The role of cytokine in the lupus nephritis

Review Article

The Role of Cytokine in the Lupus Nephritis

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Lupus nephritis (LN) is a major clinical manifestation of systemic lupus erythematosus (SLE). Although numerous abnormalities of immune system have been proposed, cytokine overexpression plays an essential role in the pathogenesis of LN. In the initial phase of the disease, the immune deposits and/or autoantibodies induce cytokine production in renal resident cells, leading to further inflammatory cytokine/chemokine expression and leukocyte infiltration and activation. Then, infiltrate leukocytes, such as macrophages (Mφ) and dendritic cells (DCs), secrete a variety of cytokines and activate naïve T cells, leading the cytokine profile towards T helper (Th)1, Th2, and/or Th17. Recent studies revealed these inflammatory processes in experimental animal models as well as human LN. The cytokine targeted intervention may have the therapeutic potentials for LN. This paper focuses on the expression of cytokine and its functional role in the pathogenesis of LN.

1. Introduction

Lupus nephritis (LN) is a major clinical manifestation of systemic lupus erythematosus (SLE); it occurs in up to 50% of patients at onset of the disease and over 60% of patients during the disease [1]. Clinical course ranges from asymptomatic urinary occult blood to nephrotic syndrome or acute kidney injury since kidney injuries in LN are so variable. Major pathologic classification is based on glomerular disease. Tubulointerstitial damage and vasculitis are also frequently encountered in LN. The patients of the WHO class IV (proliferative glomerulonephropathy) at initial renal biopsies show higher rate of end-stage renal failure (ESRF) compared with those of the other classes. The mean 50% renal survival time of class IV is 189 months in Japanese patients [2]. To understand the pathogenesis of cytokines on LN, murine models of SLE have been investigated such as MRL-Fas^{lpr} mice and NZBXNZW mice. Both strains show glomerulonephritis, splenomegaly, and lymphadenopathy. In MRL-Fas^{lpr} mice, glomerulonephritis occurs at 3 months of age. Fifty percent survival is 5-6 months of age, and the cause of death is renal failure [3]. In NZBXNZW mice, LN becomes apparent at 5-6 months of age, leading to renal failure and death at 10–12 months of age [4]. Although numerous underlying mechanisms are reported, cytokine plays a key role in disease initiation and progression. This paper focuses on the contribution of cytokine, cytokine receptors, and intracellular signaling in LN.

2. The Role of Cytokines in the Disease Initiation Phase

2.1. The Role of Renal Resident Cells. The deposit of immune complexes (ICs) has been regarded as responsible for the initiation of LN. Glomerular IC deposition is mostly found in mesangium, subendothelial, and subepithelial lesions. Especially, mesangial and subendothelial deposits cause proliferative patterns of LN. IC deposition activates complement cascade, leading to mesangial cell activation and proliferation. Once activated, mesangial cells produce various types of cytokines and chemokines, leading to amplification of glomerular disease [5]. In addition to IC-mediated glomerular injury, auto-antibodies may also promote proliferation

and activation in kidney resident cells. Yung et al. demonstrated that anti-DNA antibody induced the secretion of Interleukin (IL-) 1β, IL-6, and tumor necrosis factor (TNF-)α in human cultured mesangial and tubular epithelial cell [6]. These observations suggest that renal resident cells activated by ICs and/or auto-antibodies secret the cytokines, which may further amplify inflammatory processes. They also demonstrated that anti-DNA antibody induced protein kinase c activation, which is a signal pathway causing the synthesis of cytokines in human mesangial cell [7].

2.2. The Contribution of Proinflammatory Cytokines to LN. The role of TNF in LN is controversial. Several groups showed the beneficial effects of TNF in NZBXNZW mice [8–11], whereas some groups reported the adverse effects in MRL-*Fas^{lpr}* mice [12–17]. The protective effect is specific to NZBXNZW strain, and the mechanism is not clear [18]. As for the human LN, Yokoyama et al. showed that serum levels of TNF-α are correlated to glomerular ICAM-1 expression, which is associated with endocapillary lesions in renal biopsy specimen [19]. Aringer et al. summarized the reported 12 cases, who were treated with TNF blockers. In 9 out of 12 patients, TNF blocker therapy led to the improvement of LN and the long-term renal responses [20]. Matsumura et al. also reported that 6 out of 8 patients showed improved urinary protein and SLE activity by the anti-TNF therapy [21]. These data suggest that anti-TNF-α therapy may have therapeutic potentials in human LN. However, some groups reported that anti-TNF-α therapy in rheumatic disease induce autoantibodies formation and lead to SLE including LN [22, 23]. We should be aware that anti-TNF-α therapy could induce SLE as well.

Results from experimental animal models show the pathogenesis of IL-6 in LN. Anti-IL-6 antibody administration inhibits LN in NZBXNZW mice [24]. Blocking IL-6 receptor ameliorates LN in MRL-*Fas^{lpr}* mice [25]. Moreover, IL-6 injection exacerbates LN in NZBXNZW mice [26]. Supporting this notion, several studies demonstrated that IL-6 contributes to the production of anti-DNA antibody from B cells [24, 27]. Wan et al. reported that IL-6 inhibits the function of regulatory T cells in lupus model mice [28]. In human samples, IL-6 mRNA level in peripheral blood mononuclear cells is higher in patients with active LN than that in those with inactive LN [29]. As for the clinical therapy, Illei et al. administrated the IL-6 receptor antagonist, tocilizumab, to the SLE patients. They reported that arthritis improved all 7 patients with arthritis at base line, but there was no change of proteinuria during the study in all 5 patients with LN at the base line [30]. Further studies will be needed to determine the effects of tocilizumab on LN.

