are pathogenic. Furthermore, non-DNA binding antibodies, some arising *in situ*, also contribute to renal disease (24–25). This heterogeneity of renal depositing antibodies limits the ability of serum antibody profiles to predict LN flares (26).

Immune complexes initiate renal damage by several mechanisms (Figure 1). Complexes that deposit in the subendothelium injure endothelial cells and are the hallmark of Class III and IV proliferative disease. These deposits have access to the vascular space and may activate circulating myeloid cells that express Fc receptors, allowing them to infiltrate the renal tissue (27). By contrast, subepithelial deposits, found in Class V disease, injure podocytes but elicit a less severe inflammatory response as they contact only the urinary space. If the glomerular basement membrane ruptures however, these immune complexes can access the whole glomerulus. Immune deposits may initiate the complement cascade, or they may directly activate intrinsic glomerular cells (28–29), inducing the release of inflammatory chemokines and cytokines. Complexes containing nucleic acids additionally activate intracellular TLRs, thereby enhancing the inflammatory response.

Immune mechanisms of tissue injury

Soluble inflammatory mediators—Following immune complex deposition, a large variety of inflammatory mediators is produced in LN kidneys with spreading of the response as disease progresses (28, 30). Several locally produced cytokines and chemokines that contribute to inflammatory damage and whose absence or inhibition greatly attenuates disease activity have been identified. Examples include CCL2, a chemokine expressed early

in the glomerulonephritis process, and TNF that is expressed at proteinuria onset (31–32). A Type I IFN signature is also a feature of LN kidneys (33–34). IFN has multiple detrimental effects on the kidneys including vascular rarefaction and injury to glomerular parietal cells and podocytes (35–36). Once tissue injury occurs, soluble products released from injured cells amplify the inflammatory response by stimulating extracellular and intracellular innate immune receptors (37–41). Podocytes, for example, are sensitive to TLR-mediated signals and other inflammatory mediators such as NO, which induce foot process effacement and podocyte loss (42). Nevertheless, not all renal inflammatory mediators are necessary for the inflammatory process. For example, IL-17 deficiency alters the course of LN only in some models in which TH17 cells infiltrate the kidneys (43–44). Thus, targeting of single inflammatory mediators may not be sufficient to reverse the established renal inflammatory response that becomes more complex over time.

Cellular infiltrates—Inflammatory cells may infiltrate the kidney through glomerular or interstitial blood vessels. The anatomic organization of these infiltrates is quite variable. They may consist of scattered cells, disorganized aggregates, or rarely, organized structures containing germinal centers (45). There is also evidence for *in situ* activation of pathogenic adaptive immune responses to degraded or modified renal antigens. Both B cells and T cells from LN kidneys are clonally expanded, and the same T cell expansions have been detected in the peripheral blood (46–47). Multiple T cell cytokines such as IFNγ, IL-21 and IL-17 have also been detected in LN kidneys (48), and T cells appear in the urine of LN patients (49). In a small exploratory study, clonal CD8 T cell infiltrates were found adjacent to epithelial cells in LN biopsies and were associated with more severe disease, suggesting an effector function elicited by local antigens (47).

Strikingly, a measurable proportion of B cells derived from human LN biopsies recognize vimentin, an intracellular structural protein that is cleaved and extruded from apoptotic cells (46). Serum anti-vimentin antibodies are associated with decreasing GFR and increasing tubulointerstitial damage in other forms of CKD, and are similarly associated with severe interstitial disease in LN (46, 50). Autoantibodies to annexin1 and αenolase have also been detected in LN kidneys (51). These local adaptive immune responses may amplify inflammation independently of systemic autoimmunity.

Macrophages play a central role in both injury and repair; renal infiltration of LN kidneys with macrophages, particularly at the second biopsy, is associated with poor prognosis (52–54). Both infiltrating inflammatory macrophages and resident interstitial macrophages may be present in diseased kidneys (53, 55–56). Macrophages recruited from the peripheral blood are pro-inflammatory during acute inflammation but can then switch to a reparative phenotype (53, 57). Resident interstitial macrophages may have self-renewal properties (58), and in mouse models of chronic LN, they increase in number, become activated, and acquire MMP and cathepsin activity, suggesting that they contribute to aberrant tissue remodeling (30, 55).

It is increasingly recognized that several types of dendritic cells also infiltrate the kidneys during LN (59) potentially propagating local adaptive immune responses (60). Importantly,

an increase in both CD141^{hi} and myeloid DCs is observed in human glomerulonephritis biopsies and correlates with fibrosis (61).

Non-immune mechanisms of tissue injury in LN

Several lines of evidence suggest that non-immune mechanisms of renal damage need to be therapeutically addressed in LN. First, many patients do not adequately respond to immunologic interventions. Second, remission can take months, during which time damage may continue to accrue. Third, progression may occur even if systemic autoimmunity is controlled. Although the role of each intrinsic renal cell during the stages of injury and repair is still not fully understood, some general mechanisms of CKD should also be applicable to LN (Figure 2).

