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REVIEW

Special Issue: Novel Diagnostic and Therapeutic Approach Options in Lupus Nephritis

Transcriptome Studies in Lupus Nephritis

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Abstract

The present review is aimed at describing the main works that have used gene expression to analyze tissue kidney samples of lupus nephritis patients. Most studies used the gene expression arrays, which enormously advanced our knowledge on the possible mechanisms behind lupus nephritis. However, using bulk gene expression platforms, either as arrays, or as sequencing of RNA is not enough to go into detail of the cells and their molecular patterns and single cell mechanisms of disease. More recently, the first single cell RNA Sequencing study was published and this will also be discussed in the context of lupus nephritis. Single cell RNA sequencing allows to retrieve the genes expressed in each cell in the tissue of interest or in blood. In this context, the results of such studies give us a first glimpse of how a lupus nephritis kidney looks like, but much is still to be done to understand the changes that occur with treatment or with the different pathological subtypes of lupus nephritis and their cellular content.

Keywords Systemic lupus erythematosus · Lupus nephritis · Transcriptome · Gene expression · Genetics

Introduction

Lupus nephritis (LN) is a severe complication affecting some 40% out of all systemic lupus erythematosus (SLE) patients. It occurs more frequently in young female patients and is most severe in African Americans or patients with a low socioeconomic level (Sanchez et al. 2012).

A recent and comprehensive review on lupus nephritis in relation to urinary biomarkers or cellular abnormalities can be found in study by Morell et al. (2021). Cellular studies to detect lupus nephritis in a non-invasive manner have also been performed (Abdelati et al. 2021).

Advances in transcriptome analysis have led to a deeper understanding of the mechanisms behind the development of LN, but it has not been until more recently when the advent of single cell RNA sequencing (scRNASeq) has provided a more exhaustive analysis with the study of the transcriptome of each and every cell in the damaged kidney. However, still much needs to be done, as for example, changes in the patterns of the cells in the kidney after treatment or the relationship between the cellular content and the type of nephritis according to the WHO classification (Weening et al. 2004) and whether this classification indeed reflects the abnormalities occurring in LN, as well as the mechanisms of regulation behind the transcriptome in each cell type analyzed. Furthermore, with scRNASeq, completely novel cell types or stages of differentiation of effector cell types can be identified. One excellent example of the latter and the potential pathways of treatment is the scRNASeq paper on rheumatoid arthritis (RA), where NOTCH3 signaling was identified as an important pathway of signaling by fibroblasts in the perivascular space and lining fibroblasts in the synovium expressing CD90, and where treatment of mice with a NOTCH3 inhibitor attenuates the development of inflammatory arthritis and synovial damage (Wei et al. 2020).

In the present review, I begin by describing the genetic studies where genes have been found associated with LN. I describe briefly the studies using gene expression analysis either in blood in relation with the development of LN or in kidney tissue and its relationship with sever disease or prognosis of severe disease. I will describe the use of blood

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transcriptomic to predict lupus nephritis and the more recent use of scRNA sequencing to define the molecular patterns in individual cells (Fig. 1).

Genes and Lupus Nephritis

Several genes identified in genome wide association studies of SLE have been also found to be associated with LN, and further analysis has shown that these are significantly regulated in glomerular and tubulointerstitial compartment, suggesting their involvement in LN pathogenesis, with some clear genetic associations with the genes signal transducer and activator of transcription 4 (STAT4) (Bolin et al. 2013; Richman et al. 2012), integrin subunit alpha M (ITGAM) (Sanchez et al. 2011), or members of the Kallikrein family of genes (Liu et al. 2009). Particularly involved in the development of end stage, renal disease is the gene APOL1 (Freedman et al. 2014; Lin et al. 2012).

The polymorphism rs7574865 of STAT4 was found to be strongly associated with the presence of anti-dsDNA antibodies and quite strikingly with LN, and particularly with severe nephritis (Bolin et al. 2013; Reid et al. 2021; Taylor et al. 2008). STAT4, encodes for a transcription factor that contributes to the differentiation of helper T cells when activated by interleukin (IL)-12, being this activation enhanced by interferon (IFN)-α particularly in carriers of the LN associated single nucleotide polymorphisms (Hagberg and Ronnblom 2019).

