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Review

Macrophages in Lupus Nephritis: Insights into Its Pathogenesis and Emerging Treatments

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Abstract

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder characterized by immune system dysfunction, the production of autoantibodies, and multi-organ inflammation. Lupus nephritis (LN) is one of the most severe complications of this condition. Approximately 60% of patients with SLE develop LN, which leads to both increased morbidity and mortality. Furthermore, LN has the potential to progress to end-stage renal disease. Macrophages, key components of the innate immune system, are involved in the pathophysiology of LN through immune complex clearance, antigen presentation, regulation of inflammation, and tissue repair. Macrophage polarization into pro-inflammatory (M1) versus anti-inflammatory (M2) functional phenotypes is a component of LN disease progression. M1 macrophages are responsible for supporting pro-inflammatory immunity and promoting tissue damage, whereas M2 macrophages are necessary for tissue repair and resolution of inflammation. However, dysregulated M2 function may exacerbate the pathogenesis of LN, indicating the complex role of macrophages in LN. Novel therapeutic approaches associated with the mechanisms of macrophage polarization and/or macrophage signaling pathways have emerged as therapeutic targets to modify the progression of LN. Furthermore, proinflammatory cytokines enhance renal inflammation and autoimmunity; alternatively, anti-inflammatory cytokines play a dual role in LN, contributing positively and negatively to the disease process. The purpose of this review is to investigate the role of macrophages in the pathogenesis of LN and highlight macrophage-targeted therapies or biomarkers as diagnostic tools and new therapeutic avenues to improve long-term outcomes for patients.

Keywords: systemic lupus erythematosus; lupus nephritis; macrophage; biomarkers; therapy

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic and systemic autoimmune disease where the immune system attacks its own tissues and organs, leading to the production of autoantibodies and immune complexes that cause widespread inflammation and damage to multiple organ systems [1–5]. The term "lupus", the Latin word for "wolf", refers to the historical identification of a facial rash resembling a wolf bite, one of the clinical manifestations of this disease [6–8]. However, SLE is not limited to the skin but can affect almost every organ system in the body including the musculoskeletal, renal, cardiac, pulmonary, and central nervous systems [4,9]. The disease is highly heterogeneous and is characterized by a range of symptoms, including fatigue, fever, arthralgia, skin rashes, and renal involvement, contributing to SLE being one of the most complicated autoimmune disorders to diagnose and treat [4,9]. SLE is more prevalent in women of childbearing age, and is also more common in non-Caucasians including those of African American, Asian, and Hispanic descent [10]. The etiology of SLE remains unclear but is thought to be a combination of genetic, environmental (ultraviolet light, infections, and certain medications), and hormonal etiologies [2,4].

Lupus nephritis (LN) is one of the most severe complications of SLE, affecting up to 60% of patients with SLE during the disease course, leading to increased morbidity and mortality [11,12]. In addition, approximately 7.9% of patients diagnosed with LN progress to end-stage renal disease within 16.5 years of LN onset [4,5,11,12]. The poor prognosis of LN highlights the crucial need for more diagnostic strategies and effective United States Food and Drug Administration-approved therapies to slow kidney damage and reduce morbidity and mortality. The cellular processes involved in the development of LN diagnosis are multifactorial, involving immune mechanisms including immune complex deposition, impaired clearance of apoptotic cells, and loss of tolerance to autoantigens, while abnormal immune activation is also a contributing factor [2,4,13]. Macrophages, which are integral components of the innate immune system, play a multifaceted role in LN including clearing immune complexes, presenting antigens, regulating inflammation, and participating in tissue repair. Their complex role makes them central to imaging immune cell processes in LN [14]. The polarization of macrophages also plays a substantial role in determining disease progression, with pro-inflammatory (M1) macrophages associated with driving inflammation, tissue damage, and injury, while

anti-inflammatory (M2) macrophages promote tissue repair and restoration of inflammation back to basal levels. The prominent role of macrophages in LN suggests that therapies targeting macrophage polarization and signaling could be promising therapeutic strategies [14–16]. The increasing understanding of the cellular and molecular processes of macrophage polarization and activation will lead to a surge in the applicability of therapeutic approaches targeting macrophage signaling. Furthermore, biomarker identification may also play a role in clinical translation, aiding in early diagnosis, disease monitoring, and treatment paradigms in LN. Understanding the pathogenesis of LN, particularly the role of macrophages, is crucial for advancing therapeutics aimed at modulating organ damage and subsequent inflammation, and promoting healthy immune responses. This review provides a thorough overview of the role of macrophages in LN, discussing emerging therapeutic strategies that may improve patient outcomes.

2. Macrophage Polarization in LN

The polarization of macrophages plays an important yet paradoxical role in the pathogenesis of LN, reflecting the dynamic balance between pro-inflammatory and anti-inflammatory macrophage phenotypes. In the context of LN, macrophages exhibit remarkable plasticity in their ability to switch between M1-like (classically activated) and M2-like (alternatively activated) states in response to environmental cues (Fig. 1). This macrophage plasticity is often disrupted in autoimmune conditions and contributes to a worsening LN phenotype. Thus, maintaining a balance between these phenotypes is essential for overall immune system homeostasis, and its disruption can result in chronic inflammation and tissue damage.

2.1 M1-Like Macrophages

M1 macrophages are generally prominent in acute inflammation, and are classically activated by T helper 1 (Th1) cytokines such as interferon gamma (IFN-γ) and microbial agents like lipopolysaccharide [17]. These macrophages produce pro-inflammatory cytokines (e.g., tumor necrosis factor alpha [TNF-α], interleukin 6 [IL-6], IL-12) and reactive oxygen species (ROS), which are key to clearing pathogens but can also lead to tissue damage [18]. In LN, M1-like macrophages play a role in glomerular injury by producing pro-atherogenic mediators, including neopterin and nitrogen species that exacerbate oxidative stress and immune complex deposition [19]. In clinical studies, peripheral blood monocytes expressing M1 markers (e.g., $CD163^{-}CD14^{+}$) are positively correlated with disease severity in children with SLE, indicating their potential as a biomarker of systemic inflammation [20]. Furthermore, M1 polarization is implicated in renal damage, particularly by impairing efferocytosis (apoptotic cell clearance) and causing the accumulation of nuclear antigens, which can trigger the formation of autoantibodies [21]. Moreover, the aberrant activation of M1 macrophages in LN contributes to renal damage by promoting the deposition of immune complexes in the glomeruli, leading to inflammation and further renal damage [21].

