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The pathogenesis and therapeutic implications of tubulointerstitial inflammation in human lupus nephritis

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Abstract

Nephritis is a common complication of systemic lupus erythematosus (SLE) for which current therapies often prove inadequate. Current lupus nephritis classification systems emphasize glomerular acuity and scarring. However, tubulointerstitial inflammation (TII) and scarring are much better predictors of progression to renal failure. It is now becoming clear that the immunological features, and probable underlying mechanisms, are very different in lupus glomerulonephritis (GN) and TII at time of biopsy. While GN is a manifestation of systemic autoimmunity, TII is associated with local, *in situ* adaptive immune cell networks predicted to amplify local inflammation and tissue damage. In addition, poorly defined networks of innate immune cells and effectors likely contribute to the severity of local inflammation. Understanding these *in situ* immune mechanisms should lead to a better understanding of prognostically meaningful lupus nephritis subsets and reveal novel therapeutic opportunities.

Keywords

Lupus nephritis; Tubulointerstitial inflammation; Adaptive immunity; Innate immunity

Introduction

The most common and severe manifestation of systemic lupus erythematosus (SLE) is certainly lupus nephritis[1, 2, 3, 4, 5]. Up to 60 % of SLE patients develop lupus nephritis with most of these requiring major immunosuppressive therapies such as cyclophosphamide or mycophenolate mofetil[6, 7, 8, 9]. Yet, despite aggressive treatment, up to 50% of lupus nephritis patients progress to renal failure within 5 years of diagnosis [10, 11, 12].

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Ethnicity is a major determinant of renal failure risk, with African-Americans and Hispanics having a worse prognosis than Caucasians[11, 13]. Reflecting their worse prognosis, and possibly differing responses to therapies, the treatment recommendations for African-Americans and Hispanics are different than those for Caucasians and Asians [9]. It is not entirely clear however if African-Americans and Hispanics have a higher ultimate risk of renal failure or if they just progress to renal failure more quickly. Most studies demonstrating the risk associated with ethnicity are five years or less in duration. However, at least one study suggests that patients continue to progress to renal failure beyond five years[14]. In this Danish study, less than 20% progressed in five years while about 50% were in renal failure 25 years after diagnosis.

These more recent epidemiological studies have all been done in the modern era of treatment in which cyclophosphamide and/or mycophenolate mofetil were the standards of care. While these drugs are clearly effective in some patients, short-term response rates have not appreciably improved since the introduction of cyclophosphamide for lupus nephritis in the 1980s[14, 15, 16]. Therefore, either rapidly or eventually, half of lupus nephritis patients fail these modalities and progress to end-stage kidney disease.

The need for both more effective and less toxic therapies in lupus nephritis is obvious and pressing. However, it is unclear which therapies to pursue and in which sub-populations of lupus they might be efficacious. We suggest that this uncertainty in how to proceed reflects limitations in both our understanding of lupus nephritis and in how we classify patients and assign prognosis.

Prognostic value of renal biopsies

The current standard is to biopsy all SLE patients who present with an active urinary sediment and/or greater than 500 mg/protein in 24 hours[9, 17]. Lupus patients are then broadly categorized as having either proliferative or nonproliferative nephritis based on the activity and frequency of glomerular lesions with therapeutic decisions being based upon this classification. However, current histologic measures of disease activity, which emphasize glomerular involvement, perform poorly in identifying those patients at risk for subsequent renal failure.

The most commonly used classification system reflects this focus on glomerular inflammation. The 2003 International Society of Nephrology/Renal Pathology Society (ISN/RPS)[18] lupus nephritis classification focuses exclusively on histologic changes of the glomerulus. Similarly, the NIH activity index quantifies the severity of lupus nephritis and is scored using six pathologic features, of which five involve the glomerular compartment, with 21 of the 24 activity points awarded based on glomerular findings[13, 19]. However, the prognostic value of glomerular inflammation, at best, remains unclear.

Several studies have demonstrated that glomerular measures of disease activity do not accurately predict subsequent clinical course[1312, 19, 20, 21, 22, 23]. For the most part, these studies were performed during the modern era when all patients received cytotoxic therapies. Earlier studies clearly demonstrated that patients with proliferative nephritis have a worse prognosis than non-proliferative nephritis and that this group does better with

immunosuppressives[24]. However, in these earlier studies, other features of the biopsy, such as tubulointerstitial inflammation were not systematically assessed. Furthermore, features predictive of resistance to immunosuppressive therapy were not analyzed.