ITGAM encodes for the α chain of CD11b (complement receptor 3: CR3, Mac-1) adhesion molecule, and is expressed on myeloid cells. CD11b expression was found

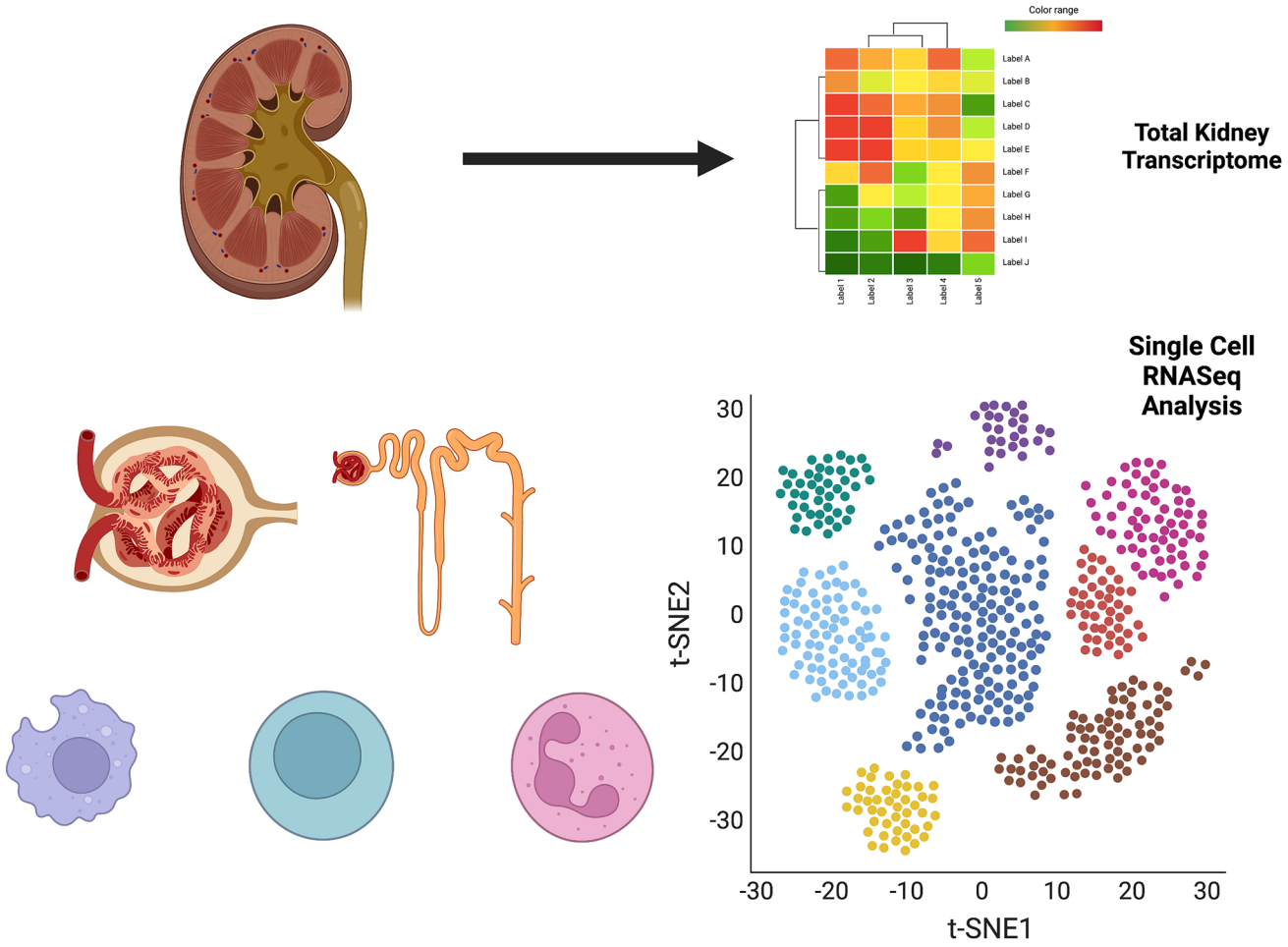

Fig. 1 Schematic representation of the two types of kidney transcriptome studies described: Top: whole tissue transcriptome where the complete kidney is processed and a general view of the kidney transcriptome is obtained. Bottom: the single cell RNA sequencing (scRNASeq) studies take the tissue and disrupt it with enzymes such as collagenase. Cells are then sorted and directly processed to obtain RNA and reverse transcription to obtain sequencing data from each cell. A minimum of 5000 cells are needed to obtain reliable results. Clustering of the data allows to define the cell types depending on the transcripts expressed. Some method, such as CITE-Seq combine protein data with gene expression data and are therefore better for identifying the cell types