Disruption of cell-cell interactions—Maintenance of the complex structure of the nephron requires cell-cell interactions (62) (Figure 1). In the glomerulus, endothelial cells directly contact mesangial cells (63). Mesangial cells sequester latent TGFβ, preventing TGFβ-mediated damage to endothelial cells (64). Endothelial cells produce PDGF-B whose interaction with PDGF-Rβ on mesangial cells is required for glomerular development. Expression of PDGF isoforms is upregulated in many forms of renal injury, causing mesangial hyperproliferation, matrix production, cytokine and chemokine release, and renal fibrosis (65).

Podocytes and endothelial cells also interact by bidirectional diffusion of cytokines/growth factors through the glomerular basement membrane (63). Podocytes secrete angiopoietin 1 and VEGF-A that support endothelial cell survival; loss of renal VEGF-A characterizes LN both in humans and mouse models and distinguishes LN from other forms of CKD (34). In diseased tissue, both activated glomerular endothelial cells and damaged podocytes release endothelin 1 that amplifies glomerular injury by causing mitochondrial stress (66). Since podocyte regenerative capacity is limited in adults, loss of podocytes eventually leads to glomerulosclerosis. As nephrons are lost, compensatory mechanisms cause a rise in intraglomerular pressure and glomerular stress in the remaining nephrons (67).

A cell that has received much recent attention is the pericyte which contacts and shares a basement membrane with capillary endothelial cells. Pericytes secrete VEGF-A, chemokines and other inflammatory mediators, they help maintain endothelial cell quiescence, they contribute to the basement membrane and they regulate both medullary blood flow and cell traffic through the endothelial barrier during inflammation (68–70). Mesangial cells are the pericytes of the glomerulus and the interstitium has its own pericyte network attached to tubular capillaries. During inflammation, these pericytes rapidly dissociate from tubular capillaries and migrate into the interstitial space where they differentiate into myofibrobasts (71).

Abnormal vascular function and tissue hypoxia—Glomerular endothelial cells are coated with a glycocalyx layer that forms a crucial barrier to protein loss (72); this barrier can be degraded by the enzyme heparanase that is induced by endothelial hypoxic stress (73). As pericytes dissociate from capillaries and VEGF-A production diminishes, the capacity for angiogenesis and capillary repair is lost, leading to capillary rarefaction in both

the glomerulus and the interstitium (71, 74). Other disturbances of angiogenesis reported in LN include a decrease in the ratio of pro-angiogenic Ang1/anti-angiogenic Ang2, downregulation of the angiogenic factor FGF-2, an increase in the VEGF inhibitor ADAMTS-1, and alterations in endothelial nitric oxide synthase (68, 75–77). In a mouse model of LN, downregulation of VEGF-A and FGF-2 persists even after induction of complete remission, suggesting that vascular injury is not completely reversible (30).

Some areas of the kidney, especially the medulla, maintain a low pO2 even under normal physiologic conditions and are sensitive to hypoxia. The interstitial blood supply derives from post-glomerular blood vessels, so glomerular hypertension and sclerosis can cause interstitial ischemia. Loss of VEGF-A, oxidative stress due to inflammation, increased energy demands, endothelial cell injury by cytokines, enhanced endothelin release, hypertension and anemia may all contribute to hypoxia (78–80); the relative contribution of each of these mechanisms is not well understood.

Tubular dysfunction and atrophy—Ischemia, hypertension or failed regeneration contribute to atrophy of tubular epithelial cells; such injury promotes both interstitial immune cell infiltrates and fibrosis. Recent studies have shown that injured renal tubular cells have a defect in fatty acid oxidation which causes mitochondrial dysfunction, reprograms them to a pro-fibrotic phenotype, and contributes to their death (30). The defect can be reversed by tubule-specific expression of the mitochondrial biogenesis regulator PGC-1α. Importantly, human fibrotic kidneys have a similar alteration in tubular fatty acid metabolism, suggesting a potential new therapeutic approach (81–82).

Renal fibrosis and progression to chronic kidney disease—Renal fibrosis is a poor prognostic feature in LN as in CKD generally. The extent of fibrosis is determined by the balance of matrix production with enzyme-mediated matrix breakdown and turnover (83). Mesangial cells are the classical myofibroblasts in the glomerulus, but parietal epithelial cells and podocytes may also contribute (83). In the interstitium, pericytes and resident fibroblasts are the major sources of myofibroblasts that produce extracellular matrix, MMP inhibitors and collagen (84). Both tissue macrophages and tubular epithelial cells produce growth factors that support myofibroblast differentiation, including TGFβ, PDGF and CTGF (85–86). These factors are balanced by local anti-fibrotic factors such as the TGFβ antagonists BMP-7 and hepatocyte growth factor. In addition, cytokines, chemokines, matrix proteins, procoagulants and remodeling enzymes produced by inflammatory cells, tubular cells and macrophages provide a pro-fibrotic microenvironment (87).