IL-1 induces endothelial adhesion molecules [31] and increases the production of IgG and anti-DNA antibody from B cell [32] in MRL-*Fas^{lpr}* mice. Anti-dsDNA antibody induces IL-1β production in mesangial cells, which lead to the overexpression of extracellular matrix, hyaluronan [6]. In human LN, IL-1β was detected in the kidney of WHO class IV [33]. These data suggest the local relevance of IL-1β in LN. However, IL-1 receptor antagonist therapy does not improve LN in MRL-*Fas^{lpr}* mice [34]. The pathogenesis and therapeutic effects of IL-1β remain to be investigated.

2.3. The Role of Intracellular Signaling Pathways. Several protein kinase cascades mediate the intracellular cytokine signal transduction, leading to various types of cell response, such as cell migration, proliferation, and inflammatory response. p38 mitogen-activated protein kinase (MAPK) is responsible for the production and signal transduction of cytokines. We found that pharmacologic inhibition of p38 MAPK significantly reduced cytokine expression and improved the renal injury in MRL-*Fas^{lpr}* mice [35]. In addition, the inhibition of p38 MAPK also reduced the number of mature DCs within injured kidney and decreased IL-12 and IL-23 expression on DCs (Figure 1) [36]. Thus, intracellular pathway might be a good therapeutic target in LN.

3. The Role of Cytokine in the Disease Amplification/Progression Phase

3.1. The Role of Infiltrated Leukocytes. Once inflamed renal resident cells produce cytokines and chemokines, leukocytes migrate to glomerulus and interstitium. In human LN, most infiltrating mononuclear leukocytes are T lymphocytes, with lesser numbers of macrophages (Mφ), B lymphocytes, and natural killer cells [37]. Infiltrate Mφ and dendritic cells (DCs) secrete a variety of cytokines and activate naïve T cells, leading the cytokine profile towards Th1, Th2, and/or Th17. Renal resident cells also secret multiple cytokines.

3.2. The Contribution of Th17 to LN. Recent studies suggest that Th17 cells play a crucial role in the pathogenesis of LN. Zhang et al. demonstrated that IL-17-producing CD3$^+$ cells from lupus prone mice induce nephritis when transferred to nonautoimmune, lymphocyte-deficient Rag-1$^{-/-}$ mice [38]. Steinmetz et al. showed that CXCR3, which is expressed on Th1 and Th17 cells, deficient lupus prone MRL-*Fas^{lpr}* mice ameliorate LN accompanied by the reduction of interferon (IFN)-γ and IL-17 producing T cells [39]. Furthermore, IL-23 receptor$^{-/-}$ B6/lpr mice are protected from the development of LN, followed by the decrease of IL-17-producing T cells [40].

In human LN, IL-17 was detected in glomerular and interstitial infiltrated T cells using laser microdissection. The expression level of IL-17 was correlated with SLE Disease Activity Index Scores [41]. Crispín et al. reported that CD4$^-$CD8$^-$ double-negative T cells produce IL-17 and infiltrate the kidneys in LN patients [42]. Interestingly, double-negative T cells have been reported as a major source of IL-17 in MRL-*Fas^{lpr}* mice as well [38].

3.3. The Contribution of Th1 Cytokines to LN. IL-12$^{-/-}$ MRL-*Fas^{lpr}* mice are protected from LN followed by the reduced production of IFN-γ [43]. Deficiency of IFN-γ in MRL-*Fas^{lpr}* mice ameliorates LN [44]. Moreover, IFN-γ receptor$^{-/-}$ MRL-*Fas^{lpr}* mice showed the decreased renal pathology and extended survival [45]. These results suggest