2.2 M2-Like Macrophages

M2 macrophages are known for their anti-inflammatory, tissue-repair, and angiogenesis-promoting roles. They are induced by agents such as Th2 cytokines (IL-4, IL-13), IL-10, and glucocorticoids, and also secrete factors like IL-10 and transforming growth factor beta (TGF-β), which contribute to their anti-inflammatory and immune-regulatory functions. M2 macrophages are categorized into subtypes (M2a, M2b, M2c, and M2d) based on their activation stimuli and respective functions. IL-4 and IL-13 stimulation induce the activation of M2a macrophages, which are characterized by the high expression of cluster of differentiation 206 (CD206) and play a role in tissue repair and fibrosis by secreting TGF-α and promoting fibroblast attachment to fibronectin [22]. M2b macrophages, also known as regulatory macrophages, are activated by immune complexes and toll-like receptor (TLR) or IL-1R agonists and exert most of their anti-inflammatory effects by secreting IL-10 [23]. M2c macrophages are stimulated by glucocorticoids, TGF-β, or IL-10, and demonstrate significant anti-inflammatory properties while also mediating tissue repair, primarily by secreting IL-10, although secretion of TGF-β from M2c macrophages can promote fibrosis [24–26]. M2c macrophages can effectively clear apoptotic cells through expression of Mer tyrosine kinase [27]. The more recently described M2d macrophages are activated by TLR and adenosine A_2A receptor agonists and can mediate angiogenesis and cancer metastasis by upregulating vascular endothelial growth factor (VEGF) [28–30].

Importantly, while these classifications exist, the accurate *in vivo* translation of M2 subtypes is difficult. This suggests that M2 classification is reflective of the stimuli for macrophage activation instead of the functions that occur after activation. Additionally, the functional attributes of macrophages are not determined by their origin, but are instead modified by the local microenvironment, indicating that macrophage polarization is dynamic and context-dependent. This nuance underscores the need for targeted therapies that modulate macrophage function in disease, especially LN, where modulation of macrophage function is essential for disease improvement. In the context of their involvement in LN pathology, M2-polarized macrophages contribute to the resolution of inflammation. However, sometimes defective M2 function, as seen with decreased heme oxygenase-1 expression, leads to LN progression due to the insufficient clearance of immune complexes, and can perpetuate the production of pro-inflammatory signaling [31]. In some cases, certain M2 subtypes, including M2b, can worsen disease by secreting both pro-inflammatory and

