Polarization of Macrophage and Lupus Nephritis

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Abstract

Lupus nephritis (LN) is one of the common and severe complications in systemic lupus erythematosus (SLE), and is a leading cause of morbidity and mortality for SLE patients. It is well known that LN is characterized by the inflammation mediated by immune response in the kidney tissues, during which macrophage (Mø) plays a vital role. According to the varied microenvironments in different stages of lupus nephritis, macrophages are divided into two categories, namely classically activated macrophages (M1) and alternatively activated macrophages (M2). Macrophages can undergo phenotypical/functional switch and play different functions depending on multiple signal pathways, including STAT transcription factors, epigenetic aspects, NF-κB pathways, IRF transcription factors and some interleukins, chemokines and its receptors. Due to the heterogeneity and plasticity, the polarization of macrophages may exert an influence on the outcome of lupus nephritis. Thus, targeting the polarization of macrophages properly may become a new therapeutic treatment for lupus nephritis. This review focuses on how polarization of macrophages regulates the pathogenesis of LN.

Key words:
Lupus nephritis; Macrophages; Polarization; Inflammation

Introduction

Systemic lupus nephritis (SLE) is autoimmune disease that affects mainly women of reproductive age and which can affect multiple different organ systems. Kidney involvement, known as Lupus nephritis (LN), is an end organ manifestation seen in upwards of 60% of SLE patients. LN is a serious complication of SLE, and is a leading cause of morbidity and mortality for SLE patients [1]. Many studies implicate macrophage (Mø) in the pathogenesis of LN, although the exact nature of their contribution has not yet been elucidated. LN is chronic inflammatory disease with macrophages playing an important role [2]. Macrophages, as a kind of crucial immunocytes, mediate the initiation and progression of renal injury in various aspects. Macrophages induce the production of autoantibodies and also produce pro-inflammatory cytokines, leading to injure the glomeruli and proteinuria onset [3]. Recently, much attention has been drawn to the relation between polarization of macrophages and LN. In the review, we mainly focus on how polarization of macrophages regulates the pathogenesis of LN.

Macrophages and LN

Heterogeneity and plasticity are hallmarks of macrophages, which drive from mononuclear phagocytes in blood system and differentiate into mature ones in peripheral tissue. Macrophages are important regulators of innate and adaptive immunity, as well as systemic metabolism, hematopoiesis, vasculogenesis and reproduction [4]. Macrophage differentiation refers to the process that cells migrate to the vessel wall from peripheral blood and then into the organizations, in which adhesion molecules, chemokinases and cytokines will affect the migration of monocytes and late maturation [5], and polarization of macrophages refers to the phenotypical/functional switch due to macrophages completely differentiated in a particular tissue responding to the external stimuli. According to the varied microenvironments in different stages of lupus nephritis, macrophages are divided into two categories, namely classically activated macrophages (M1) and alternatively activated macrophages (M2) [6]. The dynamic balance between M1 and M2 in renal tissue is regulated by the microenvironments in different stages of LN, which determine the progress and prognosis of LN. M1 macrophages initially enter the kidneys following acute renal injury and secrete pro-inflammatory cytokines [7-9]. In contrast, during the repair phase, these cells may switch their phenotype to a "M2" phenotype contributing to repair of epithelial cells and vascular endothelial cells and thus turn into renal fibrosis, correlating with poor outcome of LN [10,11].

Classical Activated M1 Macrophages in LN

The classical activation of macrophages is driven by the stimulation, such as IFN-γ, lipopolysaccharide (LPS), TNF-α and granulocyte macrophage colony- stimulating factor (GM-CSF), with an IL-12high, IL-23high, IL-10low phenotype [12]. In general, M1macrophages contribute to the inflammatory response by the secretion of pro-inflammatory cytokines such as interleukin-6 (IL-6), IL-1β, TNF, as well as IL-12 and IL-23 [13]. M1 macrophages also produce inducible nitric oxide synthase (iNOS) as an important factor in response of the attack by bacterial, fungal, and viral infections [14,15]. Some types of chemokines receptor ligands, such as CXCL9 and CXCL10 expressed by M1 macrophages mediate polarization Th1 responses [16,17]. It is suggested that phagocytosis of tissue debris may switch Mø from pro-inflammatory to anti-inflammatory [18,19]. However, increased apoptosis and impaired clearance of apoptosis cells by macrophages have found in SLE patients and mice [20-24]. And recently, researchers have reported that the dominance of M1 macrophages in kidney failed to skew towards M2 macrophages in MRL-Fas<sup>−/−</sup> and SLE-123 mice after I/R and in spontaneous LN in MRL-Fas<sup>−/−</sup> mice by inducing CSF-1 in injured TEC, playing a central role in defective renal repair and non-resolving inflammation which lead the onset of LN [25].
Laquinimod is an immunomodulatory drug that has reduced the number of M1 macrophages, inhibited the secretion of TNF-α, and increased the expression of IL-10 in both kidneys and spleen of (NZB × NZW) F1 mice, indicating that Laquinimod by inducing M1 macrophages shifting to M2 macrophages thus alleviated the progression of LN [26].