(a) Kidney pathology

(b) DCs infiltration

(c) Kidney TNF-α transcripts

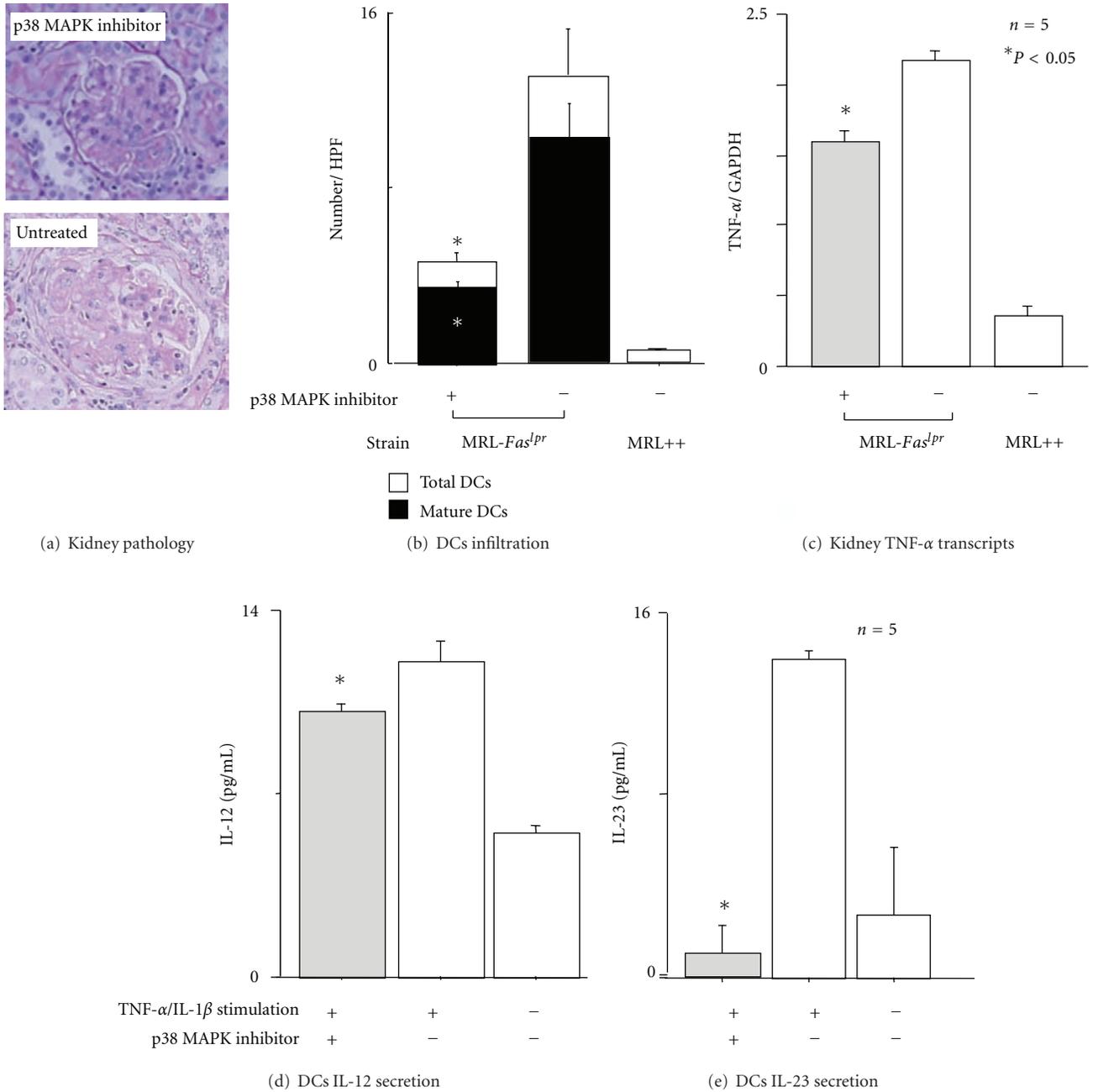(d) DCs IL-12 secretion

(e) DCs IL-23 secretion

FIGURE 1: p38 MAPK plays an essential role in the lupus nephritis in MRL-Fas^{lpr} mice. (a) p38 MAPK inhibitor ameliorates kidney injury in MRL-Fas^{lpr} mice. (b) The number of CD11c$^+$ cells and CD11c$^+$ CCR7$^+$ mature phenotype was decreased by the inhibition of p38 MAPK in the kidney. (c) The transcripts of TNF-α were reduced by the administration of p38 MAPK inhibitor. ((d) and (e)) p38 MAPK is central for the production of IL-12 and IL-23 on DCs in MRL-Fas^{lpr} mice.

that IFN-γ plays an essential role in disease progression in LN. In contrast, the role of type I IFN (IFN-α/β), which is classically thought to induce Th1 type inflammation, is equivocal. The administration of IFN-α accelerates the development of lupus in lupus-prone mice [46, 47]. Moreover, Type I IFN receptor (IFNAR)$^{-/-}$ NZBXNZW is protected from LN [48]. As opposed to this study, Hron and peng reported that IFNAR$^{-/-}$ MRL-Fas^{lpr} mice showed increased lymphadenopathy, autoantibody production, and LN [49].