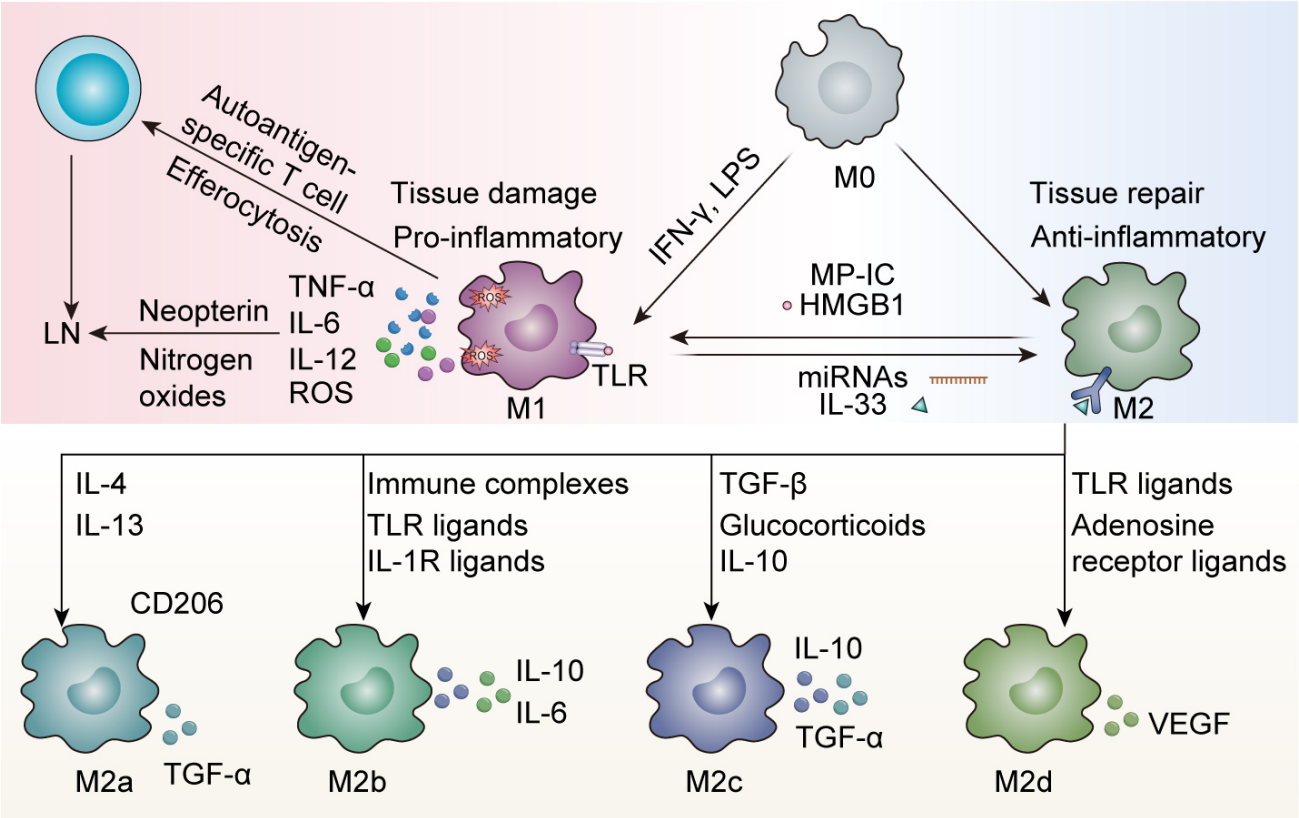

Fig. 1. Macrophage plasticity in Lupus nephritis (LN). Macrophage polarization represents a dynamic equilibrium between pro-inflammatory (M1) and anti-inflammatory (M2) phenotypes that critically influences LN pathogenesis. M1 macrophages, activated by T helper 1 (Th1) cytokines (e.g., interferon gamma (IFN-γ)) and microbial factors (e.g., lipopolysaccharide), secrete pro-inflammatory mediators including tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), IL-12, and reactive oxygen species (ROS), contribute to glomerular injury through oxidative stress (mediated by neopterin/nitric oxide), impaired efferocytosis, and nuclear antigen accumulation that promotes autoantibody production. The anti-inflammatory M2 phenotype comprises four functionally distinct subsets: M2a (induced by IL-4/IL-13 and marked by CD206 expression) mediates tissue repair via transforming growth factor (TGF)-α while potentially driving fibrosis; M2b (activated by immune complexes/toll-like receptor (TLR) agonists) secretes IL-10 but may paradoxically aggravate disease; M2c (dependent on glucocorticoids/TGF-β/IL-10) promotes efferocytosis (via Mer tyrosine kinase) and anti-inflammatory responses despite TGF-β's fibrotic potential; and M2d (triggered by TLR/adenosine A_2A signaling) supports angiogenesis through vascular endothelial growth factor (VEGF) and facilitates cancer metastasis. This polarization balance is dynamically regulated by microenvironmental cues—high-mobility group box 1 (HMGB1) (via TLR/receptor for advanced glycation end products) and microparticle-bound immune complexes (MP-ICs) drive pro-inflammatory M1 polarization and IL-33 (via ST2) and specific miRNAs (e.g., miR-150 targeting suppressor of cytokine signaling 1 (SOCS1)) promote M2 resolution, albeit with risk of fibrotic responses. The plasticity between M1 and M2 phenotypes underscores both the pathological complexity of LN and opportunities for therapeutic intervention; precise modulation remains essential to avoid exacerbating inflammation or fibrosis. These mechanistic insights highlight macrophage polarization as a pivotal determinant of disease progression and treatment outcomes in LN. All figures were created by us with Adobe Illustrator 2024 (v28. x, Adobe Inc., San Jose, CA, USA).

anti-inflammatory cytokines [21,32,33]. One particularly interesting finding is that the use of adoptively transferred M2 macrophages reduce disease severity in murine models of LN, indicating their potential therapeutic benefit if properly regulated [34]. The ability of M2 macrophages to influence the immune response and promote tissue repair makes them an attractive therapeutic target in LN.

2.3 Regulation of Polarization Dynamics

The dynamics of macrophage polarization in LN are deeply influenced by a variety of microenvironmental factors that disturb the balance between pro-inflammatory M1 and anti-inflammatory M2 phenotypes. High-mobility group box 1 (HMGB1), which is a damage-associated molecular pattern, induces M1 polarization and worsens LN severity by enhancing antigen presentation and T-cell acti-

vation [21,34,35]. HMGB1 is released from necrotic and activated immune cells and binds to TLRs and the receptor for advanced glycation end products to further exacerbate the inflammatory response [35]. Microparticle-bound immune complexes (MP-ICs) are released from apoptotic cells and carry autoantigens that lead macrophages to polarize to an M1-like phenotype, which further promotes inflammation in SLE [36]. By contrast, IL-33 is an alarmin cytokine released by damaged epithelial cells, which promotes M2 polarization and regulatory T cell (Treg) expansion through ST2 receptor signaling [37]. These processes, in turn, mitigate the severity of LN in preclinical models by promoting tissue "reparative" actions and anti-inflammatory functions. MicroRNAs (miRNAs), including miR-150, play a crucial role in regulating macrophage polarization by targeting transcription factors such as suppressor of cytokine signaling 1 (SOCS1) [38]. Dysregulation of miRNAs has been linked to fibrosis and immune dysregulation associated with LN, as miRNAs can regulate gene expression at the post-transcriptional level and contribute to excessive inflammatory responses [39]. Collectively, these factors reveal the complex interplay of molecular signals that regulate macrophage polarization and their significant contribution to both the pathogenesis and progression of LN.

3. Macrophage-Related Cytokines and Chemokines

The immunological features of LN involve immune complex deposition in the glomeruli, leading to nephritis, progressive kidney injury, and ultimately renal failure if it is not treated. Macrophages, which are vital components of the innate immune system, are fundamentally important in the pathophysiology of LN, as they contribute to both inflammation and subsequent fibrotic processes that drive disease progression. An elaborate network of cytokines and chemokines regulate macrophage activation, polarization, and recruitment in LN—all of which coordinate the immune response and the remodeling of tissue. Defining and understanding the role of these mediators is crucial for designing strategies to selectively alter renal inflammation and fibrosis in LN.

3.1 Pro-Inflammatory Cytokines

Pro-inflammatory cytokines are key mediators of renal inflammation in LN that facilitate the recruitment and activation of immune cells and production of pathogenic autoantibodies and immune complexes, which are subsequently deposited in renal tissue (Table 1). TNF-α, primarily secreted by M1-polarized macrophages, is an important exacerbator of glomerular inflammation through its role in increasing the expression of adhesion proteins, such as intercellular adhesion molecule 1 and vascular cell adhesion molecule 1, which promote leukocyte adhesion and infiltration into the kidney [14,21,40]. TNF-α inhibition in preclinical models of murine LN reduces glomerular hypercellularity and proteinuria, indicating its potential as a therapeutic target; however, clinical studies have yielded mixed results likely due to its pleiotropic effects [41]. IL-6 is another important mediator that promotes the differentiation of B cells to plasma cells, which produce autoantibodies while also enhancing the recruitment of monocytes and neutrophils by working synergistically with C-C motif ligand 2 (CCL2, also known as monocyte chemoattractant protein-1 [MCP-1]) [14,21]. Increased serum IL-6 levels are associated with active LN, and preclinical study has shown that reducing IL-6 signaling alleviates renal inflammation, suggesting that IL-6 contributes to both autoimmunity and inflammation [42]. IL-1β, which is produced by macrophages activated through the inflammasome, drives mesangial cell (MC) activation and extracellular matrix deposition, key contributors to the development of glomerulosclerosis [43]. IL-1β inhibition in experimental models of murine LN reduces inflammatory infiltrates and improves renal function [16]. Together, these data highlight the importance of IL-1β in fibrotic progression in LN. IFN-γ, which is secreted by Th1 cells and M1 macrophages, sustains chronic inflammation in LN by increasing the expression of major histocompatibility complex (MHC) class II on renal cells, thereby facilitating the presentation of autoantigens and promoting adaptive immune responses and recruitment of immune cells [44]. IFN-γ additionally increases the production of pro-inflammatory chemokines, creating a feed-forward loop to drive tissue damage. IL-12 contributes to this inflammatory milieu by promoting naïve T-cell polarization toward a Th1 phenotype and enhancing the function of natural killer cells, which work together to induce injury to the renal parenchyma [45]. Collectively, TNF-α, IL-6, IL-1β, IFN-γ, and IL-12 create an interconnected network that contributes to renal inflammation, autoimmunity, and damage to the renal structure in LN. Thus, there is a need for targeted therapeutics to mitigate the synergistic effects of these cytokines while maintaining regulatory immune function.