Rather, several studies in the immunosuppressive era of lupus nephritis treatment, extending back to the 1980s, have indicated that tubulointerstitial inflammation is prognostically more meaningful than glomerular inflammation and more likely to be correlated with elevated creatinine at time of biopsy and with risk for subsequent renal failure[13, 22, 25, 26, 27, 28]. Many of these studies noted that more active TII tended to be associated with active GN. However, multivariate analysis demonstrated that TII was an independent predictor of progression to renal failure [13] and correlated with serum creatinine at time of biopsy[13, 26]. Furthermore, TII is not associated with low complement levels, or high titers of dsDNA antibodies[13, 26], factors epidemiologically and mechanistically tied to GN. Therefore, TII is an independent and important predictor of renal failure in lupus nephritis.

The current assessments of TII are largely qualitative with severity scored as the fraction of the tubulointerstitium infiltrated with inflammatory cells on PAS stained paraffin embedded sections. By simply staining with anti-CD45 antibodies, and assessing the fraction of the tubulointerstitium infiltrated with $CD45^+$ cells, intermediate grades of TII can be more accurately assessed which are prognostically significant[13].

While the degree of TII is prognostically more important than GN activity, it is not clear how this information should inform therapy. Clinical trials have not been stratified by TII and therefore it is not clear if one therapy is relatively more effective in TII. However, the fact that severe TII predicts renal failure in all lupus patients suggests that all current therapies are relatively ineffective for this manifestation.

In contrast to commonly used indices of active glomerular inflammation, indices of scarring (glomerulosclerosis, interstitial fibrosis and tubular atrophy) are strongly predictive of subsequent renal failure[13, 22, 26, 29, 30]. The NIH chronicity index is a composite score that equally reflects scarring in both the glomeruli and the tubulointerstitium. However, prognostic value of the chronicity index lies primarily in those components that capture interstitial scarring[13]. Measures of glomerular scarring do not provide independent prognostic information to the chronicity index. In other renal diseases, interstitial scarring also identifies patients with a poor prognosis[31]. In IgA nephropathy, which is primarily considered to be a glomerulonephritis, tubular atrophy and interstitial fibrosis are more predictive of subsequent renal insufficiency than segmental glomerulosclerosis[32].

There is substantial evidence that inflammation leads to fibrosis. This central idea is an extension of the known roles of both inflammation and fibrosis, in the normal processes critical for organ repair following injury. Macrophages play a role in both processes[33] and ablation of macrophages mitigates fibrosis[34, 35, 36]. Furthermore, the extent of macrophage infiltration correlates with the extent of fibrosis[37]. Therefore, the overall effect of macrophages in these model systems appears to be to promote fibrosis. However, infusion of M2 macrophages, which act to limit inflammation, attenuate renal fibrosis in mice[38]. Adaptive immunity appears important as deletion of Rag, thereby eliminating both B and T

cells, can protect against renal fibrosis but not, interestingly, GN[39]. Furthermore, T cells are required for fibrosis following ischemia-reperfusion injury[40, 41]. However, it is not clear that monotherapy targeting adaptive immunity, or inflammation, will be sufficient to prevent fibrosis in most patients.

The pathogenesis of tubulointerstitial inflammation

While GN is a manifestation of systemic autoimmunity[42, 43, 44], lupus TII has histological features suggesting that local, *in situ* immunity might contribute to, and propagate, local tubuloinflammation and organ damage[45, 46]. What is most striking is how different the inflammatory infiltrates are in glomerular inflammation and TII. In lupus glomeruli, the degree and type of involvement varies with ISN/RPS class. In the non-proliferative lupus nephritis (classes I and II), patients have immune complex deposits in the mesangium which can be associated with mesangial hypercellularity (class II). In class V (membranous), immune complex deposition is subepithelial and is associated with thickening of the glomerular basement membrane. None of these lesions are associated with a significant influx of inflammatory cells into the kidneys. In contrast, the proliferative forms of lupus nephritis (classes III and IV) are characterized by inflammation. Active glomerular lesions have prominent subendothelial immune complexes that sometimes fill the glomerular capillary loops (hyaline thrombi). T cells and macrophages accumulate at sites of subendothelial immune complexes. This is associated with ruptured glomerular basement membranes, fibrinoid necrosis and cellular crescents. Neutrophils are not prominent within the glomerular capillaries except when fibrinoid necrosis and crescent formation are present. B cells and plasma cells are rare in glomeruli, and are usually confined to intravascular spaces.