Although it has not been shown unequivocally that an area of fibrosis will damage adjacent healthy nephrons (88), several lines of evidence indicate that fibrosis can amplify renal damage. Fibroblasts may contribute to tissue injury by producing pro-inflammatory mediators (89). Fibrotic tissue may disrupt normal anatomic structures and interfere with oxygen diffusion, thus exacerbating hypoxia (83). In addition, epigenetic changes can reprogram fibroblasts to maintain their profibrotic state even after inflammation has resolved (90–92). One epigenetic change that has received considerable attention is the upregulation

of miR-21 that protects against acute renal inflammation and damage but may also exacerbate fibrosis (93–94).

Identifying novel pathways that contribute to initiation and progression of lupus nephritis

Improved therapy for SLE will likely require disease classification based on pathogenic mechanisms. Some of these mechanisms will be common to most patients, some may be stage-specific, and others may apply to smaller patient subgroups or even individuals. Several approaches to identify commonly shared pathways have been explored.

Clinical and Epidemiologic studies

Factors associated with poor outcomes in lupus nephritis are shown in Table 1 (11, 95–96). Long term outcome depends on the degree of treatment response, with resolution of proteinuria being the best surrogate marker of a favourable prognosis (97–98). The severity of renal damage at presentation, manifested by serum creatinine and the degree of interstitial inflammation and fibrosis, strongly influences the response to treatment. These data support the need for improved monitoring of high risk individuals, and suggest that early detection of LN and prompt intervention will improve outcomes. Not surprisingly, non-response to therapy, recurrent flares and residual inflammation or fibrosis at repeat biopsy are associated with a poorer prognosis (54, 99–100). Repeat biopsies are not routinely performed but may be useful to guide tapering regimens and/or the need for changes in maintenance therapies.

Importantly, recent epidemiologic data from the US has shown an increase in ESRD in uninsured individuals and in geographic areas with poor access to ambulatory care, indicating a significant effect of healthcare policy, healthcare access and patient compliance on LN outcomes (101). Similar results have been shown in other countries (102). Unless this public health issue is addressed it is difficult to envision improved outcomes by medical management alone.

Genetic risk for LN

Genome-wide analyses (GWAS)—A recent meta-analysis of 3 GWAS identified several inherited polymorphisms that predispose to initiation of LN, including the PDGFRA locus, the glucose transporter Slc5A11, and hyaluronan synthase 2 that is involved in extracellular matrix formation (103). Other risk genes include ABIN1, TNFSF4, Stat4, ITGAM, kallikreins and FcγRIIIa low-binding alleles (104–110). These results suggest a link between inflammation and LN as well as a contribution from pathways that regulate the renal response to inflammation and injury. However the relative risk associated with most of these genetic variants is low, and some are relevant only in certain ethnic populations, making it challenging to generate a clinically meaningful genetic risk-prediction test. The function of the various polymorphisms will need to be unravelled in order to understand their clinical significance.

Only a few small studies have addressed the genetic risk for increased disease severity in LN patients. Polymorphisms in APOL1 and MYH9 confer an increased risk of renal failure in

other chronic renal diseases, and appear to confer a modest risk for LN progression that may be dependent on ethnicity (111–113). No studies have addressed the genetic basis for responsiveness to therapy.

Local epigenetic changes—The epigenetic landscape of renal injury is just starting to be described, particularly in the interstitium (114–115). Examples relevant to LN include chromatin structure modifications that regulate the production of CCL2 and TNF, DNA demethylation that regulates C3 production and histone acetylation that regulates the production of PDGF and pro-fibrotic genes (115). Histone deacetylase inhibitors alleviate progression in multiple models of renal injury and fibrosis by preventing cytokine release and cell apoptosis and by inducing the protective molecule BMP-7 (116–117). Epigenetic changes can also be mediated by non-coding RNAs. TGFβ induces several miRNAs that enhance pro-fibrotic genes while at the same time inhibiting miRNAs that are protective (93–94). The utility of blood and urine miRNA signatures as biomarkers for LN is starting to be examined (118–119).

Molecular and proteomic signatures of renal disease

Molecular and/or proteomic phenotyping of the kidney or urine may identify the immunologic and/or injury process currently affecting each individual, and could deliver biomarkers to improve patient stratification for clinical trials and a more rational therapeutic approach.

Molecular profiling of LN kidneys—Several studies have shown signatures of immune cell infiltration and activation, extracellular matrix formation and fibrosis, endothelial cell activation, fibrinolysis, mitochondrial dysfunction, and tubular injury (34, 120–121). Because pre-nephritis and repeat biopsies are rarely available from humans, mouse models have been useful for characterizing renal molecular profiles at sequential disease stages. Overlay of these data onto data from human LN biopsies allows identification of pathways that are relevant to human disease. Using this approach in NZB/W lupus-prone mice we identified two dominant gene clusters that are dynamically regulated during disease progression; the first is detected at proteinuria onset and reflects the inflammatory component of nephritis – the second occurs during established proteinuria and reflects the mitochondrial and metabolic signature of chronic disease. Remission induction therapy administered promptly after nephritis onset reverses most of this abnormal gene expression profile but we noted that the mitochondrial and metabolic signature recurred before clinical relapse, perhaps reflecting an increased propensity to tissue hypoxia conferred by the initial tissue insult (30). By following mice from remission to relapse, we further identified podocyte loss, renal tubular dysfunction, endothelial cell activation and tissue remodeling as the functional features associated with the progression to renal failure (30). Some of these processes may be resistant to standard immune suppression (34, 122).