3.2 Anti-Inflammatory Cytokines

Anti-inflammatory cytokines such as IL-10, TGF-β, and IL-4 have opposing functions in LN (Table 1). IL-10 is an anti-inflammatory cytokine that exhibits both protective and pathogenic effects on LN. More specifically, IL-10 is capable of inhibiting the production of inflammatory cytokines, including TNF-α and IFN-γ, which can limit tissue damage and excessive immune responses [44,46]. On the other hand, IL-10 can also promote the survival of B cells and autoantibodies, which are central to the disease pathology of LN [47]. Macrophages, particularly the M2-like phenotype, are an important source of IL-10 in the kidney, and studies have noted increased levels of IL-10 in the kidney of patients with LN [48,49]. Thus, the opposing actions of IL-10 make it challenging to target IL-10 therapeutically, since inhibiting IL-10 may en-

Table 1. Macrophage-related cytokines and chemokines in LN.

Category	Key mediators	Source	Role in LN pathogenesis	Therapeutic implications
Pro-inflammatory cytokines	TNF-α	M1 macrophages	Increases adhesion proteins (ICAM-1, VCAM-1) Promotes leukocyte infiltration	Inhibition reduces glomerular hypercellularity and proteinuria in preclinical models
	IL-6	Macrophages, B cells	Promotes B-cell differentiation Enhances monocyte and neutrophil recruitment	Targeting IL-6 signaling alleviates renal inflammation
	IL-1β	Macrophages (inflammasome)	Drives MC activation Enhances glomerulosclerosis	Inhibition reduces inflammatory infiltrates and improves renal function
	IFN-γ	Th1 cells, M1 macrophages	Increases MHC class II expression Sustains chronic inflammation	Contributes to autoantigen presentation and immune cell recruitment
	IL-12	Macrophages, DCs	Promotes Th1 polarization Enhances killing function of natural killer cells	Drives renal parenchyma injury
Anti-inflammatory cytokines	IL-10	M2 macrophages	Inhibits TNF-α and IFN-γ Promotes B cell survival and autoantibody production	Dual role: protective (limits inflammation) and pathogenic (promotes autoimmunity)
	TGF-β	M2 macrophages	Promotes tissue repair Contributes to fibrosis	High levels correlate with disease activity and fibrosis
	IL-4	Th2 cells, M2 macrophages	Promotes Th2 differentiation Activates M2 macrophages	Limits inflammation but may contribute to fibrosis
Chemokines	CCL2 (MCP-1)	Renal endothelial/epithelial cells	Recruits monocytes and macrophages via CCR2 Sustains renal inflammation	Blocking CCL2/CCR2 reduces macrophage infiltration and improves renal function
	CX3CL1 (Fractalkine)	Glomeruli, renal arteries	Recruits monocytes and macrophages via CX3CR1 Localized role in renal inflammation	Inhibition reduces macrophage numbers and inflammation
	CCL3/CCL4/CCL5	Macrophages, T cells	Recruits immune cells via CCR1/CCR5 Drives immune infiltrate into the kidney	CCR1/CCR5 signaling suppression reduces inflammation
	CXCL9/CXCL10	Renal tubular epithelial cells	Recruits CXCR3$^+$ T cells and macrophages Upregulated by IFN-γ	Blocking CXCL9/CXCL10 may limit immune cell recruitment and inflammation

ICAM-1, intercellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1; DCs, dendritic cells; MC, mesangial cell; MHC, major histocompatibility complex; CCL2, C-C motif ligand 2; MCP-1, monocyte chemoattractant protein-1; CCR2, C-C chemokine receptor type 2; CX3CL1, C-X3-C motif ligand 1; LN, Lupus nephritis; TNF-α, tumor necrosis factor alpha; IFN-γ, interferon gamma; IL-6, interleukin 6; TGF-β, transforming growth factor beta; CX3CR1, C-X3-C motif chemokine receptor 1.

hance inflammation, while IL-10 overexpression may promote autoimmunity. Additional studies are required to better define the context-dependent, temporally regulated roles of IL-10 during the initiation, progression, and resolution of LN [48]. In addition to IL-10, macrophages also produce other anti-inflammatory mediators, such as TGF-β, which play important roles in regulating inflammation and promoting reparative processes. For LN, the balance between pro-inflammatory and anti-inflammatory macrophages is critical to determining disease progression. For example, in mouse models of lupus-prone mice, regulatory macrophages (M2 phenotype) play a crucial role in resolving inflammation by secreting IL-10 and TGF-β; however, excessive levels of these cytokines can contribute to pathological outcomes like fibrosis and chronic kidney injury [46]. In patients with LN, those with elevated IL-10 and TGF-β levels in their renal tissues tend to have more active disease [50]. However, future studies are needed to elucidate the specific contributions of IL-10 and TGF-β to disease progression and resolution. IL-4 is another cytokine that limits inflammation while contributing to anti-inflammatory and fibrotic processes in LN, underscoring its complex role. IL-4 and IL-13 promote Th2 cell differentiation and activate M2-like macrophages, which secrete anti-inflammatory cytokines and suppress the activation of pro-inflammatory M1 macrophages [51]. IL-4 also promotes collagen production and other extracellular matrix proteins, which contribute to kidney fibrosis [46]. Although inhibiting IL-4 may limit (or reduce) fibrosis in LN, inhibition can also impact anti-inflammatory processes crucial for tissue repair and resolution of inflammation. Thus, the last three examples—IL-10, TGF-β, and IL-4—illustrate the complex roles of anti-inflammatory cytokines in LN, as they help modify the immune response during LN initiation and repair, but can also contribute to fibrosis and chronic kidney injury. These processes must be leveraged, defining either the plausible benefits for targeted therapies in LN or plausible detriments for therapies targeting pro-inflammatory functions.