increased in renal macrophages, as it was, as previously mentioned, associated genetically with SLE and LN (Nath et al. 2008; Yang et al. 2009). The ITGAM coding variant rs1143679, previously associated with SLE (Nath et al. 2008) was found to be associated with renal disease (Kim-Howard et al. 2010; Sanchez et al. 2011). Interestingly, a study found urinary CD11b (as Mac-1, a subunit of CD11b) and CD16b to be associated with disease activity in patients with LN (Khan et al. 2018; Kitagawa et al. 2019). The levels of CD11b were reduced following successful glucocorticoid treatment. As CD11b is expressed in the surface of several important cells such as dendritic cells and neutrophils or B cells, mechanisms behind how the variants of ITGAM may lead to LN have been proposed (Kahn et al. 2018).

APOL1, the gene encoding Apolipoprotein 1, represents a particular genetic mutation that is common in Africa, where the mutated variants protect carriers against Trypanosomiasis, reason probably why the variants are common in Africa. However, in the homozygous form, kidney become vulnerable to damage, making African-American patients with lupus particularly at risk (Blazer et al. 2021; Freedman et al. 2014).

The Kallikrein genes Kallikrein 1 and Kallikrein 3 were found associated with SLE and LN, a study based on animal models where a large number of this gene family was found to be downregulated through microarray analysis. The Kallikreins are serine esterases that when upregulated, favor kidney protection against kidney disease induced by anti-glomerular basement membrane antibodies (Liu et al. 2009). Other genes have been associated with LN in individual studies and not until a clear confirmation of that genetic association, such genes cannot be considered as clearly associated with LN.

Blood Transcriptome Analysis and Its Relationship with LN

Table 1 summarizes the relationship between the various transcriptome studies and clinical phenotypes. A first and seminal study analysed the transcriptome of blood in patients with biopsy-proven LN (Jourde-Chiche et al. 2017). Most interesting was the presence of a neutrophil signature in 65% of SLE patients strongly associated with LN, and particularly strong in patients with LN as compared with patients without LN. This gene expression signature or module did not correlate with IFN modules, nor the SLEDAI or with anti-dsDNA antibodies. It did moderately correlate with cyclophosphamide therapy. This module was stronger

Table 1 Relationship between clinical phenotypes and transcriptome studies

Type of transcriptome data (references)	Signature or pathway	Clinical phenotype related to transcriptome signature or pathway
Total blood adult SLE (Jourde-Chiche et al. 2017)	Neutrophil signature	Active nephritis, no correlation IFN signature of anti-dsDNA antibodies
Total blood adult SLE (Wither et al. 2018)	Neutrophil signature	Presence of flares, no importance of neutrophil signature at baseline
Total blood pediatric SLE (Banchereau et al. 2016)	IFN signature, plasmablast and neutrophil modules	Severe nephritis, anti-dsDNA antibodies, modified by MMF in proliferative nephritis patients
Total blood adult and pediatric (Toro-Dominguez et al. 2018)	Cluster of IFN signature and neutrophil	Increased neutrophils, C3 levels, and ESR, lymphopenia, proliferative nephritis risk
Total blood adult and pediatric (Toro-Dominguez et al. 2018)	Cluster lymphocytes	Low risk of nephritis, high lymphocytes, skin disease, antiphospholipid syndrome, Sjögren´s
Kidney whole transcriptome (Ju et al. 2015)	Epidermal growth factor	Biomarker of chronic kidney disease
Kidney whole transcriptome double biopsy (Mejia-Vilet et al. 2019)	IFN signature	Flaring
Kidney transcriptome (Peterson et al. 2004)	Fibrosis signature	Glomerulosclerosis
Transcriptome on archived biopsies (Pamfil et al. 2018)	T- and B-cell and antigen presentation	Reduced glomerular filtration rate
scRNASeq of kidney (Arazi et al. 2019)	Renal IFN signature	Correlation with kidney damage
scRNASeq kidney and skin (Der et al. 2019)	Expression of four genes, *COL1A1*, *COL14A1*, *COL1A2*, and *COL5A2* keratinocytes, and tubular kidney (FGFR3) and FGF13 in leukocytes	Prediction of NO response to therapy. No relationship with activity or chronicity. A separate kidney disease?
(Der et al. 2019)	TNF and type I IFN, TNFRI upregulation	Proliferative nephritis

