Libyan International Medical University

Faculty of basic medical science

Systemic Lupus erythromatosis associated Glomerular Diseases

Abdulmajd Abdulbasit

Supervisor: Dr. ABIR Muftah

Assisted by: Dr.Sarah Gawaiafi

Report Submitted to fulfill the requirements for Scientific Research Activity

Date of Submission: 0/02/2020

Abstract

A combination of systemic autoimmunity and tissue response to immune injury underlie renal involvement in lupus erythematosus. In lupus glomerulonephritis, glomerular immune complexes were believed to be the primary mediators of renal disease. Recent studies make it apparent that autoantibodies of multiple specificities participate in the formation of immune complexes, deposited in the kidneys. Renal infiltration by T cells, macrophages, and dendritic cells have a dominant role in the progression of lupus glomerulonephritis leading to renal failure. Activation of Toll-like receptors modulates autoantibody production and systemic interferon responses. However, glomerular cell responses to immune injury influence disease outcome. In addition, new insights on the genetics of susceptibility to end-organ damage in lupus glomerulonephritis have been discovered. Lupus glomerulonephritis is a prototype of immune complex disease mediated by autoantibodies of multiple specificities, one of which is anti-DNA. Murine models of spontaneous systemic lupus erythematosus have been critical for understanding the underlying disease. Recent studies demonstrate that in addition to systemic autoimmunity, end-organ responses, and end-organ resistance to damage are also critical in determining disease outcome. This understanding should influence design of novel therapeutic approaches in systemic lupus erythematosus.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disorder affecting multiple organ systems including kidney, skin, lung, heart, the hematopoietic system and brain, Glomerulonephritis (GN) is a term used to refer to several kidney diseases (usually affecting both kidneys). Many of the diseases are characterized by inflammation either of the glomeruli or of the small blood vessels in the kidneys, also Glomerulonephritis leading to severe persistent proteinuria, chronic renal failure and end-stage renal disease which remains one of the most severe complications of SLE and its associated with significant morbidity and mortality. Despite intensive

investigation that aimed to understand the disease , the real mechanism that underlies renal injury in lupus glomerulonephritis is not completely understood.

Detection of antinuclear antibodies in serum is one of the most frequent laboratory tests for diagnosis of SLE. Anti-dsDNA antibodies are considered a hallmark of SLE and anti-Sm antibodies have a significant association with lupus nephritis However, not all anti-dsDNA antibodies can deposit in the kidney, and it hasn't been possible to replicate the disease of lupus nephritis with passive transfer of anti-DNA antibodies ,the ability of anti-DNA antibodies to induce glomerulonephritis and transient proteinuria has been attributed to their cross-reactivity to glomerular antigens such as alpha actinin and laminin. Deposition of positively charged nucleosomes on glomerular basement membrane (GBM) as targets for autoantibodies has been previously described.[2] the recent series of studies demonstrate that electron dense deposits are seen in proteinuric, lupus-susceptible These deposits are oligo-nucleosomes, recognized by anti-dsDNA reactive monoclonal antibodies, and caused by ineffective fragmentation and clearance of apoptotic material in the renal glomerulus. In addition, These antibodies react specifically with the electron dense deposits and not with surrounding tissues containing alpha actinin or laminin. It was concluded that the accumulation of chromatin fragments on the glomerular basement membrane and high-affinity antibodies to nucleosomal DNA, not cross-reactivity to glomerular proteins determines pathogenic capacity of anti-DNA antibodies. The monospecificity of the anti-DNA antibodies requires further documentation. Thus, the specificities of autoantibodies in immune complex deposits initiating the disease remain to be determined.[1,2,3]

Aim of Study

This report is made in order to investigate theoretical mechanisms that underlie glomerulonephritis in SLE patients

Materials and Methods

The absolute requirement for anti-DNA or antinuclear antibodies in lupus glomerulonephritis is also challenged by studies from patient samples. Immunoglobulin eluted from kidney tissue obtained from 25 lupus patients were

screened against a panel of 14 different antigens including dsDNA, chromatin, collagen-like regions of C1q complement, Sm, SSA, SSB and histones ,A cumulative reactivity to all these antigens in the different samples ranged from 0.3 to 41.3% of the total IgGs.[5]

Results

Reactivity of 200 monoclonal antibodies generated by isolating single IgG+ memory B cells from four lupus patients and one healthy control showed that 15–26% of the antibodies were poly reactive between a diverse antigen panel that included ssDNA, dsDNA, LPS, and insulin. Surprisingly, there was no significant difference between the patients and controls in the autoreactivity of the memory IgG+ B cells, implying that poly reactive autoantibody populations are a common occurrence in all individuals. However, this can be explained by the increasing recognition that many B and T cell receptors are poly reactive, The findings presented above suggest that development of lupus glomerulonephritis is not associated with pathogenic autoantibodies of singular specificities. In fact, majority of the antigens recognized by glomerular IgG deposits are unknown. In view of the recent findings that immune complexes per se are insufficient to cause end stage renal failure and that end-organ responses to these deposits are important factors for the progression of lupus nephritis, identifying specificities of autoantibodies that are deposited in glomeruli of lupus patients may not be critical for prognosis of renal disease.