3.3 Chemokines

Chemokines, small signaling proteins that are critical to activating immune cells, contribute to the pathogenesis of LN by recruiting monocytes, macrophages, and any immune cell type into the kidney that can promote inflammation and tissue injury (Table 1). Among the chemokines studied, CCL2 and its receptor, C-C chemokine receptor type 2 (CCR2), have garnered the most research attention. CCL2 is produced by renal endothelial and epithelial cells in response to inflammatory stimulation, and acts as a chemoattractant for monocytes and macrophages, which bind to CCR2 and are subsequently recruited to the kidney [52]. Immune cell recruitment is important for both initiating renal inflammation and sustaining renal inflammation. In the lupus-prone mouse models, MRL/MpJ strain with the lymphoproliferation mutation in the Fas gene (MRL/lpr) and *New Zealand Black* $\times$ *New Zealand White F1 hybrid* (NZB/W F1), increased levels of CCL2 and CCR2 were found in the kidney, specifically in the tubulointerstitial compartment, which corresponded to the areas of CCR2 macrophage infiltration and kidney damage [53,54]. Furthermore, blocking, CCL2/CCR2 signaling, either pharmacologically or genetically, has been shown to reduce macrophage and T-cell infiltration into the kidney, decrease proteinuria, and improve renal function, indicating the therapeutic benefits of blocking CCL2/CCR2 signaling [55,56]. In patients with LN, elevated urinary CCL2 (uCCL2) levels correlate with disease severity and can predict whether a patient's LN flares, suggesting its potential as a non-invasive and reliable biomarker for monitoring disease activity and response to treatment [57–59]. C-X3-C motif ligand 1 (CX3CL1, also known as fractalkine) and C-X3-C motif chemokine receptor 1 (CX3CR1) represent another notable pair of chemokine and receptor in the context of LN. CX3CL1 is expressed in the kidney, interstitial microvasculature, and renal arteries in both soluble and membrane-bound forms, where it binds to CX3CR1 expressed on monocytes and macrophages and recruits them to the kidney [15,60,61]. In the MRL/lpr model of LN, inhibiting CX3CL1/CX3CR1 signaling reduces macrophage numbers and inflammation, but has no effect on systemic autoimmunity, indicating that they may have a localized role in renal inflammation in LN [61,62]. In patients with LN, CX3CL1 is increased in glomeruli, especially in class IV glomerulonephritis, and correlates with CX3CR1 macrophage infiltration, indicating that CX3CL1 may be an important mediator in more severe disease [61,63]. Additional chemokines contributing to inflammatory processes in LN are CCL3/CCL4/CCL5-CCR1/CCR5. CCL5 is a chemokine that binds to the CCR1 or CCR5 receptors expressed by monocytes, macrophages, and T cells, among others, and is increased in the kidneys of lupus-prone mice or patients with LN. It is thought to contribute to the recruitment of immune cells into the kidney via the CCR1/CCR5 receptor [64–66]. CCR1 and CCR5 associated signaling can suppress inflammation in murine models, and infiltrating mononuclear cells involved in this process exhibit characteristics similar to those observed in nephritic-like or nephritic conditions in rabbit models, suggesting the importance of contextual cellular functions in maintaining health [54,67]. Similarly, in patients with LN, a high number of CCR1-expressing macrophages are found within the tubulointerstitial compartment, indicative of another context-dependent functional role for CCR1 in the pathogenesis of LN [66,68]. CXCL9 and CXCL10 are key chemokines involved in recruiting T cells and macrophages into the kidney, specifically those that express the CXCR3. They are produced by renal tubular epithelial cells in response to IFN-γ [69]. Although the MRL/lpr C57BL/6 CXCL9 deficient model of LN exhibits a high level of LN, and

the immune system in this model has an increased number of CXCR3$^+$ T cells, it does not demonstrate further progression of nephritis nor an increased number of CXCR3$^+$ T cells in the kidney (no retaliation) [70], indicating that CXCL9 plausibly works as an upstream driver of renal inflammation compared to CXCL10, which is also upregulated but does not appear to have a similar impact. Thus, blocking these CXC chemokines could represent a clinically relevant therapeutic target for limiting immune cell recruitment and inflammation in LN.

The interplay of cytokines and chemokines significantly contributes to the complex networks that drive the pathogenesis and progression of LN. For example, mesangial-derived IL-6 can induce CCL2 expression in macrophages, which recruits additional monocytes to the kidney, leading to inflammation [71]. TNF-α can also induce CXCL10 expression, which is also involved in the recruitment of inflammatory cells to the kidney [72]. These networks are complex webs that are pivotal for enabling therapeutic interventions aimed at improving patient outcomes in LN. Collectively, interactions among chemokine and cytokines play a critical role in driving immune cell infiltration and inflammation in LN. To develop novel targeted therapies, researchers must investigate the individual functional roles of those interactions to determine if a specific functional interaction can control recruitment, relative to the other functional behaviors of cells in that context.

4. Macrophage Cellular Interactions With Other Cells in LN

Macrophages serve as important coordinators of the immune response in LN, establishing complex interactions with both immune and non-immune cells that mediate disease progression (Fig. 2).

4.1 Engaging With Immune Cell Networks

In the immune compartment, macrophages interact with T cells, B cells, and dendritic cells (DCs) to modulate adaptive immune responses by promoting either Th1, Th17, or Treg responses, depending on the macrophage polarization. In turn, the interactions among T cells, B cells, and DCs determine whether macrophages produce pro-inflammatory or anti-inflammatory cytokines, creating the inflammatory environment in LN.

M1-like macrophages play a crucial role in driving amplified Th1 and Th17 responses, which lead to increased injury and inflammation via inflammatory cytokines such as IFN-γ and IL-17 [73–75]. M2-like macrophages contribute to immune suppression and tissue repair by promoting Treg activity through the secretion of anti-inflammatory cytokines like IL-10 and TGF-β [76–78]. Macrophages regulate T-cell polarization, exhibiting the dual role of promoting or suppressing inflammation in LN. Macrophages play a key role in clearing pathogenic debris and then activating and presenting these antigens to B cells [15,79]. Impaired clearance of apoptotic debris by macrophages leads to the accumulation of nuclear antigens (e.g., double-stranded DNA [dsDNA], histones), which are internalized and presented to B cells via MHC class II, stimulating autoreactive B cell expansion. Additionally, macrophages secrete key cytokines (B-cell activating factor, IL-6, and IL-21) that promote B cell survival, class switching, and plasma cell differentiation, further amplifying autoantibody production [80]. Macrophages also interact with DCs to help regulate immune activity and control the development of autoreactive T cells, ultimately regulating this process in LN via DC activation, maturation, and functionality [81].