Of note, Schwarting et al. reported that the IFN-β therapy reduces the activity of LN in MRL-Fas^{lpr} mice [50]. These results indicate the different role of IFN-α and IFN-β in LN though IFNAR is the common receptor for both IFNs [51]. Supporting this notion, Satchell et al. reported that IFN-β had an effect on barrier properties, increasing electrical resistance across monolayers of either glomerular endothelial cells or podocytes and decreasing transmonolayer passage of albumin [52].
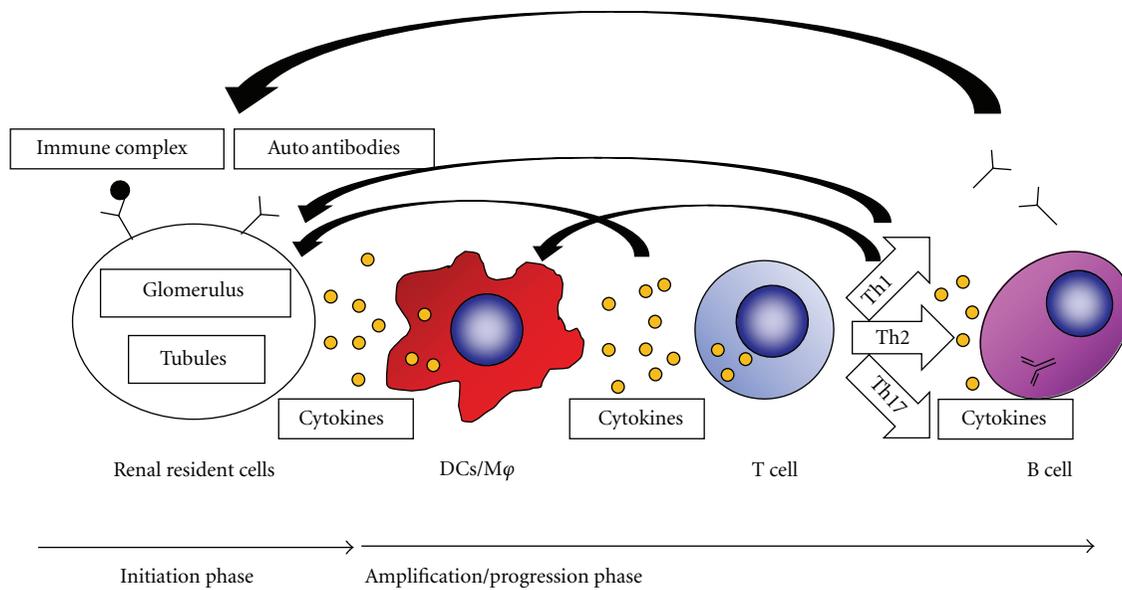
Figure 2: Cytokines contribute to the pathogenesis of lupus nephritis from the initiation phase to the amplification/progression phase. Immune deposits and/or autoantibodies induce the secretion of cytokine in the renal resident cells, which promote the infiltration and activation of leukocytes in the disease initiation phase. Activated leukocytes also produce cytokines, which leads to the further immune response in the disease amplification/progression phase.

IL-18, which is a strong inducer of IFN-γ, is upregulated in MRL-Fas^{lpr} mice. The tubular epithelial expression of IL-18 is correlated with disease activity [53]. IL-18 expression was also detected in mesangial cells in NZBXNZW mice [54]. In addition, the therapy targeted to IL-18 protects mice from LN [55]. Interestingly, docosahexaenoic acid in fish oil decreased serum levels of IL-18 and attenuated lupus nephritis in NZBXNZW mice [56].

In human LN, Masutani et al. detected that infiltrated cells expressed IFN-γ in LN. They also demonstrated that IFN-γ/IL-4 ratio in peripheral blood CD4$^+$ cell was correlated with pathological activity index [57]. Yokoyama et al. revealed that serum level of IFN-γ is related to proliferative and active lesions, and the level is decreased by methylprednisolone pulse therapy [58]. Another group also showed the expression of IFN-γ in human LN [59]. Chan et al. reported the correlation between glomerular expression of the Th1 transcription factor (T-bet), IFN-γ, and IL-2 with serum C3, C4 and anti-double-strand-DNA antibody level [60]. Tucci et al. demonstrated the IL-18 expression within glomeruli in patients with severe LN [61].

3.4. The Contribution of Th2 Cytokines to LN. Several groups reported the Th2 contribution to LN. Charles et al. revealed that autoreactive IgE and IL-4 are essential for lupus model mice and SLE patients. They showed that activated basophils secret IL-6 and IL-4, which promote Th2 response and B cell activation, resulting in autoantibodies production [62, 63]. Other groups reported the relationship between Th2 dominance and membranous nephropathy in LN. IL-27 receptor$^{-/-}$ MRL-Fas^{lpr} mice showed membranous glomerulonephritis with the predominance of Th2 systemic reaction [64]. In lupus patients with WHO type V (membranous

nephropathy), IFN-γ/IL-4 expression ratio was lower in peripheral blood T cell, whereas IFN-γ/IL-4 expression ratio was higher in those with WHO type IV (proliferative glomerulonephropathy) [65]. Furthermore, Th2 cytokine dominance is also reported in the kidney tissue from the patients with WHO type V [59].

3.5. The Contribution of IL-10 to LN. Originally, Th2 cells and antigen-presenting cells have been reported as a source of IL-10. However, recent reports show that Th1 cells and Th17 cells in addition to Th2 cells produce IL-10 [66–69]. Ishida et al. reported that anti-IL-10 therapy delayed the onset of lupus nephritis in NZBXNZW mice. Interestingly, they showed that anti-IL-10 therapy increased the serum levels of TNF-α, which contributed to the protection from autoimmunity [70]. Ravirajan et al. also described that anti-IL-10 therapy reduced proteinuria in human ds-DNA Ab-induced lupus model mice [71]. Continuous overexpression of low levels of IL-10 delayed the production of autoantibodies and decreased the severity of LN [72]. This is somehow contradictory to other studies. These differences may be related to the mice strain, disease models, and/or the amount of IL-10 expression. In SLE patients, anti-IL-10 therapy ameliorates skin and joint lesions in all 6 patients [73]. However, the effect of anti-IL-10 therapy on LN is not clear in this study.