Evidence for the importance of T cells as effectors in lupus glomerulonephritis comes from several approaches. The first approach was the finding that renal disease is present in MRL/lpr lacking circulating Ig but with B cells expressing a B cell receptor transgene ,The study showed that MRL/lpr expressing a surface transgenic B cell receptor to 4-hydroxy-3-nitrophenyl develop unique renal disease characterized by glomerular sclerosis and interstitial inflammation despite the absence of circulating Ig. Secondly, NZB/W F1 with established chronic glomerulonephritis treated with CTLA4Ig and a suboptimal dose of cyclophosphamide showed a significant delay in mortality without reduction in glomerular immune complex deposits, Thus, blocking T cell activation by CTLA4Ig could prevent disease progression. This reaffirms the

original observation that anti-T cell antibody therapy reduced glomerular inflammation, severe proteinuria and early mortality. In other patients , early immune complex deposits and acute proliferative glomerulonephritis was associated with glomerular and peri-glomerular T cell infiltration In addition, MHC II positive, CD11c dendritic cells were seen in the glomeruli. This was accompanied by increased frequency of CD4+ T cell activation ,All these findings suggest a local T cell response in kidney and regional lymph nodes are involved in the pathogenesis of disease**.**[4,5,6]

Discussion

- **Autoreactive T cells and lupus glomerulonephritis**

Since autoantibodies of multiple specificities are a hallmark of SLE, it is natural that the role of B cells and autoantibodies has been a dominant focus of study in SLE in general and in lupus glomerulonephritis in particular. T cells were considered mainly for the provision of help to B cells for the production of autoantibodies. During the past several years, the focus on the role of T cells in lupus glomerulonephritis has been changed to the emphasis of these cells as effectors mediating tissue injury.

Recently, using a transgenic mouse model system, Heymann et al. have demonstrated a role for CD4 and CD8 T cells in glomerular injury. Transgenic mice expressing ovalbumin and hen egg lysozyme proteins in glomerular epithelial cells, in the podocytes,. Ovalbumin-specific transgenic CD8+ T cells injected into these mice could get activated and expanded in the renal lymph nodes. The T cell activation was prevented by depletion of CD11c dendritic cells. These studies suggest that uptake of podocyte antigens by dendritic cells and cross-presentation to CD8+ T cells occurs in the renal lymph nodes. Transfer of ovalbumin-specific CD4+ T cells did not result in expansion or division. However, repeated co-injection of ovalbumin-specific activated CD4 and naïve CD8 T cells caused renal disease characterized by peri-glomerular inflammation, infiltration of macrophages and dendritic cells, and onset of mild proteinuria. Although this model does not completely mimic the regional CD4+ T cell activation in lupus mice, it is the first direct demonstration for the role of dendritic cells and CD4+ and CD8+ T cells in glomerular injury. Another significant difference of this model from lupus glomerulonephritis is the absence of glomerular immune

complex deposits. These differences should be taken into account in its applicability to lupus nephritis.

- **Pathogenic contribution of end-organ responses**

Glomerular immune complex deposition is one of the earliest signs of renal involvement in SLE, this is followed by production of chemokines like MCP-1 and RANTES in the glomeruli, primarily by mesangial cells. The initial mesangial cell stimulation leads to acute proliferative glomerulonephritis characterized by mesangial expansion and cellular infiltration into the glomeruli. This may progress to chronic glomerulonephritis characterized by glomerulosclerosis, interstitial fibrosis and tubular atrophy, along with severe persistent proteinuria and fatal renal failure. We have previously demonstrated that acute glomerulonephritis need not progress to chronic glomerulonephritis. This lack of disease progression is also seen in a subset of patients. To investigate molecular changes associated with progressive glomerular disease, microarray analyses for glomerular gene expression patterns at different stages of glomerulonephritis were carried out and classified into four distinct clusters, that is normal, acute, transitional and chronic glomerulonephritis. Acute glomerulonephritis was dominated by inflammatory chemokines and cytokines and markers of myeloid cells. The chronic glomerulonephritis stage was characterized by glomerular fibrosis and sclerosis, with increase in tissue repair and remodeling genes. Severe proteinuria and progressive loss of renal function is associated with chronic glomerulonephritis. The micro-array analysis identified a transitional glomerulonephritis stage showing increased expression of seven genes including matrix metalopeptidase, Mmp10; transforming growth factor beta 2, TGFβ2; insulin-like growth factor binding protein 2, igfbp2; and lipocalin 2, Lcn2. Activation of TGF beta signaling appears to be the final common pathway leading to fibrosis and irreversible glomerular damage, resulting in end-stage renal disease Considerable interest has been focused on the role of Toll-like receptors (TLRs) in the autoimmune disease and has been reviewed recently ,It is mentioned here to emphasize the importance of the TLR expression on renal cells and their role in activation of end organ responses in tissue injury.[4,5,6,7]