4.2 Cross-Talk With Non-Immune Cell Populations

In addition to their dialogue with immune cells, macrophages also interact with various non-immune renal cells, including glomerular endothelial cells, MCs, podocytes, and renal tubular epithelial cells, contributing to renal tissue injury, fibrosis, and dysfunction. Macrophages, through the secretion of cytokines, chemokines, and matrix-degrading enzymes, exacerbate inflammation and disrupt the structural integrity of the kidney; in turn, renal cells subsequently regulate the recruitment, polarization, and survival of these macrophages.

Macrophages release pro-inflammatory cytokines, including TNF-α and cathepsin L, which can damage the glycocalyx of glomerular endothelial cells (ECs), contributing to vascular permeability and the extravasation of inflammatory cells [43,82]. ECs subsequently express and secrete chemokines like CCL2 and CX3CL1, which recruit macrophages to the injured area, thus creating a feedback loop triggering further inflammation [66]. Similar interactions occur with MCs, where macrophages secrete cytokines, such as CXCL12, IL-1 and IL-6, which stimulate MC proliferation and accumulation of the extracellular matrix, contributing to glomerular fibrosis and sclerosis [83]. Interestingly, MCs also may modulate macrophage polarization, causing greater M1 polarization during the acute phase of LN and promoting M2 cell polarization during the chronic phase of LN, which may aid in resolving inflammation and promoting tissue repair [14]. Macrophage crosstalk may also lead to podocyte injury when cytokines such as TNF-α and IL-1β are released, downregulating nephrin expression, which is a critical protein for maintaining normal podocyte structure and function [84]. Additionally, M2 macrophages secrete TGF-β1, leading to short-term podocyte mesenchymal transition and dysfunction, which contributes to proteinuria [85]. In the renal tubulointerstitium, macrophages are abundant and positively correlate with severity of interstitial inflammation and fibrosis in the tubules. Macrophages drive inflammation early in LN and act as antigen-presenting cells, whereas later in the disease course, they contribute to remodeling the extracellular matrix and secreting growth factors that assist in tissue repair. Additionally, renal tubular epithelial cells mediate

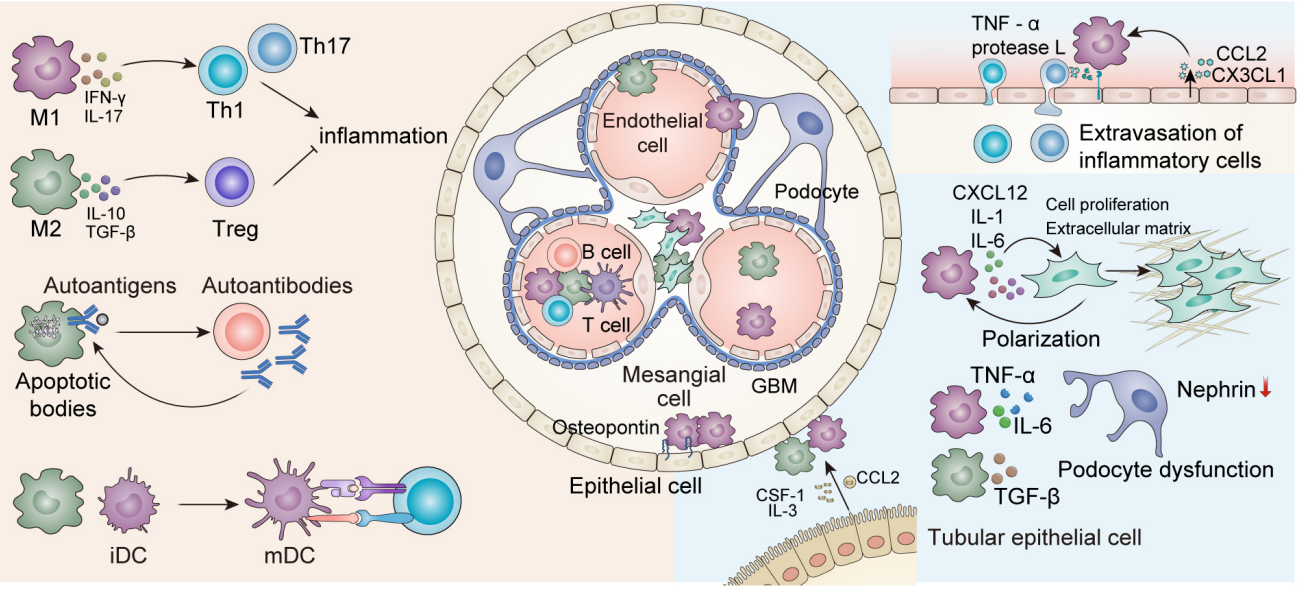

Fig. 2. Interactions of Macrophages with other cells in LN. Within the adaptive immune system, macrophages engage in bidirectional crosstalk with T cells, influencing T-cell polarization. M1-polarized macrophages promote Th1/Th17 immune responses via IFN-γ and IL-17 secretion, whereas M2 macrophages facilitate Treg-mediated immunosuppression by releasing IL-10 and TGF-β. M2 macrophages also impair B-cell function by facilitating autoantigen presentation through impaired clearance of apoptotic debris. These immunomodulatory functions are complemented by macrophage–DC interactions that shape T-cell autoreactivity. In renal microenvironments, macrophages form pathogenic feedback loops with glomerular endothelial cells via TNF-α- and cathepsin L-mediated glycocalyx disruption and CCL2/CX3CL1-driven recruitment, while their interplay with MCs drives extracellular matrix deposition through CXCL12, IL-1β, and IL-6 signaling. Podocyte injury occurs through macrophage-derived TNF-α and IL-1β, which downregulates nephrin expression, compounded by TGF-β1-induced epithelial-mesenchymal transition. Tubulointerstitial fibrosis is driven by macrophage activation, which is initiated by tubular epithelial cells releasing factors such as colony-stimulating factor 1 (CSF-1), IL-3, and miRNA-containing exosomes. Parietal epithelial cells also contribute by secreting osteopontin (OPN), which further amplifies macrophage infiltration.

the proliferation and survival of macrophages via colony-stimulating factor 1 (CSF-1) and IL-34 [86,87]. Furthermore, stimuli from tubular epithelial cells including exosomes containing miRNAs or CCL2 can be internalized by macrophages and influence their polarization and migration [88]. Although there has been less emphasis in the literature, there is also evidence of interaction between parietal epithelial cells and macrophages in LN. For example, parietal epithelial cells express osteopontin (OPN), which promotes macrophage infiltration and contributes to inflammation [89].