MMF mycophenolate mofetil, *ESR* erythrocyte sedimentation rate, *C3* complement 3, *NO* nitric oxide, *TNF* tumor necrosis factor, *IFN* interferon

in patients with proliferative LN and associated with past, present and future renal flares. A second study confirmed this observation, where again, the abundance of neutrophil-related transcripts was found in patients with active LN (Wither et al. 2018). In both studies, the correlation between blood neutrophil counts and the neutrophil transcript signature was moderate, mainly due to therapy. In the second study (Wither et al. 2018), the authors mention that there was no relationship between having the neutrophil signature at baseline with changes over the first-year follow-up.

The work by Banchereau et al. (2016), identified patient specific co-expressed gene modules, by means of the WGCNA method, using longitudinal gene expression data from pediatric SLE patients. WGCNA, created by Chaussabel et al. (2008), allows for the identification of modules composed of a number of genes which may be found in healthy individuals or in the transcriptome data under study. Interestingly, when Banchereau et al. (2016), selected the most correlated module for each patient with SLEDAI and projected their expression profiles to the Chaussabel modules, seven groups of patients were revealed, corresponding to five immune signatures that were different from each other in terms of the types of cellular mechanisms: lymphoid, erythropoiesis, plasma cell, neutrophil/myeloid, and type I IFN. No differences were observed across the groups in terms of demographic parameters, with the exception of one group where all patients had nephritis and correlated with the IFN, neutrophil and plasmablast-associated modules. These patients had the most severe disease and the presence of anti-dsDNA antibodies. In addition, the neutrophil and IFN signatures correlated strongly with development of lupus nephritis and were modified by mycophenolate mofetil treatment, particularly in patients with proliferative rather than membranous glomerulonephritis. The most important aspect of this work is that such transcriptional groups of patients may serve as a basis to personalized treatment and could be used for drug repurposing analysis, mainly to find if there are indeed differential pathophysiological pathways modulated by specific drugs behind the different transcriptional profiles and cell types.

A latest attempt was performed by us, using pediatric data and a new set of adult SLE patients from the Johns Hopkins University School of Medicine, Baltimore, MD, USA (Toro-Dominguez et al. 2018). Instead of taking a module to define the transcriptome stratification, individual genes were selected by their correlation with the SLEDAI, followed by unsupervised clustering. The WGCNA was then used to investigate the functionality of the genes within each cluster. This study gave three clusters that were replicated in the adult set. It should be noted, however, that the SLEDAI is a semi-quantitative score with many drawbacks and that a continuous score based on real measurements that may be correlated with transcriptome data in a longitudinal fashion would be the ideal. The three clusters had particular characteristics: cluster 1 was heterogeneous and contained features of clusters 2 and 3, but the patients from that cluster could not be assigned to any of the other two. Cluster 2 was very differentiated and showed a clear relationship with the type I IFN signature. This signifies that during disease activity, with higher SLEDAI scores, the type I IFN signature genes correlated positively with the score. There was also a correlation with increases in levels of neutrophils, C3 and the erythrocyte sedimentation rate, and a negative correlation with levels of lymphocytes. In adult data, this cluster was also associated with lymphopenia. On the other hand, cluster 3 was complete opposite of cluster 2, showing instead a positive correlation between SLEDAI and lymphocytes and a negative correlation between the SLEDAI and neutrophil numbers or proportions. Interestingly, in pediatric patients the definition of the three clusters was very clear, less so in the adults. However, this has two clear explanations: one, that adult SLEDAI scores are much weaker and show less variation that in the pediatric patients, and second, that less adult patients were available. To perform these analyses, two conditions need to be met: a variable SLEDAI and at least three time points of transcriptome data to perform the correlation, which makes this sort of study somewhat difficult. In addition, a somewhat large number of patients (the study used 80 pediatric of the Banchereau study and 65 adults) is needed to meet the statistical requirements.