4. Conclusion

Cytokine is upregulated by the immune deposits and/or autoantibodies in disease initiation phase, leading to inflammatory cytokine/chemokine expression and leukocyte infiltration and activation. Activated leukocytes produce

cytokines, which amplify the inflammatory response. Then, sustained cytokine production by multiple triggers is associated with progression of LN. Thus, cytokine is essential from the initiation to progression phase of LN (Figure 2). Some animal models provide the evidence of anticytokine therapy. However, sufficient evidence is not yet available to clarify the efficacy of anticytokine therapy for human LN. A major challenge will identify novel targets for therapeutic intervention for human LN.

References

[1] A. S. Bomback and G. B. Appel, "Updates on the treatment of lupus nephritis," *Journal of the American Society of Nephrology*, vol. 21, no. 12, pp. 2028–2035, 2010.

[2] H. Yokoyama, T. Wada, A. Hara et al., "The outcome and a new ISN/RPS 2003 classification of lupus nephritis in Japanese," *Kidney International*, vol. 66, no. 6, pp. 2382–2388, 2004.

[3] V. R. Kelley, "Leukocyte-renal epithelial cell interactions regulate lupus nephritis," *Seminars in Nephrology*, vol. 27, no. 1, pp. 59–68, 2007.

[4] D. Perry, A. Sang, Y. Yin, Y. Y. Zheng, and L. Morel, "Murine models of systemic lupus erythematosus," *Journal of Biomedicine and Biotechnology*, vol. 2011, Article ID 271694, 19 pages, 2011.

[5] C. Gómez-Guerrero, P. Hernández-Vargas, O. López-Franco, G. Ortiz-Muñoz, and J. Egido, "Mesangial cells and glomerular inflammation: from the pathogenesis to novel therapeutic approaches," *Current Drug Targets*, vol. 4, no. 3, pp. 341–351, 2005.

[6] S. Yung, R. C. W. Tsang, J. K. H. Leung, and T. M. Chan, "Increased mesangial cell hyaluronan expression in lupus nephritis is mediated by anti-DNA antibody-induced IL-1β," *Kidney International*, vol. 69, no. 2, pp. 272–280, 2006.

[7] S. Yung, Q. Zhang, Z. Z. Chen, W. C. Kwok, L. L. Sing, and M. C. Tak, "Anti-DNA antibody induction of protein kinase C phosphorylation and fibronectin synthesis in human and murine lupus and the effect of mycophenolic acid," *Arthritis and Rheumatism*, vol. 60, no. 7, pp. 2071–2082, 2009.

[8] C. Gordon, G. E. Ranges, J. S. Greenspan, and D. Wofsy, "Chronic therapy with recombinant tumor necrosis factor-α in autoimmune NZB/NZW F1 mice," *Clinical Immunology and Immunopathology*, vol. 52, no. 3, pp. 421–434, 1989.

[9] C. Gordon and D. Wofsy, "Effects of recombinant murine tumor necrosis factor-α on immune function," *Journal of Immunology*, vol. 144, no. 5, pp. 1753–1758, 1990.

[10] D. Kontoyiannis and G. Kollias, "Accelerated autoimmunity and lupus nephritis in NZB mice with an engineered heterozygous deficiency in tumor necrosis factor," *European Journal of Immunology*, vol. 30, no. 7, pp. 2038–2047, 2000.

[11] N. Jacob, H. Yang, L. Pricop et al., "Accelerated pathological and clinical nephritis in systemic lupus erythematosus-prone New Zealand mixed 2328 mice doubly deficient in TNF receptor 1 and TNF receptor 2 via a Th17-associated pathway," *Journal of Immunology*, vol. 182, no. 4, pp. 2532–2541, 2009.

[12] C. K. Edwards III, T. Zhou, J. Zhang et al., "Inhibition of superantigen-induced proinflammatory cytokine production and inflammatory arthritis in MRL-Ipr/Ipr mice by a transcriptional inhibitor of TNF-α," *Journal of Immunology*, vol. 157, no. 4, pp. 1758–1772, 1996.

[13] Y. Deguchi and S. Kishimoto, "Tumour necrosis factor/cachectin plays a key role in autoimmune pulmonary inflammation in lupus-prone mice," *Clinical and Experimental Immunology*, vol. 85, no. 3, pp. 392–395, 1991.

[14] T. Wada, T. Naito, R. C. Griffiths, T. M. Coffman, and V. R. Kelley, "Systemic autoimmune nephritogenic components induce CSF-1 and TNF-α in MRL kidneys," *Kidney International*, vol. 52, no. 4, pp. 934–941, 1997.

[15] T. Wada, A. Schwarting, M. S. Chesnutt, D. Wofsy, and V. R. Kelly, "Nephritogenic cytokines and disease in MRL-Faslpr kidneys are dependent on multiple T-cell subsets," *Kidney International*, vol. 59, no. 2, pp. 565–578, 2001.

[16] X. Su, T. Zhou, P. Yang, C. K. Edwards, and J. D. Mountz, "Reduction of arthritis and pneumonitis in motheaten mice by soluble tumor necrosis factor receptor," *Arthritis and Rheumatism*, vol. 41, no. 1, pp. 139–149, 1998.