These various cell interactions highlight the multifaceted role of macrophages in LN, which drives and modulates inflammation and tissue damage by directly interacting in a complex manner with a variety of cell types. The reciprocal crosstalk between macrophages and immune and non-immune cells highlights their central role in LN pathogenesis and demonstrates the importance of developing therapeutic strategies to target their interactions.

5. Therapeutic Strategies Targeting Macrophages

Macrophages play a critical role in the development of LN and are therefore a promising target for therapeutic interventions (Table 2). As mediators of inflammation, kidney injury, and fibrosis, macrophages also interact with immune and non-immune cells in the kidney. Strategies that could be utilized to manipulate macrophages include targeting the pro-inflammatory actions of macrophages, enhancing the actions of anti-inflammatory or reparative macrophages, and/or blocking the ability of macrophages to migrate to the kidney. Targeting macrophages is a new and exciting approach for managing LN that holds promise for improving outcomes in this complicated and burdensome disease.

5.1 Enhancing Macrophage Phagocytic Efficiency

Macrophages are essential for the clearance of apoptotic cells and immune complexes, both of which are thought to be involved in the pathogenesis of LN. Augmenting the phagocytic activity of macrophages has been proposed as a therapeutic strategy to reduce renal inflamm-

Table 2. Therapeutic strategies targeting macrophages in LN.

Strategy	Mechanism	Key targets/agents	Effects	Challenges
Enhancing phagocytic efficiency	Boosting macrophage clearance of apoptotic cells & immune complexes	- EPO signaling (ARA290, non-erythropoietic EPO derivative)	- Reduces autoantibodies & renal inflammation	- EPO agonists cause hypertension/thromboembolism
		- PPARγ agonists	- Shifts macrophages to anti-inflammatory phenotype	- Need optimized PPARγ agonists
		- Efferocytosis enhancers (Hv1, serum amyloid P component, milk fat globule epidermal growth factor 8, growth arrest-specific gene 6)		
Blocking macrophage recruitment	Inhibiting chemokine-driven infiltration into kidneys	- CCL2/CX3CL1 inhibitors (Mizoribine, Disulfiram)	- Reduces renal macrophage infiltration	- Long-term safety of chemokine blockade unclear
		- CSF-1R inhibitor (GW2580) - TLR7/9 inhibitors (dexamethasone nanogels)	- Lowers proteinuria & chronicity index	
Shifting polarization	Promoting anti-inflammatory M2 macrophages	- IL-33/ST2 pathway	- Decreases pro-inflammatory cytokines (TNF-α, IL-6)	- Risk of over-suppressing immune responses
		- Natural compounds (paeonol) - MSCs - LXRα agonists - Azithromycin (PI3K/Akt pathway)	- Improves renal function	- Notch pathway modulation complexities
Suppressing cytokine secretion	Inhibiting pro-inflammatory cytokine release	- NLRP3 inhibitors (MCC950)	- Reduces IL-1β, IL-18, TNF-α	- Glucocorticoid side effects
		- Natural compounds (paeoniflorin, luteolin) - HMGB1 antagonists - MSC-derived exosomes (miR-146a-5p, miR-16)	- Attenuates NF-κB activation	- Need for targeted delivery
Reprogramming metabolism	Shifting glycolysis (M1) → oxidative phosphorylation (M2)	- Glycolysis inhibitors	- Reduces IL-1β & renal inflammation	- Metabolic pathways are complex & interconnected
		- CPT1a enhancers (promotion of fatty acid oxidation) - mTOR modulators - PPARγ agonists (pioglitazone)	- Enhances tissue repair	
miRNA-based therapy	Regulating macrophage polarization & inflammation via miRNAs	- miR-181d-5p antagonists	- Suppresses pyroptosis & NLRP3 activation	- Delivery challenges
		- MSC exosomes (miR-13896, miR-146a-5p) - miR-155/miR-21 inhibitors	- Promotes M2 polarization	- Off-target effects possible

EPO, erythropoietin; PPARγ, proliferator-activated receptor gamma; MSCs, mesenchymal stem cells; LXRα, Liver X receptor alpha; PI3K, phosphoinositide 3-kinase; NF-κB, nuclear factor kappa B; NLRP3, NLR family pyrin domain containing 3; mTOR, mammalian target of rapamycin.

ation and preserve renal function in LN. One approach is to target erythropoietin (EPO) signaling, which is a critical mediator of the phagocytic clearance of apoptotic cells. In lupus mouse models, EPO has been shown to decrease autoantibody production and improve renal function, partly by enhancing macrophage phagocytic activity [90]. However, the ability to clinically utilize EPO agonists is limited by adverse effects, particularly hypertension and thromboembolism [91]. To address some of these challenges, a non-erythropoietic EPO derivative of ARA290 is being investigated. ARA290 also enhances macrophage phagocytosis of apoptotic cells, inhibits the differentiation of pro-inflammatory M1 macrophages, and inhibits the production of pro-inflammatory cytokines such as IL-6 and TNF-α, thereby decreasing renal inflammation related to LN [92]. This underscores the possible application of targeting EPO signaling to enhance macrophage phagocytosis and reduce inflammation in LN.

An additional and alternative therapeutic strategy is targeting peroxisome proliferator-activated receptor gamma (PPARγ), which would both enhance macrophage phagocytosis and regulate immune responses. Specifically, activating PPARγ can improve the clearance of apoptotic cells and inhibit pro-inflammatory cytokine production, leading to reduced renal inflammation [93–95]. In lupus-prone mouse models of LN, PPARγ agonists improve renal function and decrease autoantibody production [96]. Thus, PPARγ agonists show promise in aiding phagocytic activity and potentially decreasing renal inflammation in LN; however, future studies are needed to optimize their use and minimize side effects.