Clinically very interesting differences were observed. Patients from cluster 1 had the highest risk to develop proliferative nephritis while those from cluster 3 had a very low risk. This was particularly obvious in adults where 65% of the patients from cluster 1 were at risk to develop proliferative nephritis against 13% of cluster 3. Cluster 2 also had a high risk to develop proliferative nephritis, but somewhat lower. Patients from cluster 3 showed features of skin disease, antiphospholipid syndrome and enhanced liver enzymes. Disease activity did not condition the clusters, and indeed, there were no differences in the SLEDAI components or in the magnitude of the components between clusters. Also, when treatment was verified, it was observed that this did not condition the assignment of the patients into the clusters, and again, no differences in treatment between the groups were observed. Furthermore, neutrophils appeared to be important in defining the clusters, and treatment did not influence the numbers of neutrophils. In fact, when performing a feature (gene) selection against treatment doses, for each type of therapy for which the data was available, only 2% of the genes selected overlapped with the genes selected when correlating with the SLEDAI. In summary, the clusters had molecular patterns that most likely reflected the drivers

of the disease activity, being primarily differentiated by the cell types: neutrophils on the one hand, and lymphocytes on the other.

It is certainly possible that once the groups have been stratified into molecular blood patterns, patterns in tissues may create a sub-stratification of each cluster, and such sub-stratification may be important in the treatment of, for example, lupus nephritis. I believe this would be the case in SLE, particularly with the differences we observe in the risk to develop nephritis in clusters 1 and 2. Cluster 3, a cluster formed by individuals with secondary Sjogren's syndrome and antiphospholipid syndrome.

Whole Tissue Transcriptome Studies in LN

SLE is a particularly heterogeneous autoimmune disease, involving a variety of different organs; a number of different affected tissues have been shown to have a type I IFN signature, including the glomeruli (Peterson et al. 2004), synovium (Nzeusseu Toukap et al. 2007), skin (Dey-Rao et al. 2014) or bone marrow (Nakou et al. 2008), and hence a number of tissues can be analyzed in the study of this disease.

Transcriptome studies have also been performed to determine the efficacy of treatment or the development of chronic kidney disease. For instance, one study used transcriptional data from two cohorts where a significant correlation of estimated glomerular filtration rate with mRNA levels of epidermal growth factor (EGF) was found, where downregulation of renal EGF could be considered as a biomarker of prediction of chronic renal disease progression (Ju et al. 2015).

Another study looked into immune gene expression in kidney biopsies of LN patients at diagnosis and at flare (Mejia-Vilet et al. 2019). In this study, patients were biopsied twice. The samples were from paraffin archived biopsies where cells were obtained by microdissection, taking all available glomeruli and tubulointerstitium from where RNA was extracted. The study revealed great heterogeneity, but the first biopsy corresponded to what was found in the second biopsy (at flaring). In the glomerular compartment, pathways such as IL-6 and lipopolysaccharide-stimulated pathways, NF-κB activation pathway, T-cell pathways and B-cell signaling pathways were identified. In the tubulointerstitial compartment, similar pathways as in the glomeruli were defined as well as BAFF signaling, OX40 signaling, PI3K signaling. In addition, Tool-like receptor pathways (TLR7) were also found. IFN type I transcripts, that is, IFN signature genes (genes inducible by IFN type I) were found particularly during flaring in a group of patients suggesting the importance of this analysis in the potential treatment required in each sort of cases.

Another study stratified LN patients into two subgroups (Peterson et al. 2004): one subgroup with high expression of genes related to fibrosis and pathological evidence of glomerulosclerosis, and the other subgroup with a type I IFN signature. However, the relevance of the stratification is questionable because of the non-comparable features of each of the two subgroups (Peterson et al. 2004). Glomerulosclerosis is an advanced clinical feature of lupus nephritis, and long-term longitudinal analysis is needed to verify if indeed some patients are prone to developing glomerulosclerosis and if these patients express fibrosis-related genes during the early stages of disease.