One important observation in mice is that glomerular disease does not always progress to tubular and endothelial dysfunction (123–124). For example, BAFF deficient or BAFF-R-Ig treated lupus-prone mice have autoantibodies, glomerulonephritis and interstitial inflammatory infiltrates but do not die of renal failure (30, 123). Similarly, a genetic model

has been generated in which acute glomerular injury occurs, but progression to CKD does not (125). How this transition from renal inflammation to renal failure is regulated is not completely understood (126–128) and is an important knowledge gap that needs to be filled (121–123). In addition, there are several LN models in which renal deposition of immune complexes does not induce the recruitment of effector cells. These include myeloid cell deficiency of Fc receptors, CCL2 deficiency and intense costimulatory blockade (27, 129–130). These studies, in sum, suggest that there are several opportunities for therapeutic intervention that target the effector response in the kidney, regardless of systemic autoimmunity.

A problem with the interpretation of molecular profiles of whole tissues is that the signatures are biased towards the most frequent cell types and towards infiltrating cells that are rare in normal kidneys. The only way to overcome these biases is to study each cell type individually. No studies of this type have as yet been performed in human LN biopsies and even the data from mouse models is still quite limited. Molecular studies in both mice and humans have suggested that macrophages/DCs are key players in the development of LN (34). Comparative molecular profiling of isolated renal macrophages from young and nephritic NZB/W mice and NZW/BXSB mice (34, 55) revealed that several functional pathways are upregulated in nephritic macrophages including the alternate complement pathway, cell adhesion, phagocytosis and efferocytosis, Fc receptor signaling, the nucleic acid sensing pathway and tissue repair. Pathways that are downregulated include fatty acid metabolism and angiogenesis. This profile suggests aberrant resolution of inflammation which may be driven by ongoing immune complex deposition and/or tissue damage. It remains to be determined whether it is possible to harness the reparative function of macrophages for optimal tissue repair without fibrosis.

Proteomic analysis of LN kidneys—Proteomic analysis of kidneys has been challenging due to the limited amount of available tissue and the inability to detect small or low abundance proteins; the feasibility of this approach is increasing with new technical advances. A proteomic analysis of human lupus glomeruli revealed loss of podocyte proteins, activation of the alternate complement pathway, loss of anti-oxidants and downregulation of normal metabolic pathways, consistent with the findings of the molecular studies (131–132). Analyses of proliferative LN biopsies using a targeted set of 500 immune response genes showed that activation of IFN pathways, production of IL-10 and T and B cell signaling pathways are associated with lack of response to therapy (6). These data are consistent with the clinical observation that interstitial infiltrates are associated with poor prognosis. It is also becoming clear that variability in the renal proteome can occur within a WHO Class, adding potential for subclassification based on proteomic analysis (133).

In sum, the preliminary molecular and proteomic studies of LN kidneys have extended mechanistic knowledge beyond the histologic data by identifying two phases of disease characterized by inflammation and metabolic dysfunction, have identified both shared and unique effector signatures and have identified a number of checkpoints along the path to irreversible renal damage that could potentially be targeted by new therapies. The molecular studies have been less successful at identifying the earliest features of LN since only few genes are upregulated in the kidneys prior to the onset of proteinuria (30); a proportion of

these is associated with steroid and lipid metabolism. Proteomic and metabolomic studies may be more suitable for detecting such early changes (134–135).

Analysis of urines—Longitudinal monitoring of urine offers a window into the kidney that could be used for treatment decisions. The technical challenges inherent in this approach have recently been reviewed (133). The major clinical use of urine proteomics has so far been to identify biomarkers that either predict an impending renal flare (6, 136) or identify response to therapy. There are several longitudinal studies of single urine biomarkers including the chemokine CCL2, the tubular marker lipocalin2, the acute phase protein hepcidin and the TNF-like molecule TWEAK (reviewed (133, 137)). These studies are still preliminary and have not yet been reliably reproduced or tested in the setting of a clinical trial. Combination panels of these and other potential biomarkers identified in cross-sectional studies may have a higher predictive value than single analytes alone.

It is important to note that cells and microparticles of cells are also shed into the urine during inflammation and this could be exploited for discovery of other protein and RNA-based biomarkers and for early detection of podocyte loss.

Using therapeutics to test the pathogenicity of target molecules—A final approach to identifying key pathways in LN is to identify molecules that are potentially pathogenic based on their known biology and then test their role in pre-clinical models either by genetic depletion or therapeutic targeting. This approach is often successful when the correct preclinical model expressing the protein of interest is used and the treatment is timed either before or at the first presentation of LN (138). Nevertheless this is proving to be a cumbersome and expensive approach in human LN that has been hampered by the primitiveness of disease phenotyping, the confounding effects of standard medications such as glucocorticoids and the absence of a uniformly accepted definition of renal outcome (139).