In contrast, B cells and plasma cells are a common, almost invariant, feature of TII. Likewise, T follicular helper-like cells (described below) are only found in the inflamed tubulointerstitium. In about 50% of patients, immune complexes are deposited throughout the tubulointerstitium with characteristic accumulations of immune complexes in the tubular basement membranes[46, 47]. These immune complexes are often associated with C3c and C1q deposition. Immune complexes in the tubulointerstitium can be associated with more severe inflammation[13] although this point is controversial[47, 48, 49]. The distribution of immune complex deposits within the tubulointerstitum speaks against the immune complexes having a purely hematogenous origin. Interestingly, the isotypes of antibodies deposited in the glomeruli and tubulointerstitium can be quite divergent in the same patient[47]. These observations suggest that different mechanisms underlie immune complex deposition in GN and TII.

Furthermore, many renal biopsies with TII have features of lymphoid organization[45, 46]. In up to 8% of clinical biopsies, germinal center-like structures are observed. More commonly, well-formed aggregates of B and T cells are seen in up to 50% of biopsies. Lymphoid-like structures were associated with both more severe inflammation and with the presence of tubular basement membrane immune complexes[46]. These histological features suggest that interstitial B and T cell infiltrates are being selected *in situ* by locally occurring antigen. Consistent with this, sampling of expressed immunoglobulin repertoires from the

tubulointerstitum has revealed local clonal expansion and ongoing somatic hypermutation[46, 50]. Analysis of the distribution of mutations in those regions of expressed antibodies containing the variable regions (Complementarity determining regions or CDRs) indicted that mutations arising from somatic hypermutation were being subsequently selected by antigen. Furthermore, T cell populations in approximation with tubulointerstitial B cells exhibit clonality[51]. Such characteristics are defining features of *in situ* adaptive immunity or tertiary lymphoid neogenesis.

To identify the antigens driving *in situ* B cell selection, variable region heavy and light chain immunoglobulin pairs from clonally expanded B cell populations were cloned and expressed[50]. Remarkably, most of these antibodies, expressed from seven patients, were reactive with cytoplasmic, and not nuclear, antigens in HEp-2 cells. Subsequent studies identified vimentin as the most common antigen targeted by these anti-cytoplasmic antibodies. This result was not totally expected, because vimentin is generally considered to be an intermediate filament, and therefore has been assumed to primarily play a structural role. However, mice deficient in vimentin are relatively normal[52]. Furthermore vimentin is highly expressed in activated T cells and macrophages[53]. In the latter cells, vimentin is expressed on the cell surface. Consistent with these observations, vimentin was highly expressed in TII and many of our anti-cytoplasmic antibodies bound inflamed, but not normal, tubulointerstitium[50]. Vimentin is a large, complex and charged protein that might be expected to be very immunogenic. Furthermore, vimentin can bind dectin 1, a C-type lectin receptor expressed on dendritic cells, macrophages and B cells[54]. Therefore, vimentin might be an immunodominant pattern of inflammation and the *in situ* adaptive immune response we have observed is against inflammation.

Interestingly, most anti-vimentin antibodies were also reactive with other antigens on large protein arrays and were reactive with other cytoplasmic structures[50]. Such polyreactivity could be an intrinsic property of anti-vimentin antibodies. Alternatively, this polyreactivity could be a consequence of the unique environment in which antibodies are selected. In contrast to germinal centers, antigen is not limiting in TII and therefore there might not be sufficiently stringent selection to diminish polyreactivity. Polyreactivity could also arise from poly-selection in which clonal populations are selected on different antigens over time. Persistent polyreactivity might reflect the fact that many antibodies arose from T:B aggregates or plasmablast foci in which selection might not be as stringent. Alternatively, it could be that the inflammatory milieu, and inflammatory cytokines alter the stringency with which repertoire is selected.

Remarkably, in serum, high-titer antibodies were almost exclusively restricted to those patients with severe TII[50]. Therefore, anti-vimentin antibodies appear to serve as biomarker of a specific disease manifestation. Mechanistically, this correlation suggests that *in situ* anti-vimentin antibody responses might function as a local amplification or feed-forward mechanism to drive severe inflammation. It remains to be determined how anti-vimentin antibodies vary with disease activity or if high anti-vimentin antibody titers identity specific therapeutic opportunities.