**Alternatively Activated M2 Macrophages in LN**

Markedly different from M1 macrophages, studies have divided alternatively activated M2 macrophages into M2a, M2b, and M2c. Of these, M2a macrophages induced by IL-4 and IL-13 are capable of producing TGF-β and arginase, as well as their ability to produce certain ECM components that play a role in tissue-repair; M2b macrophages, which are induced by TLR ligation or immune complexes, promote the production of IL-10 and decreases production of IL-12, exerting potent anti-inflammatory properties; M2c macrophages induced by IL-10 and glucocorticoids have a anti-inflammatory role and deactivating M1 macrophages [27,28]. In an induced model of LN induced by activated lymphocytes derived DNA (ALD-DNA), intra-renal Mø polarize Mø toward an M2b phenotype [29]. In contrast, LN patients with both anti-dsDNA antibody and anti-Ro60 antibody positivity in serum showed significantly high levels of CD163 and Mer, which are M2c macrophages makers, and these correlate with SLEDAI [30]. Exposure to helminth immunomodulator, ES-62, secreted by the filarial nematode for two weeks, decreased deposition of IgG and C3 in the kidneys and increased the infiltrating of anti-inflammatory F4/80+CD11c+CD206+Ly6G++M2 macrophages and afforded protection against pathology in the MRL/Lpr mouse model of SLE [31]. In addition, the chemokine receptor 1 inhibitor amilorinated glomerular and tubular injuries, delayed proteinuria by decreasing kidney accumulation of both M1 and M2 macrophages [32]. As lupus nephritis may be triggered by a diversity of mechanisms, it is reasonable that varied macrophages phenotypes reflect differences within patient populations with distinct mechanisms.

**Regulatory Factors of Macrophage Polarization and Therapeutic Targets in LN**

Macrophages are closely related to the pathogenesis of LN, so recently, much importance has been attached to heterogeneity and plasticity of macrophage polarization and the regulatory factors. Numerous lines of evidence suggest that macrophage polarization is associated with some signalling pathways, transcription factors, non-coding RNA, epigenetic and some interleukins (eg. MCP-1, CSF-1), chemokines and its receptors (eg. CX3CL, CX3CR), etc. Research on these regulatory mechanisms has been deep into the genetic level, thus providing important implications for targeted LN therapies.

**Signal Transducers and Activators of Transcription**

The signal transducers and activators of transcription (STAT) regulates many aspects of growth, survival and differentiation in cells and activated by Janus kinase (JAK). Transcription factors STAT1 activation promotes M1, whereas STAT3/6 activation promotes M2 macrophage polarization [33]. IFN-γ can activate the phosphorylation STAT-1, leading to M1 macrophages activation; STAT-3, plays an important role in the inflammatory response by regulating inflammation-related proteins, can promote M2 macrophages activation in response to IL-10; IL-4 and IL-10 promote M2 macrophages associated proteins, arginase-1 (Arg-1), with the help of STAT-6 [34]. Studies have demonstrated that total amount of STAT-3 and the activity was higher in bone marrow-derived mononuclear cells in patients with SLE than that in healthy patients. Inhibition of STAT-3 in LN mice leads to diminish the total number of T cells, weakens their capability of migration and also reduces antibody production [35].

Inhibitors of JAK/STAT pathway are currently in clinical trials for treating rheumatoid arthritis [36]. Therefore, inhibitors of JAK/STAT pathway are a promising immunomodulatory therapeutic agent for use in human LN.

**Interferon Regulatory Factor**

Interferon regulatory factor (IRF) is a class of transcription factor family regulating host defense and composed in humans of 9 distinct proteins. Besides to autoantibodies, the high prevalence of type I interferon (IFN-I) in serum is another hallmark of SLE [37]. Researchers have identified the IFN-I master regulator gene IRF7 is only hypomethylated in lupus patients with renal involvement. IRF-7 is an upstream transcription factor that regulates several loci demethylated only with renal involvement, such as CD80, interferon-inducible protein 44 (IFI44), interferon-stimulated gene15 (ISG15), ISG20, integrin αx (ITGAX) and poly ADP-ribose polymerase 12 (PARP12) [38]. In addition, IRF5 mediates the secretion of pro-inflammatory cytokines relating to SLE by Toll-like receptor (TLR), such as IL-6, IL-12, IL-17, IL-23 and TNF-α [39]. IRF not only can regulate the expression of IFN-α, but also plays an important role in macrophage polarization. IRF3, IRF5 promote the M1 macrophages polarization, and IRF4 promote M2 polarized macrophages [40]. As a target for treatment of LN, regulation of IRF switch a new state of equilibrium for M1 and M2, thus alleviating the pathological progression of LN.