When choosing such targets, it is important to consider the sometimes opposing effects of pleiotropic immune pathways and cytokines on systemic immunity vs. local effector responses. Genetic deficiencies of TNF, TGFβ, components of the innate pathway such as TLR9 and STING and Nox2, and inflammasome components NLRP3 and ASC all induce or exacerbate autoimmunity in mice (140–142). This may be due to the loss regulatory functions of these proteins or to diminished capacity to fully control infectious insults. On the other hand both TNF and TGF beta are highly expressed in inflamed kidneys and their inhibition at this stage of disease improves disease outcome in mouse models (32, 143). TNF inhibition does indeed improve chronic LN in patients without inducing systemic flares although its clinical utility has been limited by other toxicities (144). Nevertheless, targeting these types of pathways will need to be approached with caution.

Implications for treatment

Targeting systemic autoimmunity

Given the role of systemic autoimmunity in the initiation of LN, a major focus of management should be on prevention. Indeed in mouse models of lupus, LN can be

completely prevented by immune interventions that prevent the renal deposition of autoantibodies or by genetic manipulations that prevent tissue responses to immune complex deposition (145). There are however many obstacles to a similar approach in humans including the heterogeneity of immune responses in individual patients, the absence of non-invasive monitoring tools for early detection, the potential toxicities of new therapies in patients with quiescent disease and the expense of time-to-flare studies that need large study cohorts.

Once disease onset occurs, there may only be a limited time window before disease mechanisms that are insensitive to preventive strategies arise. In mice it is much easier to prevent disease onset than to treat established disease with drugs that target T or B lymphocytes and in some strains drug combinations are needed to induce remission (138, 145). Delay in diagnosis and treatment may result in the recruitment of inflammatory amplification circuits or the onset of metabolic or structural changes in the kidneys that are difficult to reverse with immunotherapy. Variability in treatment responses may also be due to intrinsic differences between patients. Considerable variations in responses to immunotherapy are observed in different mouse models of LN even when intervention is initiated at disease onset (138); this may reflect heterogeneity in the severity of inflammation, the relative involvement of innate vs. adaptive immune pathways, the balance of inflammation vs. metabolic abnormalities and the degree of tissue hypoxia, nephron loss and tubular regenerative capacity (Figure 3).

Although biologic agents have not yet been successful in patients with LN (146–147) many new approaches remain to be tested (146, 148). Obvious targets include key cytokines expressed in inflamed kidneys such as IL1, IL6, M-CSF, IFNγ, Type I IFN, BAFF, IL17 and IL21, signaling pathways such as tyrosine kinases, costimulatory molecules such as ICOS and TWEAK (149) and effector molecules such as those in the complement pathway (reviewed (150)). Chemokines are also appealing targets but despite extensive efforts have not yet successfully been translated to human autoimmune disease (151–152). One successful pilot approach has been to deplete plasma cells with a proteasome inhibitor, thus clearing immune complexes and allowing the kidney to heal (153). Nevertheless, the overall experience with immune suppression shows that non-immune based approaches to preventing disease progression (154) also need to be considered in order to optimize the resolution and repair process (Table 2). This field is still in its infancy but new approaches are being tested and developments in this field may also be applicable to LN.

Targeting endothelial cell dysfunction

An improved understanding of the mechanisms of endothelial dysfunction and hypoxia may lead to novel therapies. Endothelial glycocalyx deterioration may be prevented by angiotensin 2 inhibition and mycophenolate can inhibit PDGF-B production (155). ACE inhibitors also reduce endothelial activation by increasing NO production independently of their anti-hypertensive effects (76). Podocytes lacking both endothelin receptors are protected from damage in animal models of diabetes and an endothelin antagonist reduced proteinuria in patients with diabetic nephropathy (156). Targeting of VEGF-A (157) or PDGF has proved more challenging because the relationships between angiogenesis,

inflammation and fibrosis are still not fully understood. For example, some proangiogenic factors also enhance inflammation or fibrosis (76) and PDGF may be involved in tubular regeneration (85). In addition angiogenesis may be detrimental early in disease, helping to mediate glomerular hypertrophy, before becoming dysfunctional at later stages (76).

Preventing and reversing renal fibrosis

Several strategies for preventing or reversing renal fibrosis are in clinical development and include monoclonal antibodies to TGFβ and CTGF or their downstream signaling pathways, growth factor antagonists such as BMP-7 mimetics, phosphodiesterase inhibitors and NADPH oxidase inhibitors (85, 158). Nevertheless, the wide array of potentially profibrotic factors that arise in inflamed kidneys (87) suggest that broad approaches may be needed. One exciting new therapeutic area is the prevention of tubular epithelial injury based on a better understanding of the mechanisms of tubular stress. Data from mouse models suggests that pharmacologic enhancement of fatty acid oxidation may protect tubules from death and help prevent fibrosis (82).