It is likely that anti-vimentin antibodies are not a unique feature of lupus. In allograft transplantation, high titers of anti-vimentin antibodies are associated with rejection[55, 56, 57] and immunization with vimentin can accelerate cardiac rejection in a mouse model[58]. Therefore, anti-vimentin immune responses might arise when tolerance to inflammation is broken in a variety of disease contexts.

Antigen is usually insufficient to drive B cells to secrete antibodies; second signals are required. In lupus, much work has focused on the role of toll-like receptors (TLRs) and the role of TLR7 and TLR9 contributing to anti-RNP and and-dsDNA responses respectively[59, 60]. However, remarkably, these specificities were not found to be selected in the tubulointerstitium suggesting that other mechanisms are likely driving *in situ* selection.

In secondary lymphoid organs, necessary second signals for B cell selection are usually provided by T follicular helper cells (T_{FH} cells), a subset of $CD4^+$ T cells that express ICOS and high levels of IL-21 which contribute to B cell activation[61]. While *in vitro* studies of circulating putative T_{FH} populations have given insights into potential T_{FH} cell capacities, there have been no methods to assess if T_{FH} cells were contributing to B cell activation *in situ*. To address this experimental limitation, we developed computational tools to analyze the spatial relationships between different lymphocyte subsets in clinical biopsies imaged by multicolor confocal microscopy[62]. Interestingly, only competent T_{FH} cells came within a short critical distance (less than 0.5 Pm) of B cells. Three-dimensional imaging and other modalities indicated that these tight juxtapositions of cells represented the formation of complex supramolecular activation complexes (SMACs) and the delivery of cognate help[63].

Quantifying the prevalence of cell-cell interactions allowed us to determine how commonly one type of interaction occurred between two different cell populations. Remarkably, when T_{FH} cells were present on biopsy, almost all of the B cells in that biopsy were organized around them with predictable geometries and stochastic relationships reminiscent of those found in germinal center light zones[62]. However, none of these biopsies had discernable germinal centers histologically. These observations provide insights into why T:B aggregates form in the TII and reveal mechanistic links between these histological features and frank germinal centers. Furthermore, for those with more severe TII, one general mechanism, T_{FH} help, primarily maintained B cell within the interstitium. This is consistent with the remarkably restricted repertoire of B cells present in TII for a protein antigen, vimentin[50].

Ultimately, many studies in humans are unavoidably descriptive with the only true *in vivo* mechanistic experiments being clinical trials. Therefore, studies in mice are very attractive. Furthermore, murine models have been critical to understanding many fundamental mechanisms of lymphocyte tolerance and systemic autoimmunity[42]. However, it appears that most available murine models of lupus nephritis do not accurately mimic key pathological features of the human disease. Lymphocytic infiltrates in the kidneys of both NZB/NZW and $MRL/Mp^{lpr/lpr}$ mice contain B cells and/or plasma cells that can express antibodies with broad repertoires[64, 65, 66, 67]. However, NZB/NZW and $MRL/Mp^{lpr/lpr}$ mice have diffuse or perivascular intrarenal lymphocytic infiltrations. The *in situ* organization of B and T cells into lymphoid-like structures appears to be a unique feature of human lupus

nephritis. Furthermore, tubular basement membrane immune complexes are not found in common murine models. Therefore, it is not reasonable to assume that any murine model will provide universal insights into the specifics of the human disease. Rather what is needed is a quantitative and comprehensive understanding of human lupus nephritis. This will then allow aspects of the human disease to be modeled in rational murine models that accurately reflect specific and relevant pathogenic processes.

Beyond T:B collaboration in tubulointerstitial inflammation

Our initial studies have focused on B cells and their interplay with T cells. In part, this reflects both technical limitations and the central role B cells play in the autoimmunity associated with SLE. Furthermore, recent clinical trials suggest that B cells might not be the critical therapeutic target for many SLE patients[9]. However, there are many more T cell and antigen presenting cell populations resident in lupus TII. The cortex of normal human kidneys contains a network BDCA-1^{+}DC-SIGN^{+} and DC-SIGN^{-} myeloid DCs (mDCs) as well as fewer numbers of BDCA-2^{+}DC-SIGN^{-} plasmacytoid DCs (pDCs)[68]. The cortex also contains macrophages that have similar surface phenotypes, and possibly functions, as DCs[69]. In murine models, these populations appear to actively maintain tolerance in normal tissue, limit inflammation in response to tissue damage[70, 71, 72, 73], drive inflammation in response to ischemia, infection and ureteral obstruction[70, 74, 75, 76] and resolve inflammation to allow repair[77, 78]. In NZB/W mice, kidneys are infiltrated with pro-inflammatory macrophages and DCs[79] and both human and murine lupus is associated with a pattern of *in situ* mRNA expression indicative of activated macrophages and dendritic cells[80]. Histologically, human lupus is associated with increased DC infiltration[81] and increased chemokine expression[82]. However, the specific phenotype and activation state of these DCs remains unclear[81].