[17] R. Segal, M. Dayan, H. Zinger, and E. Mozes, "Suppression of experimental systemic lupus erythematosus (SLE) in mice via TNF inhibition by an anti-TNFα monoclonal antibody and by pentoxifylline," *Lupus*, vol. 10, no. 1, pp. 23–31, 2001.

[18] A. Rahman and D. A. Isenberg, "Systemic lupus erythematosus," *The New England Journal of Medicine*, vol. 358, no. 9, pp. 929–939, 2008.

[19] H. Yokoyama, M Takaeda, T. Wada et al., "Glomerular ICAM-1 expression related to circulating TNF-α in human glomerulonephritis," *Nephron*, vol. 76, no. 4, pp. 425–433, 1997.

[20] M. Aringer and J. S. Smolen, "The role of tumor necrosis factor-alpha in systemic lupus erythematosus," *Arthritis Research and Therapy*, vol. 10, no. 1, article 202, 2008.

[21] R. Matsumura, K. Umemiya, T. Sugiyama et al., "Anti-tumor necrosis factor therapy in patients with difficult-to-treat lupus nephritis: a prospective series of nine patients," *Clinical and Experimental Rheumatology*, vol. 27, no. 3, pp. 416–421, 2009.

[22] M. De Bandt, J. Sibilia, X. Le Loët et al., "Systemic lupus erythematosus induced by anti-tumour necrosis factor alpha therapy: a French national survey," *Arthritis Research & Therapy.*, vol. 7, no. 3, pp. R545–551, 2005.

[23] M. B. Stokes, K. Foster, G. S. Markowitz et al., "Development of glomerulonephritis during anti-TNF-alpha; therapy for rheumatoid arthritis," *Nephrology Dialysis Transplantation*, vol. 20, no. 7, pp. 1400–1406, 2005.

[24] B. Liang, D. B. Gardner, D. E. Griswold, P. J. Bugelski, and X. Y. R. Song, "Anti-interleukin-6 monoclonal antibody inhibits autoimmune responses in a murine model of systemic lupus erythematosus," *Immunology*, vol. 119, no. 3, pp. 296–305, 2006.

[25] B. A. Kiberd, "Interleukin-6 receptor blockage ameliorates murine lupus nephritis," *Journal of the American Society of Nephrology*, vol. 4, no. 1, pp. 58–61, 1993.

[26] B. Ryffel, B. D. Car, H. Gunn, D. Roman, P. Hiestand, and M. J. Mihatsch, "Interleukin-6 exacerbates glomerulonephritis in (NZB × NZW)F1 mice," *American Journal of Pathology*, vol. 144, no. 5, pp. 927–937, 1994.

[27] H. B. Richards, M. Satoh, M. Shaw, C. Libert, V. Poli, and W. H. Reeves, "Interleukin 6 dependence of anti-DNA antibody production: evidence for two pathways of autoantibody formation in pristane-induced lupus," *Journal of Experimental Medicine*, vol. 188, no. 5, pp. 985–990, 1998.

[28] S. Wan, C. Xia, and L. Morel, "IL-6 produced by dendritic cells from lupus-prone mice inhibits CD4+ CD25+ T cell regulatory functions," *Journal of Immunology*, vol. 178, no. 1, pp. 271–279, 2007.

[29] Y. Nishitani, A. Kubo, M. Iwano et al., "Imbalance between interleukin-6 and adrenomedullin mRNA levels in peripheral blood mononuclear cells of patients with lupus nephritis,"

Clinical and Experimental Immunology, vol. 124, no. 2, pp. 330–336, 2001.

[30] G. G. Illei, Y. Shirota, C. H. Yarboro et al., "Tocilizumab in systemic lupus erythematosus: data on safety, preliminary efficacy, and impact on circulating plasma cells from an open-label phase I dosage-escalation study," *Arthritis and Rheumatism*, vol. 62, no. 2, pp. 542–552, 2010.

[31] J. F. McHale, O. A. Harari, D. Marshall, and D. O. Haskard, "TNF-α and IL-1 sequentially induce endothelial ICAM-1 and VCAM-1 expression in MRL/lpr lupus-prone mice," *Journal of Immunology*, vol. 163, no. 7, pp. 3993–4000, 1999.

[32] T. V. Lebedeva and A. K. Singh, "Increased responsiveness of B cells in the murine MRL/Lpr model of lupus nephritis to interleukin-1β," *Journal of the American Society of Nephrology*, vol. 5, no. 7, pp. 1530–1534, 1995.

[33] T. Takemura, K. Yoshioka, K. Murakami et al., "Cellular localization of inflammatory cytokines in human glomerulonephritis," *Virchows Archiv*, vol. 424, no. 5, pp. 459–464, 1994.

[34] B. A. Kiberd and A. W. Stadnyk, "Established murine lupus nephritis does not respond to exogenous interleukin-1 receptor antagonist; a role for the endogenous molecule?" *Immunopharmacology*, vol. 30, no. 2, pp. 131–137, 1995.

[35] Y. Iwata, T. Wada, K. Furuichi et al., "p38 mitogen-activated protein kinase contributes to autoimmune renal injury in MRL-Faslpr mice," *Journal of the American Society of Nephrology*, vol. 14, no. 1, pp. 57–67, 2003.