Reparative macrophages that arise during the healing phase of acute inflammation may act to reverse early fibrosis by endocytosis and degradation of collagen (159) or by secreting enzymes that break down collagen and matrix. These macrophages can also stimulate tubular epithelial cell regeneration through a mechanism involving the Wnt pathway (160). Importantly however, prolonged exposure to reparative macrophages may cause renal fibrosis or excessive remodeling (161). Strategies targeting dysfunctional macrophage repair have included antagonism of the interstitial macrophage receptor CCR1 and of the resident macrophage receptor CX3CR1 (162). More effective targeting of macrophages awaits a better understanding of how their inflammatory, pro-fibrotic and reparative functions are regulated during the various stages of disease.

Conclusions

Progress continues to be made in our understanding of the mechanisms of acute and chronic renal injury as they pertain to LN. Although immunosuppressive agents continue to be the mainstay of treatment, new biologic agents continue to be tested and development of treatments that protect the kidneys against endothelial and tubular injury and fibrosis may help prevent chronic damage. Progress in developing new therapies for LN will require the formation of LN consortia, patient and physician engagement in research protocols, improved clinical trial design, improved definitions of renal outcome that may include second biopsies, testing of molecular and proteomic analyses in clinical trials and, finally, strategies for prevention and treatment based on these results. The most cost effective current approach involves early recognition (163) with prompt intervention and treatment of reversible risk factors. This requires ensuring access both to properly trained health care providers and to medications and is the necessary foundation upon which individualized care can eventually be built.

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Biography

Biography

Anne Davidson received her MBBS degree from the University of Melbourne, Australia and is a board-certified rheumatologist. She is an Investigator at the Feinstein Institute for Medical Research and Professor of Molecular Medicine at Hofstra North Shore LIJ School of Medicine New York. Dr Davidson's research focuses on the pathogenesis and therapy of SLE. One interest is to understand how B-cell tolerance is dysregulated in SLE. A second interest is to understand mechanisms of kidney inflammation using both systems biology approaches and functional studies. She is a past recipient of the Dubois Award and the ACR Basic Science Distinguished Investigator Award.

Review criteria

Pubmed searches were carried out for lupus nephritis, renal fibrosis, CKD and treatment, AKI to CKD progression, renal interstitial inflammation, renal macrophages. In addition the personal library of the author containing >4000 references was used. The search was confined to articles written in English.

Key points

- Lupus nephritis remains a major cause of morbidity and mortality in SLE with approximately 40% of affected individuals developing some degree of renal impairment.

- Long term prognosis is influenced by both extrinsic and intrinsic renal factors and depends on the severity of disease at presentation, the response to immunosuppressive therapy and access to high quality healthcare

- Current methods for classifying LN are based solely on light microscopy of kidney biopsies and do not adequately predict response to therapy or long term outcomes. Additional phenotyping based on mechanisms of injury may improve clinical decision making.

- Mechanisms of renal injury involve both local immune responses and aberrant responses by the renal parenchyma including disruption of cell-cell interactions that maintain nephron structure, loss of renal microvasculature, tubular atrophy and renal fibrosis. Some of these processes are not reversible with immunosuppressive therapy and may require different approaches based on targeting non-immune mechanisms for disease progression.

- Although LN is initiated by immune complex deposition, the response to injury in individual patients is variable and may reflect the balance of innate vs adaptive immunity, inflammation vs metabolic changes, the degree of hypoxia and the capacity for regeneration and fibrosis.

- Genetic analyses, molecular profiling and proteomic analyses are being used to discover mechanisms of renal injury and suggest new and more individualized therapeutic approaches.

- Studies in mouse models show that progression to CKD is not inevitable even if systemic autoimmunity persists and that several checkpoints in the progression pathway are susceptible to therapeutic intervention.

- Because clinical remission and renal histologic remission are not always correlated, improved disease monitoring and/or second biopsies may help identify patients at risk of progression and in need of more intense maintenance therapy
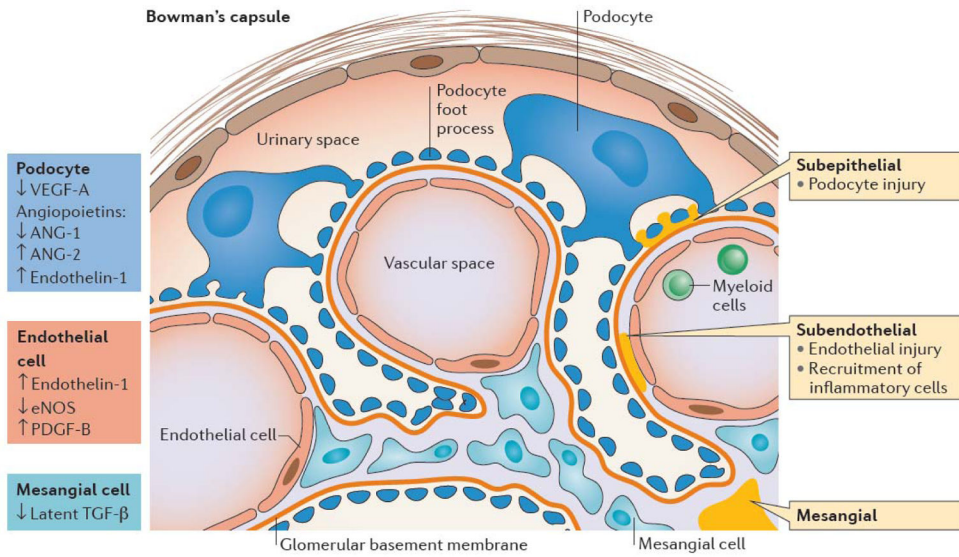
Figure 1.