Other inflammatory pathways are clearly active within TII with tumor necrosis factor (TNF) being one of the most interesting and potentially relevant. TNF can play a central role in inflammatory cascades[83] and has been successfully targeted in other inflammatory diseases including rheumatoid arthritis and inflammatory bowel disease. MRL/lpr mice have high levels of TNF in both the serum and kidneys which correlates with disease activity[84, 85]. Renal TNF is also elevated in NZB/W mice[86]. In human lupus, class III and IV lupus nephritis is associated with elevated TNF in inflamed glomeruli and tubulointerstitium, especially in infiltrating mononuclear cells[87, 88].

Clinical trials suggest that targeting TNF might be efficacious for some SLE manifestations. In a small trial of nine patients, Infliximab diminished SLEDAI scores [89], while in a trial including four lupus nephritis patients [83] proteinuria was reduced and this benefit lasted as long as four years in some patients[90]. These four patients did experience an increase in dsDNA titers but this did not correspond to increased disease activity. Anti-TNF therapies are well known to be associated with the development of autoantibodies and SLE-like manifestations including pericarditis, neuritis, and nephritis[91, 92]. Therefore, more clinical studies are needed to define which lupus patients might benefit from anti-TNF therapy.

A possibly more specific target than TNF is TWEAK (TNF-related weak inducer of apoptosis), which is a member of the TNF superfamily. TWEAK and its receptor FN14, have also been found to promote inflammation in SLE[93, 94]. In the graft versus host murine model of lupus, gene targeting of FN14 diminished proteinuria, glomerular immune complexes and intrarenal inflammatory cytokines[95]. In these studies, anti-TWEAK antibodies were also beneficial. In human lupus nephritis, TWEAK is elevated in the glomeruli, tubulointerstitium and urine[96, 97]. Furthermore, high urinary TWEAK levels are associated with renal flares and correlated more closely with lupus nephritis than serum anti-dsDNA titers and complement levels[98]. A clinical trial with a monoclonal anti-TWEAK antibody (BIIB023) is underway in lupus nephritis.

Possible mechanistic relationships between GN and TII

By the time most patients go to renal biopsy, the immunological processes apparent in inflamed glomeruli and inflamed tubulointerstitium are very distinct. As discussed above this is consistent with different mechanisms driving inflammation in each renal compartment. However, there are at least three mechanisms by which inflammation initiated in glomeruli could, in turn, initiate TII (Figure 1).

One possible relationship is ischemia. The glomerular efferent arteriole feeds the peritubular vascular bed. Therefore, it has been postulated that severe GN results in tubulointerstitial ischemia, damage and secondary inflammation. Interestingly, proximal tubules are likely more susceptible to hypoxia as they are dependent on aerobic oxidative metabolism[99]. Severe glomerular and tubulointerstitial inflammation are both associated with hypoxia. Indeed, the transcriptional signature of hypoxia has been observed in both murine models of lupus and human lupus nephritis[100, 101, 102]. Furthermore, in experimental models of nephritis, strategies targeting hypoxia have shown promise in impeding progressive fibrosis. These include inhibiting Angiotensin II, calcium channel blockers, inhibiting endothelin and activation of hypoxia-inducible factors (HIFs)[103, 104, 105, 106, 107]. In renal ischemia-reperfusion models, ischemia induces endogenous ligands that directly activate complement and therefore targeting complement might mitigate both renal injury and inflammation[108].

Progression to tubulointerstitial fibrosis evokes additional mechanisms that feed-forward to worsen renal disease and accelerate progression to renal failure. Fibrosis attenuates peritubular vessels and, through exuberant matrix deposition, creates barriers to the diffusion of oxygen. Increasing hypoxia then feeds forward to drive further fibrosis and worsening hypoxia and renal failure[109].