**Micro-RNA**

MicroRNAs (miRNAs) are a family of regulatory RNA molecules, similar to endogenous mediators of RNA interference that modulate apoptosis, differentiation, and activation of immune cells. It's indicated that there are six kinds of miRNAs dysfunction in peripheral blood mononuclear cells of SLE patients, including miRNA-21, miRNA-25, miRNA-125a, miRNA-146a, miRNA-148 and miRNA-186 that are known to regulate the immune and inflammation [41]. Banerjee et al [42] found that, miRNA-125a-5p regulated polarization of macrophages by Toll-like receptor. In miRNA-125a-5p deficient mice, the expression of TNF-α, IL-12 and iNOS by M1 increased, and the expression of Arg-1 by M2 decreased, in contrast to over-expression of miRNA-125a-5p. According to discovering the experiment, Krüppel-like factor 33 (KLF33) is the target gene of miRNA-125a-5p, thus regulating macrophage polarization. There are other miRNAs, such as miRNA-17, miRNA-20a, and miRNA-106a that regulate macrophage function with signal-regulated protein a as common target genes, but the mechanism remains for further study [43]. Thus, regulation of macrophage polarization by miRNAs may also provide another treatment for LN.

**Nuclear Factor-κB**

Nuclear factor-κB (NF-κB), a class of multi-effect of nuclear transcription factor, regulates the expression of many inflammatory genes in response to various physiological and environmental stimuli [44]. Studies on human LN have shown the increased activation of NF-κB pathway, as well as increased expression of TNF-α, IL-1β, IL-6 and...
intercellular adhesion molecule 1 (ICAM-1), the downstream factor of classical activated NF-κB pathway [45,46]. TNF-α is the critical pro-inflammatory cytokine produced primarily by macrophages upon injury, and then stimulates the activation of classical pathway of NF-κB, which in turn regulates the production of TNF-α [47,48]. Derived from monocytes and macrophages, IL-6 in the areas of inflammation release chemokines by stimulating endothelial cells to promote leukocyte infiltration and monocyte/macrophage migration [49]. In all patients with LN in kidney tissue in line with WHO standards, it is found that a kind of high mobility group protein (HMGB1) distributes along the glomerular epithelial and mesangial [50], such protein stabilizes nucleosome structure, but plays a pro-inflammatory role when released from the nucleus, mainly to promote the maturation of dendritic cells, macrophages promote pro-inflammatory cytokine release. By activating the NF-κB pathway, HMGB1 regulate the transcription of cell proliferation related proteins D1, promote mesangial cell proliferation, and thus participate in the pathogenesis of LN [51]. NF-κB activation in glomeruli is related to SLE activity index and the levels of macrophage infiltration. Numerous reports found that NF-κB p65/p50 promoted Mo to polarize to M1 [52]. Mesenchymal stem cells, with anti-inflammatory and immunosuppressive effects, are found to relieve kidney infiltration in LN mice by increasing the number of M2 macrophages and their phagocytic ability [53]. Moreover, bone marrow-derived mesenchymal stem cells promote M2 macrophages polarization by inhibiting NF-κB pathway [54]. Lately, our study suggests that treated by Demethylzeylasteral (T-96), one of triterpenoids isolated from the root xylem of Tripterygium wilfordii Hook F, MRL/lpr mice showed a significant improvement in 24-hour proteinuria and the levels of anti-ds DNA antibody in serum. Additionally, renal pathological lesions were attenuated, which mainly attributed to reduced secretion of IL-23 and TNF-α by M1 and inhibition of NF-κB pathway [55]. Thus, by selective inhibition of NF-κB pathway to further regulate macrophages polarization; it can be used as a target for the treatment of LN.

Conclusion

In summary, LN is characterized by inflammation reaction at early stage and fibrosis in later stage. LN is a severe complication of SLE that greatly diminishes patient quality of life and negatively affects survival. Highly specific treatment methods are lacking, with the primary clinical option continuing to the use of broadly immunosuppressive drugs. The macrophages in LN at different stages regulated by a variety of signalling pathways undergo a dynamic balance and closely related to the prognosis, which is closely related to the progress and prognosis of LN. Due to macrophages plasticity, not only unpolarized macrophages will switch to a certain phenotype, but also polarized M1/M2 macrophages will shift to another phenotype in response to microenvironments. Therefore, some agents or drugs by reducing the number of macrophages or altering their phenotype in the LN therapy will be possible as a new target for the treatment of LN.

References

vitro, while only SLE macrophages have impaired uptake of apoptotic cells. Ann Rheum Dis 65: 216-221.