Glomerular injury in LN: View of a glomerular loop containing endothelial cells (yellow) lined by a glycocalyx (orange), mesangial cells (ochre) and podocytes (brown). Podocytes are separated from endothelial cells by the glomerular basement membrane (GBM -red). The glomerulus is contained by Bowman's capsule (BC) that is lined by parietal epithelial cells. Immune deposits (blue) may be found in the mesangium, subendothelium, or subepithelium. Subendothelial deposits are in contact with the vascular space (V) and can recruit myeloid cells (My) into the renal parenchyma. Subepithelial cells are in contact with podocytes and the urinary space (U). Podocytes and endothelial cells communicate with each other by transfer of soluble growth factors across the GBM, whereas mesangial cells and endothelial cells can interact directly via receptors and their ligands. Alterations of these factors in LN are shown by the arrows and color coded according to cell type.
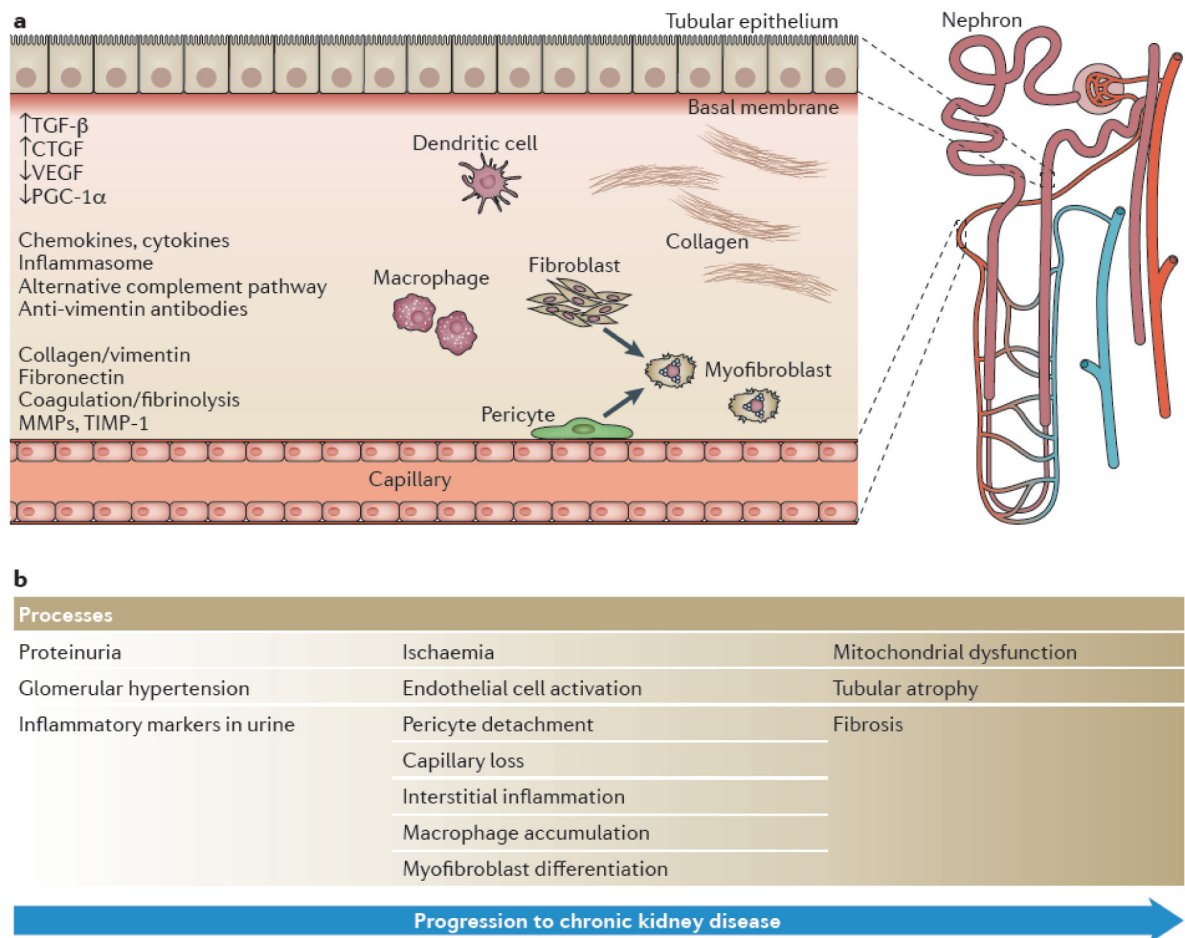
a