The tubulointerstitium also lies downstream of glomerular eluent and there is a well-described relationship between proteinuria and tubulointerstitial injury[110, 111]. Loss of glomerular integrity allows proteins to pass through and come into direct contact with proximal tubules. Albumin and transferrin are among the best studied and they can induce multiple inflammatory and fibrogenic mediators including monocyte chemoattractant protein 1 (MCP-1), IL-8, RANTES and TGFβ[110, 112, 113, 114]. *In vitro* studies of tubular cells showed that apical presentation of proteins leads to the release of inflammatory mediators across the basolateral membrane[110, 115]. Albumin might also be directly toxic to tubular

cells and induce apoptosis. Similar direct toxicity might be mediated by other filtered proteins including complement and IgG[116]. Interestingly, in crescentic glomerular diseases, breaks are induced in Bowman's capsule that can lead to leakage of protein containing glomerular ultrafiltrate directly into the tublointerstitium[110]. This mechanism is consistent with our own observations that TII can be severe at the Bowman's capsule border.

In contrast to these potential physiological links between GN and TII, an immunological link has been described[117]. In this study, model antigens were expressed in the glomeruli and antigen specific effector $CD4^+$ and $CD8^+$ cells repeatedly transferred. In this defined system, dendritic cells in both draining lymph nodes and in the tubulointerstitium amplified immune responses in the tubulointerstitium including production of intrarenal cytokines, chemokines and infiltration by monocyte-derived DCs and macrophages. These data provide a mechanism whereby breaking of tolerance in glomeruli leads to TII. This mechanism might be very relevant to the anti-vimentin immune response described above as vimentin is highly expressed in normal glomeruli and is only abundant in the tubulointerstitium after injury and inflammation.

While there is likely a strong mechanistic interplay between GN and the initiation of TII, it is unclear if these same mechanisms are propagating TII at time of biopsy. Rather, it is likely that many of the additional *in situ* mechanisms described above (Figure 2), worsen local inflammation and tissue damage. In human lupus nephritis, the severity of interstitial nephritis does not necessarily correlate with glomerular activity. Could we add some histopath here?Cases in which very active glomerulonephritis is associated with little tubulointerstitial inflammation are common. Conversely, there are rare cases of lupus nephritis in which severe interstitial nephritis occurs in the absence of appreciable glomerulonephritis[118, 119]. Therefore, glomerulonephritis and interstitial nephritis can occur independently. Finally, as described above, the immunological milieus resident in the glomeruli and TI of lupus nephritis are very different.

This seeming disparity between animal models of pathogenesis and observations of the human disease might be resolved in one of two ways. First, simply, the pathogenic mechanisms of lupus nephritis are almost certainly many and complex. Therefore, it is likely that TII arises in different patients through different mechanisms that have variable relationships to GN. Second, while the mechanisms that initiate TII might be linked to GN, the mechanisms that propagate each process, and that are present at time of biopsy, might be very different.

Therapeutic Implications

Current therapies are either non-specific or are predicated on the idea that SLE is a systemic autoimmune disease in which adaptive immune responses, arising in secondary lymphoid organs, play a central role. However, it is becoming apparent that in those lupus nephritis patients with a poor prognosis, additional *in situ* adaptive immune cell networks are present that likely contribute to disease severity. We do not know if our current B and T cell targeted therapies disrupt these networks. Furthermore, there are additional innate immune and fibrogenic renal intrinsic processes that are poorly understood and for which relevant

clinical trial data is largely lacking. Defining these renal intrinsic mechanisms of disease, and targeting them effectively, should provide a path towards better therapies for the most severe cases of lupus nephritis.