[36] Y. Iwata, K. Furuichi, N. Sakai et al., "Dendritic cells contribute to autoimmune kidney injury in MRL-Fas lpr mice," *Journal of Rheumatology*, vol. 36, no. 2, pp. 306–314, 2009.

[37] V. D. D'Agati, "Renal Disease in Systemic Lupus Erythematosus, Mixed Connective Tissue Disease, Sjögren's Syndrome, and Rheumatoid Arthritis," in *Heptinstall's Pathology of the Kidney*, 2006.

[38] Z. Zhang, V. C. Kyttaris, and G. C. Tsokos, "The role of IL-23/IL-17 axis in lupus nephritis," *Journal of Immunology*, vol. 183, no. 5, pp. 3160–3169, 2009.

[39] O. M. Steinmetz, J. E. Turner, H. J. Paust et al., "CXCR3 mediates renal Th1 and Th17 immune response in murine lupus nephritis," *Journal of Immunology*, vol. 183, no. 7, pp. 4693–4704, 2009.

[40] V. C. Kyttaris, Z. Zhang, V. K. Kuchroo, M. Oukka, and G. C. Tsokos, "Cutting edge: IL-23 receptor deficiency prevents the development of lupus nephritis in C57BL/6-lpr/lpr mice," *Journal of Immunology*, vol. 184, no. 9, pp. 4605–4609, 2010.

[41] Y. Wang, S. Ito, Y. Chino et al., "Laser microdissection-based analysis of cytokine balance in the kidneys of patients with lupus nephritis," *Clinical and Experimental Immunology*, vol. 159, no. 1, pp. 1–10, 2010.

[42] J. C. Crispín and G. C. Tsokos, "Human TCR-$\alpha\beta^+$ CD4$^-$ CD8$^-$ T cells can derive from CD8$^+$ T cells and display an inflammatory effector phenotype," *Journal of Immunology*, vol. 183, no. 7, pp. 4675–4681, 2009.

[43] E. Kikawada, D. M. Lenda, and V. R. Kelley, "IL-12 deficiency in MRL-Faslpr mice delays nephritis and intrarenal IFN-γ expression, and diminishes systemic pathology," *Journal of Immunology*, vol. 170, no. 7, pp. 3915–3925, 2003.

[44] C. E. Carvalho-Pinto, M. I. García, M. Mellado et al., "Autocrine production of IFN-γ by macrophages controls their recruitment to kidney and the development of glomerulonephritis in MRL/lpr mice," *Journal of Immunology*, vol. 169, no. 2, pp. 1058–1067, 2002.

[45] A. Schwarting, T. Wada, K. Kinoshita, G. Tesch, and V. R. Kelley, "IFN-γ receptor signaling is essential for the initiation, acceleration, and destruction of autoimmune kidney disease in MRL-Fas(lpr) mice," *Journal of Immunology*, vol. 161, no. 1, pp. 494–503, 1998.

[46] M. Ramanujam, P. Kahn, W. Huang et al., "Interferon-α treatment of Female (NZW $\times$ BXSB)F1 mice mimics some but not all features associated with the Yaa mutation," *Arthritis and Rheumatism*, vol. 60, no. 4, pp. 1096–1101, 2009.

[47] Z. Liu, R. Bethunaickan, W. Huang et al., "Interferon-α accelerates murine systemic lupus erythematosus in a T cell-dependent manner," *Arthritis and Rheumatism*, vol. 63, no. 1, pp. 219–229, 2011.

[48] H. Agrawal, N. Jacob, E. Carreras et al., "Deficiency of type I IFN receptor in lupus-prone New Zealand mixed 2328 mice decreases dendritic cell numbers and activation and protects from disease," *Journal of Immunology*, vol. 183, no. 9, pp. 6021–6029, 2009.

[49] J. D. Hron and S. L. Peng, "Type I IFN protects against murine lupus," *Journal of Immunology*, vol. 173, no. 3, pp. 2134–2142, 2004.

[50] A. Schwarting, K. Paul, S. Tschirner et al., "Interferon-β: a therapeutic for autoimmune lupus in MRL-Fas lpr mice," *Journal of the American Society of Nephrology*, vol. 16, no. 11, pp. 3264–3272, 2005.

[51] A. N. Theofilopoulos, R. Baccala, B. Beutler, and D. H. Kono, "Type I interferons (α/β) in immunity and autoimmunity," *Annual Review of Immunology*, vol. 23, pp. 307–336, 2005.

[52] S. C. Satchell, O. Buchatska, S. B. Khan et al., "Interferon-β reduces proteinuria in experimental glomerulonephritis," *Journal of the American Society of Nephrology*, vol. 18, no. 11, pp. 2875–2884, 2007.

[53] J. Faust, J. Menke, J. Kriegsmann et al., "Correlation of renal tubular epithelial cell-derived interleukin-18 up-regulation with disease activity in MRL-Faslpr mice with autoimmune lupus nephritis," *Arthritis and Rheumatism*, vol. 46, no. 11, pp. 3083–3095, 2002.

[54] H. A. Shui, S. M. Ka, W. M. Wu et al., "LPS-evoked IL-18 expression in mesangial cells plays a role in accelerating lupus nephritis," *Rheumatology*, vol. 46, no. 8, pp. 1277–1284, 2007.