↑TGF-β
↑CTGF
↓VEGF
↓PGC-1α

Chemokines, cytokines
Inflammasome
Alternative complement pathway
Anti-vimentin antibodies

Collagen/vimentin
Fibronectin
Coagulation/fibrinolysis
MMPs, TIMP-1

Tubular epithelium
Nephron
Basal membrane
Dendritic cell
Collagen
Macrophage
Fibroblast
Myofibroblast
Pericyte
Capillary

b

Processes		
Proteinuria	Ischaemia	Mitochondrial dysfunction
Glomerular hypertension	Endothelial cell activation	Tubular atrophy
Inflammatory markers in urine	Pericyte detachment	Fibrosis
	Capillary loss	
	Interstitial inflammation	
	Macrophage accumulation	
	Myofibroblast differentiation	

Progression to chronic kidney disease →

Figure 2.
Interstitial injury in LN: A single nephron with its tubular and capillary system is shown. Cellular components that contribute to interstitial injury include tubular cells, endothelial cells (Cap), pericytes (P), fibrobasts (F), inflammatory lymphocytes (Ly), infiltrating and resident macrophages (Mac) and infiltrating dendritic cells (DC). Both pericytes and fibrobasts can differentiate into myofibroblasts (Myo). The sequential processes occurring during the progression to CKD are shown on the right and key molecules are shown on the left.
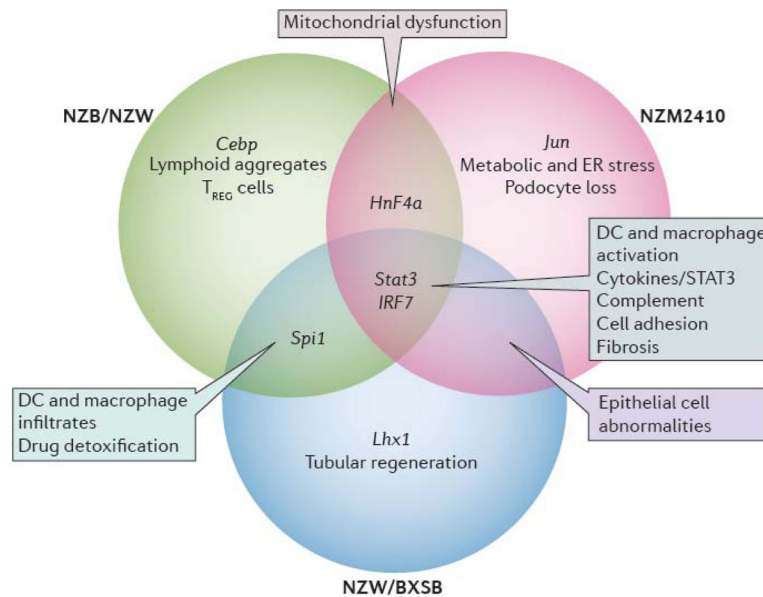
Figure 3.
Shared pathogenic pathways identified in the kidneys of the three different lupus-prone mouse strains. NZB/W and NZW/BXSB mice develop proliferative glomerulonephritis and NZM2410 mice develop glomerulosclerosis with limited inflammation. Pathways that are shared between all three strains and human LN are shown in green. The major functional pathway that is overrepresented in each of the three individual strains is shown in purple. Transcription factors are shown in blue and other pathways shared by two strains are shown in black. (adapted from (122))

Table 1

Factors associated with poor prognosis in LN (7, 9, 11–12, 54, 97–98, 164)

Renal extrinsic
Genetic
African-American race
Male gender
Older age
Socio-economic
Delay in diagnosis
Poor compliance
Limited access to qualified providers
Lack of health insurance
Renal intrinsic
ISN/RPS histologic classes III, IV and V
Increased serum creatinine
Interstitial infiltrates
Fibrosis
Mixed renal intrinsic/extrinsic
Anemia
Hypertension
Inadequate response to therapy
Failure to resolve proteinuria by 6–12 months
Recurrence
Inflammation, macrophage infiltration, fibrosis at second biopsy

Table 2

Potential targets of therapy in LN (76, 147, 154, 158, 162, 165)

Immune based therapies
Innate immune mechanisms, eg inflammasome
Adaptive immunity eg costimulatory blockade
Effector cells, eg plasma cells, macrophages
Effector pathways, eg alternative complement pathway, TWEAK/Fn14 pathway
Soluble inflammatory mediators, eg cytokines/chemokines
Signaling molecules eg, kinases, mTOR
Protection of intrinsic renal cells
Renin angiotensin system
Endothelin 1
Growth factors, eg PDGF
Oxidative stress, eg NADP oxidases
Improved microcirculation
Phosphodiesterase 5
Anti-fibrotics
Growth factors, eg TGFβ, CTGF
Growth factor antagonists, eg HGF mimetic, BMP7 mimetic
Others
Epigenomic reprogramming
Mesenchymal stem cells