

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 (M ϕ) 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 secrete 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 (M ϕ), B lymphocytes, and natural killer cells [37]. Infiltrate M ϕ 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 secrete 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

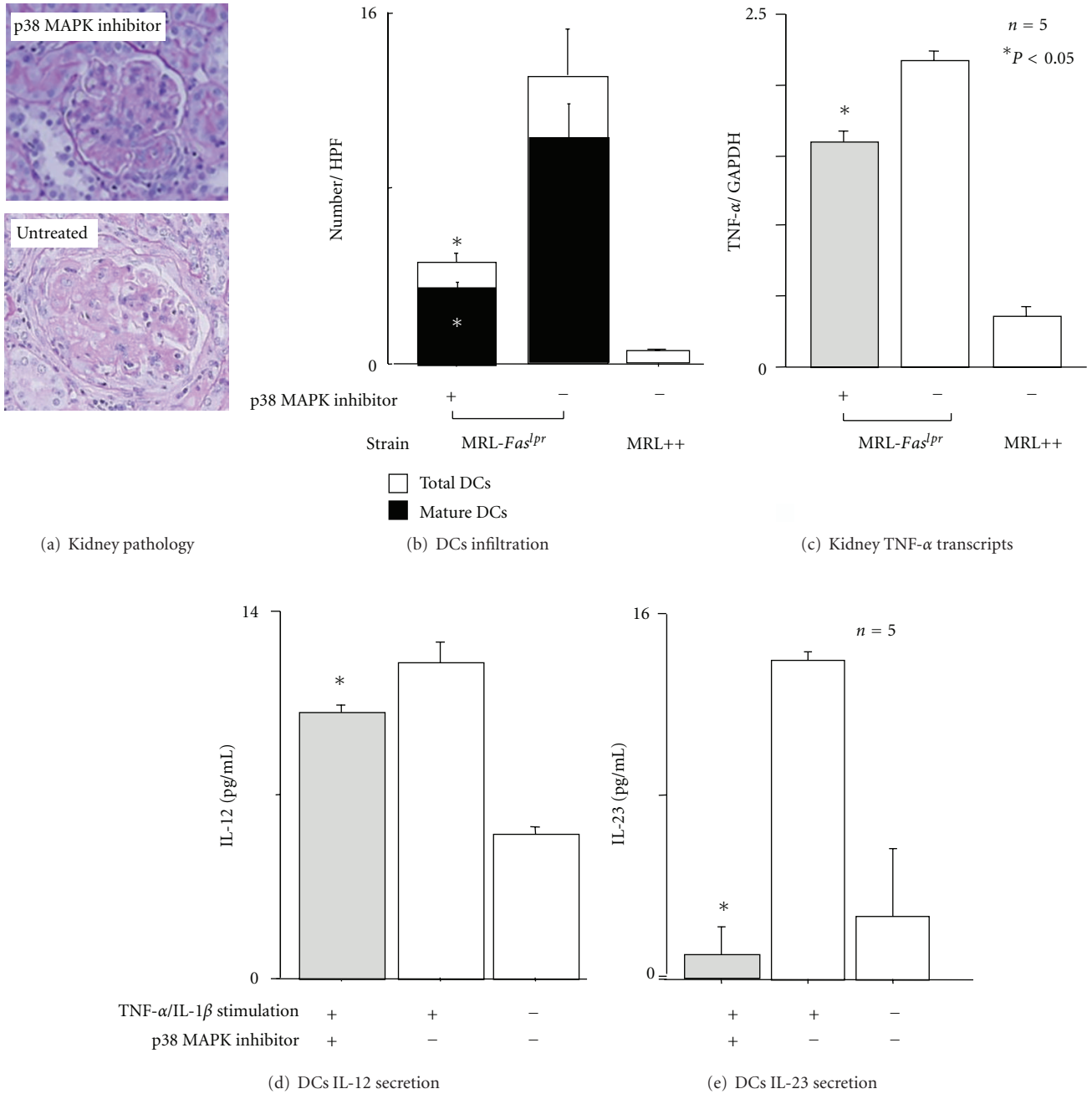


FIGURE 1: p38 MAPK plays an essential role in the lupus nephritis in MRL-*Fas*^{lpr} mice. (a) p38 MAPK inhibitor ameliorates kidney injury in MRL-*Fas*^{lpr} mice. (b) The number of CD11c⁺ cells and CD11c⁺ CCR7⁺ mature phenotype was decreased by the inhibition of p38 MAPK in the kidney. (c) The transcripts 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].

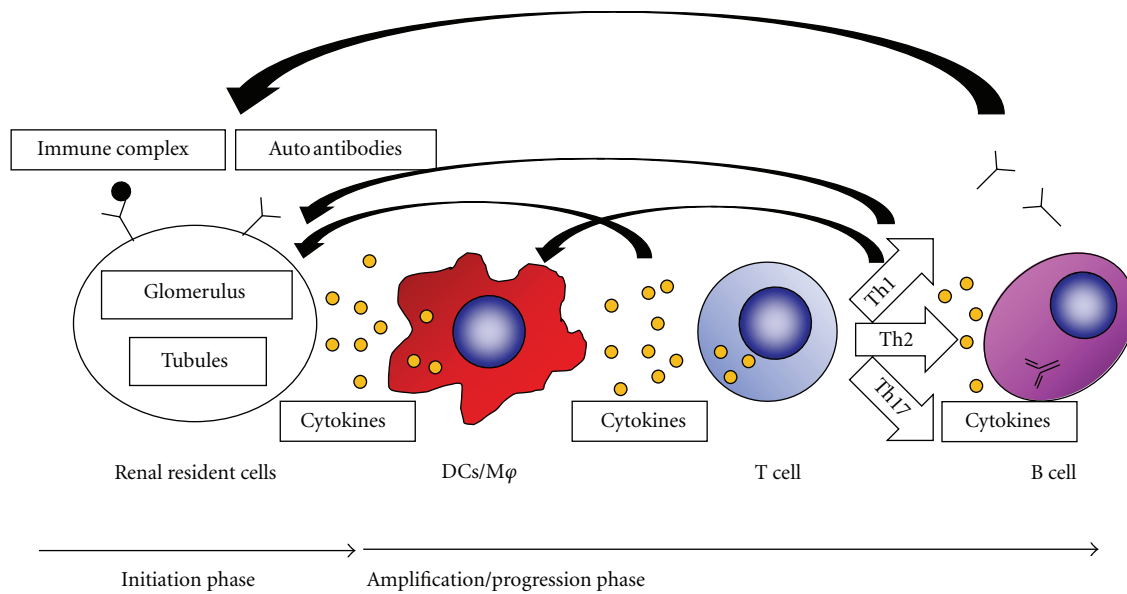


FIGURE 2: Cytokines contribute to the pathogenesis of lupus nephritis from the initiation phase to the amplification/progression phase. Immune deposits and/or autoantibodies induce the secretion of cytokine in the renal resident cells, which promote the infiltration and activation of leukocytes in the 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 secrete 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.

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