[55] P. Bossù, D. Neumann, E. Del Giudice et al., "IL-18 cDNA vaccination protects mice from spontaneous lupus-like autoimmune disease," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 100, no. 2, pp. 14181–14186, 2003.

[56] G. V. Halade, M. M. Rahman, A. Bhattacharya, J. L. Barnes, B. Chandrasekar, and G. Fernandes, "Docosahexaenoic acid-enriched fish oil attenuates kidney disease and prolongs median and maximal life span of autoimmune lupus-prone mice," *Journal of Immunology*, vol. 184, no. 9, pp. 5280–5286, 2010.

[57] K. Masutani, M. Akahoshi, K. Tsuruya et al., "Predominance of Th1 immune response in diffuse proliferative lupus nephritis," *Arthritis and Rheumatism*, vol. 44, no. 9, pp. 2097–2106, 2001.

[58] H. Yokoyama, T. Takabatake, M. Takaeda et al., "Up-regulated MHC-class II expression and γ-IFN and soluble IL-2R in lupus nephritis," *Kidney International*, vol. 42, no. 3, pp. 755–763, 1992.

[59] W. S. Uhm, K. Na, G. W. Song et al., "Cytokine balance in kidney tissue from lupus nephritis patients," *Rheumatology*, vol. 42, no. 8, pp. 935–938, 2003.

[60] R. W. Y. Chan, F. M. M. Lai, E. K. M. Li et al., "Intrarenal cytokine gene expression in lupus nephritis," *Annals of the Rheumatic Diseases*, vol. 66, no. 7, pp. 886–892, 2007.

[61] M. Tucci, C. Quatraro, L. Lombardi, C. Pellegrino, F. Dammacco, and F. Silvestris, "Glomerular accumulation of plasmacytoid dendritic cells in active lupus nephritis: role of interleukin-18," *Arthritis and Rheumatism*, vol. 58, no. 1, pp. 251–262, 2008.

[62] N. Charles, D. Hardwick, E. Daugas, G. G. Illei, and J. Rivera, "Basophils and the T helper 2 environment can promote the development of lupus nephritis," *Nature Medicine*, vol. 16, no. 6, pp. 701–707, 2010.

[63] S. V. Kaveri, L. Mouthon, and J. Bayry, "Basophils and nephritis in lupus," *The New England Journal of Medicine*, vol. 363, no. 11, pp. 1080–1082, 2010.

[64] S. Shimizu, N. Sugiyama, K. Masutani et al., "Membranous glomerulonephritis development with Th2-type immune deviations in MRL/lpr mice deficient for IL-27 receptor (WSX-1)," *Journal of Immunology*, vol. 175, no. 11, pp. 7185–7192, 2005.

[65] M. Akahoshi, H. Nakashima, Y. Tanaka et al., "Th1/Th2 balance of peripheral T helper cells in systemic lupus erythematosus," *Arthritis and Rheumatism*, vol. 42, no. 8, pp. 1644–1648, 1999.

[66] D. J. Huss, R. C. Winger, G. M. Cox et al., "TGF-β signaling via smad4 drives IL-10 production in effector Th1 cells and reduces T cell trafficking in EAE," *The European Journal of Immunology*, vol. 41, no. 10, pp. 2987–2996, 2011.

[67] A. O'Garra and P. Vieira, "TH1 cells control themselves by producing interleukin-10," *Nature Reviews Immunology*, vol. 7, no. 6, pp. 425–428, 2007.

[68] D. Jankovic, D. G. Kugler, and A. Sher, "IL-10 production by CD4$^+$ effector T cells: a mechanism for self-regulation," *Mucosal Immunology*, vol. 3, no. 3, pp. 239–246, 2010.

[69] R. L. Brunsing and E. R. Prossnitz, "Induction of interleukin-10 in the T helper type 17 effector population by the G protein coupled estrogen receptor (GPER) agonist G-1," *Immunology*, vol. 134, no. 1, pp. 93–106, 2011.

[70] H. Ishida, T. Muchamuel, S. Sakaguchi, S. Andrade, S. Menon, and M. Howard, "Continuous administration of anti-interleukin 10 antibodies delays onset of autoimmunity in NZB/W F1 mice," *Journal of Experimental Medicine*, vol. 179, no. 1, pp. 305–310, 1994.

[71] C. T. Ravirajan, Y. Wang, L. A. Matis et al., "Effect of neutralizing antibodies to IL-10 and C5 on the renal damage caused by a pathogenic human anti-dsDNA antibody," *Rheumatology*, vol. 43, no. 4, pp. 442–447, 2004.

[72] K. R. M. Blenman, B. Duan, Z. Xu et al., "IL-10 regulation of lupus in the NZM2410 murine model," *Laboratory Investigation*, vol. 86, no. 11, pp. 1136–1148, 2006.

[73] L. Llorente, Y. Richaud-Patin, C. García-Padilla et al., "Clinical and biologic effects of anti-interleukin-10 monoclonal antibody administration in systemic Lupus erythematosus," *Arthritis and Rheumatism*, vol. 43, no. 8, pp. 1790–1800, 2000.