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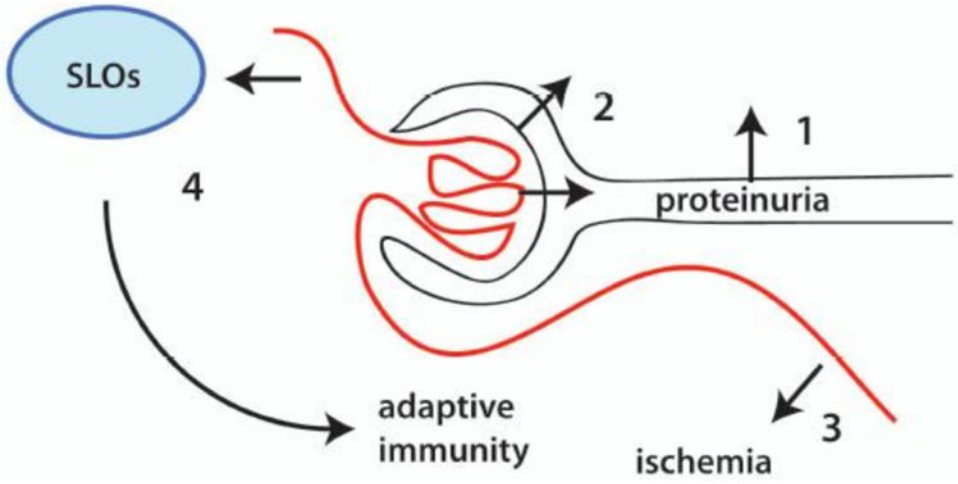

Figure 1. Potential mechanisms for how glomerulonephritis might initiate tubulointerstitial inflammation

1. GN leads to proteinuria that both activates and damages tubular epithelial cells leading to the release of inflammatory mediators in the tubulointerstitium and inflammation. 2. Inflammation can also result when severe GN ruptures Bowman's capsule. 3. Severe GN can induce tubulointerstitial ischemia, damage and inflammation. 4. Adaptive immune responses which begin with a break in tolerance in glomeruli can be established in secondary lymphoid organs (SLOs) and amplified in the tubulointerstitium.

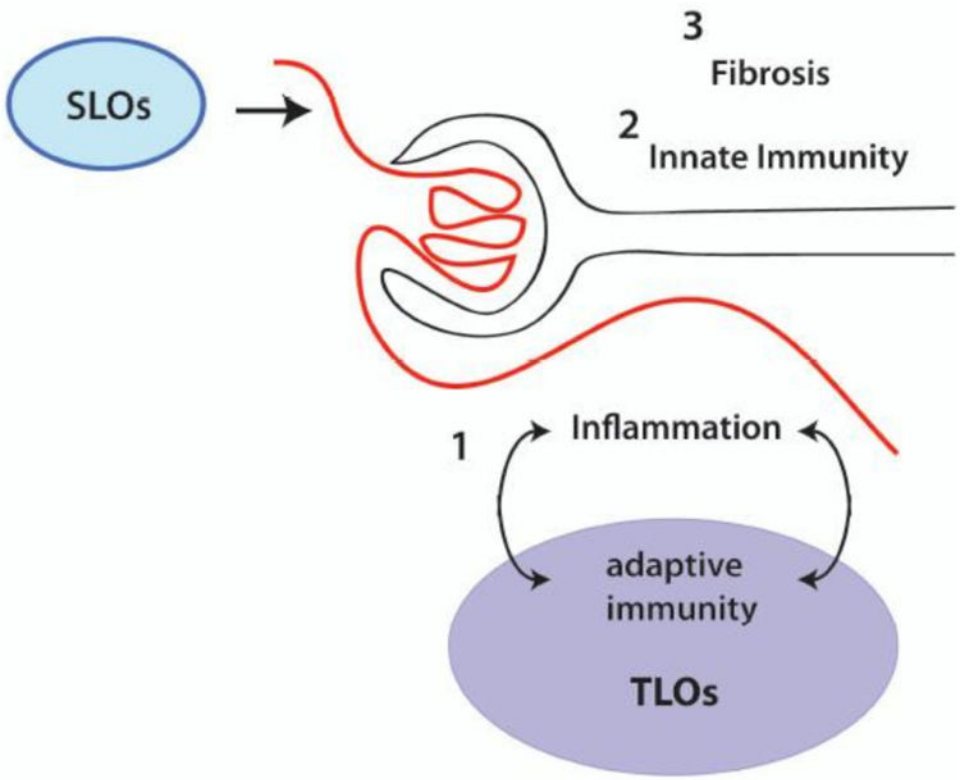

Figure 2. Propagation of tubulointerstitial inflammation

While many mechanisms might initiate tubulointerstitial inflammation, additional *in situ* mechanisms likely propagate and amplify local inflammation and tissue damage. 1. Within tertiary-like organ (TLO) structures, including T:B aggregates and plasmablast foci, local adaptive immune responses to antigenic features of inflammation are propagated. This feeds forward to worsen inflammation and tissue damage. In addition, networks of innate cells and mediators (2) and fibrogenic pathways (3) lead to progressive functional loss and ultimate renal failure.