The concept of end-organ resistance is also illustrated by the recent studies of Mohan and colleagues using a murine model of immune complex glomerulonephritis. Immune complex glomerulonephritis was induced by immunizing mice with rabbit IgG in Complete Freunds' Adjuvant (CFA) followed by injection of rabbit anti mouse GBM serum in 20 different mouse strains. Strains like NZW, DBA/1, 129/SvJ developed severe glomerulonephritis, whereas C57BL/6 and BALB/C mice did not. The severity of renal disease did not corelate with the strength of the immune response to rabbit IgG. These studies showed strain-dependent differences in renal disease and therefore potentially genetic control of susceptibility to kidney injury[1,2,3,4]

Conclusion

The current concepts of lupus nephritis have important clinical implications and suggest that autoantibodies have an important role in lupus nephritis pathogenesis along with detection of immune complexes . The realization of the importance of T cells as central players of this disease suggests that anti-T cell agents are required for inducing remission. The role of inflammation as seen in the early proliferative nephritis can best be dealt with using anti-inflammatory reagents such as prednisone(Treatment). The importance of cellular response to inflammatory signals by glomerular endothelial and mesangial cells identifies these cells as therapeutic targets.

Future Work

The next advance in lupus nephritis is the identification of target antigens that activate autoreactive T cells leading to glomerular and interstitial infiltration of inflammatory cells

References

1. Danchenko N., Satia J.A., Anthony M.S. Epidemiology of systemic lupus erythematosus: A comparison of worldwide disease burden. Lupus. 2006;15:308–318. doi: 10.1191/0961203306lu2305xx. [PubMed] [CrossRef] [Google Scholar]

2. Osio-Salido E., Manapat-Reyes H. Epidemiology of systemic lupus erythematosus in Asia. Lupus. 2010;19:1365–1373. doi: 10.1177/0961203310374305. [PubMed] [CrossRef] [Google Scholar]

3. Korbet S.M., Schwartz M.M., Evans J., Lewis E.J. Severe lupus nephritis: Racial differences in presentation and outcome. J. Am. Soc. Nephrol. 2007;18:244–254. doi: 10.1681/ASN.2006090992. [PubMed] [CrossRef] [Google Scholar]

4. Rovin B.H., Zhang X. Biomarkers for lupus nephritis: The quest continues. Clin. J. Am. Soc. Nephrol. 2009;4:1858–1865. doi: 10.2215/CJN.03530509. [PubMed] [CrossRef] [Google Scholar]

5. Winfield J.B., Faiferman I., Koffler D. Avidity of anti-DNA antibodies in serum and IgG glomerular eluates from patients with systemic lupus erythematosus. Association of high avidity antinative DNA antibody with glomerulonephritis. J. Clin. Investig. 1977;59:90–96. doi: 10.1172/JCI108626. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

6. Kalunian K.C., Panosian-Sahakian N., Ebling F.M., Cohen A.H., Louie J.S., Kaine J., Hahn B.H. Idiotypic characteristics of immunoglobulins associated with systemic lupus erythematosus. Studies of antibodies deposited in glomeruli of humans. Arthritis Rheumatol. 1989;32:513–522. doi: 10.1002/anr.1780320502. [PubMed] [CrossRef] [Google Scholar]

7. Termaat R.M., Assmann K.J., van Son J.P., Dijkman H.B., Koene R.A., Berden J.H. Antigen-specificity of antibodies bound to glomeruli of mice with systemic lupus erythematosus-like syndromes. Lab. Investig. 1993;68:164–173. [PubMed] [Google Scholar]

8. Vlahakos D.V., Foster M.H., Adams S., Katz M., Ucci A.A., Barrett K.J., Datta S.K., Madaio M.P. Anti-DNA antibodies form immune deposits at distinct glomerular and vascular sites. Kidney Int. 1992;41:1690–1700. doi: 10.1038/ki.1992.242. [PubMed] [CrossRef] [Google Scholar]

9. Yung S., Cheung K.F., Zhang Q., Chan T.M. Anti-dsDNA antibodies bind to mesangial annexin II in lupus nephritis. J. Am. Soc. Nephrol. 2010;21:1912–1927. doi:.1681/ASN.2009080805. [PMC free article] [PubMed] [CrossRef] [Google Scholar]