Another study (Pamfil et al. 2018) analyzed biopsies of lupus nephritis on archived kidney biopsies combined with immunostaining and histological scoring. The authors used unsupervised clustering based on the gene expression feature to group the samples. The authors found overexpression of transcripts related with antigen presentation and T and B cells in some samples and these were characterized by lower glomerular filtration rate at the time of biopsy compared to other samples. Other relevant characteristics were no different between groups (C3, anti-dsDNA antibodies, etc.). The importance of this paper is that tubulointerstitial infiltration of adaptive cells was observed revealing the importance of the renal tubules in the development of kidney disease.

Single Cell Transcriptome in Tissues

The AMP RA/SLE Consortium published two papers that performed single cell transcriptome sequencing of two main tissues: the kidney and the skin of lupus patients. The study analyzing skin did so together with the kidney data, showing a certain reflection of kidney differentially expressed genes in specific cell types in the skin.

Arazi et al. (2019) performed a single cell analysis of lupus kidneys. The authors identified 21 subsets of infiltrating cells with pro-inflammatory responses. Also, the authors found a high correlation between the renal and the systemic IFN response. Interestingly, the authors found local B-cell activation with of a subset of B cells showing a signature similar to that of pro-inflammatory cells also called age associated B cells (Rubtsova et al. 2015) which are similar to the so-called DN2 cells described by others (Zumaquero et al. 2019). Most of the cells infiltrating the kidneys showed an IFN gene signature and in particular two chemokine genes were broadly expressed, *CXCR4* and *CX3CR1*, suggesting an important role of cell trafficking. The authors also analyzed urine cells and found an important correlation between these and the gene signatures found in the kidney. This has important clinical implications in that urinary cell markers could be used instead of kidney biopsies as proposed previously (Abdelati et al. 2021; Morell et al. 2021).

Der et al. (2019), analyzed kidney and skin biopsies in conjunction. The authors focused more on the kidney tubular cells and identified an IFN signature in these cells also expressed by keratinocytes of the skin. They could also see a fibrotic signature in the tubular cells associated with failure to respond to therapy, and in a sense similar to what was found in synovial tissue in RA (Lewis et al. 2019). This is very interesting because it suggests that some of the nephritis observed in lupus patients might not be immunologic or might be the result of a rapid fibrotic process without immune cell contribution. In fact, mesangial cells are capable of producing extracellular matrix proteins and structural proteins in the glomeruli, similarly to how fibroblasts do in other tissues. Mesangial cells interact with podocytes and endothelial cells, and respond to lupus stimuli in a varied array of pathways. Their detailed study is of major importance for the understanding of the role of these cells in LN (Marciano 2019; Nowling 2022). In fact, it may be of interest to study the trajectories of the differentiation of mesangial cells in animal models of lupus. In the case of the lupus tubular cells, the genes *TIMP1* and *SERPING* were shown, in a pathway analysis to be extracellular matrix-interacting molecules, as mentioned previously. The authors also noted in the non-responders an upregulation of the complement and coagulation cascades, including the genes *C1S* and *C1R*. A similar pattern was observed in keratinocytes in non-responders. In this case, the non-responders also showed some collagen genes that partly overlapped with those found in the kidney, such as *COL1A1* in both tissues, or *COL17A1* only in keratinocytes. Using a predictive model authors found that the expression of four genes, *COL1A1*, *COL14A1*, *COL1A2*, and *COL5A2* could predict response to treatment with an accuracy of 92% (AUC of 0.96). Importantly, the signature fibrotic scores found did not correlate with other disease activity or chronicity scores. The authors also could not correlate the fibrotic gene expression profiles with the histological pattern of fibrosis using light microscopy. In addition, peripheral blood mononuclear cells of the same individuals did not show any fibrotic markers. Looking into infiltrating cell receptor–ligand interactions, interactions between infiltrating leukocytes and potential ligands within tubular cells was found. For example, genes such as the fibrosis receptor *FGFR3* was expressed in tubular kidney cells, while its ligand *FGF13* was found expressed in leukocytes. Authors then analyzed separately biopsies with proliferative, membranous and mixed nephritis and identified different inflammatory pathways. The authors found that the proliferative histological class of nephritis, and their keratinocytes upregulated tumor necrosis factor and type I IFN pathways which were not observed in the membranous class. In the tubular cells, the proliferative class had an upregulation of *TNFR1* signaling.

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