Efferocytosis (the process of macrophages clearing apoptotic cells) is inhibited in LN by the continuing deposition of autoantigens, which allows for the development and persistence of autoimmunity, thereby inhibiting efferocytosis. Several researchers have been interested in the restoration of efferocytosis as a possible therapeutic approach to limit inflammation in the kidney and improve renal function in LN. One potential target is voltage-gated proton channel 1 (Hv1), which is required for acidification of the phagosome for efferocytosis. Increased Hv1 activity promotes the clearance of apoptotic cells and decreases autoantibody production in lupus-prone mouse models [97]. The serum amyloid P component shifts macrophage polarization from the pro-inflammatory M2b phenotype to the anti-inflammatory M2a phenotype, thus promoting efferocytosis and reducing the severity of LN [98,99]. Additionally, molecules such as milk fat globule epidermal growth factor 8 and growth arrest-specific gene 6 can facilitate the removal of apoptotic cells (efferocytosis) by binding to phosphatidylserine [100,101]. These mechanisms provide breakthroughs in restoring efferocytosis to help limit inflammation and improve renal function in LN.

5.2 Blocking Macrophage Recruitment

Targeting macrophage recruitment to the kidneys is a promising therapeutic approach in LN, as macrophages play a key role in kidney inflammation and tissue damage. The recruitment of macrophages is mediated through chemokine signaling, adhesion molecules, and TLR activation, each of which has been targeted in preclinical and clinical studies. For example, the chemokines CCL2 and CX3CL1 are upregulated in LN, promoting the recruitment of inflammatory cells to the kidney [46]. Mizoribine, a purine synthesis inhibitor, reduces macrophage infiltration into the kidney by downregulating OPN, a key chemokine in monocyte recruitment. Mizoribine has shown efficacy in clinical studies in preventing macrophage infiltration and reducing the chronicity index in patients with LN [102–106]. Disulfiram, an alcohol withdrawal drug, inhibits monocyte/macrophage migration via *FROUNT*, a cytoplasmic protein that promotes chemotaxis via CCR2 and CCR5 and suppresses pro-inflammatory elements such as TNF-α and CCL2 while decreasing renal injury and proteinuria [106,107]. Another class of targets is adhesion molecules, such as integrins and selectins, as these proteins mediate the extravasation of monocytes and macrophages into the kidney. GW2580, a selective inhibitor of the CSF-1 receptor kinase, effectively depletes glomerular macrophages in LN models and reduces albuminuria, suggesting macrophage survival and recruitment pathways may be targetable for treating LN [108–111]. The reduction of TLRs, particularly TLR7 and TLR9, also shows promise as they play a crucial role in monocyte and macrophage recruitment in LN [112,113]. To scavenge cell-free DNA (a TLR9 ligand), dexmethasone-loaded nanogels have been developed to inhibit TLR9 in order to reduce inflammation and cytotoxicity and lessen toxicity to the patient [114]. The abovementioned studies provide clear therapeutic targets for preventing macrophage recruitment in LN. Further assessments of each should be undertaken to determine their long-term efficacy and safety in patients. Learning about the complex mechanisms involved in monocyte/macrophage recruitment may provide information about novel potential therapeutic strategies in LN.

5.3 Shifting Macrophage Polarization Dynamics

The polarization of macrophages is a significant factor in the pathogenesis of LN, as the balance of pro-inflammatory M1-like and anti-inflammatory M2-like forms is part of the disease pathogenesis and resolution. The characterization of pathways, mechanisms, and molecular regulators involved in macrophage polarization has broadened the therapeutic landscape for LN. IL-33 is one of these regulators and has been defined as one of the strongest potential macrophage polarization regulators discovered to date. IL-33 promotes M2 macrophage polarization and Treg proliferation by upregulating ST2, leading to the autoregulation of M2 macrophages and Tregs [115–117]. Pre-

clinical studies in mouse models in LN have shown that treatment with IL-33 leads to decreased renal inflammation and proteinuria, indicating that IL-33 may be a promising therapeutic target in LN [115,116]. Similarly, another therapeutic approach using natural compounds (e.g., paeonol) induces M2 polarization of macrophages through inhibition of mitogen-activated protein kinase and nuclear factor kappa B (NF-κB) [118]. Preclinical models of LN have shown that paeonol reduces both the vegetative symptoms of lupus and the symptoms of renal damage, suggesting its potential as a novel therapeutic agent for LN. Mesenchymal stem cells (MSCs) direct macrophage polarization to M2 while also inhibiting NLR family pyrin domain containing 3 (NLRP3) inflammasome activation through inhibition of Pim-1 kinase, suggesting its promising therapeutic potential in LN [119]. Treatment with MSCs has helped reduce renal inflammation and improve symptomatic lupus disease, again demonstrating the potential for macrophage polarization as a therapeutic approach. Liver X receptor alpha (LXRα) agonists induce M2 polarization and improve outcomes in mouse models of LN [120]. LXRα agonists increase the expression of anti-inflammatory markers in mice while blocking the production of other pro-inflammatory cytokines, making them a clinically relevant therapeutic approach for LN. The therapeutic shift to targeting M2 is not without limitations, as inhibiting Notch in murine lupus models improves outcomes by preventing M2b polarization, suggesting a link between Notch modulation and M2b in LN; however, the exact correlation and extension to the pathophysiology of LN in humans remains unclear [121]. Finally, azithromycin (a macrolide antibiotic) likewise induces M2-like macrophage polarization through the phosphoinositide 3-kinase (PI3K)/Akt pathway, resulting in decreased inflammation in SLE [122]. Thus, the immunomodulatory properties of azithromycin could make it a novel therapeutic in the treatment of LN, but it could also cause confounding side effects.

Endoplasmic reticulum stress (ERS) is increasingly understood to be a fundamental driver of LN pathobiology through the activation and polarization of macrophages. ERS is considered the initial event leading to the unfolded protein response, a cellular stress response that restores protein homeostasis. Prolonged ERS leads to the production of pro-inflammatory cytokines and NLRP3 inflammasome activation, both of which promote renal inflammation and injury in LN [123]. Therefore, modulation of ERS pathways is an attractive therapeutic strategy to reduce inflammatory responses, potentially mediated by macrophages, and restore renal function. Advances in drug development and structure-based drug design have resulted in the development of selective small molecule inhibitors and drugs that can be assessed in preclinical and clinical trials. For example, several inhibitors of IRE1α and protein kinase RNA-like ER kinases have been shown to reduce macrophage activation and renal inflammation in preclinical models of lupus [124]. Furthermore, there are many chemical chaperones that can relieve ERS, including 4-phenylbutyric acid, which exerts protective effects by limiting protein misfolding and restoring cellular homeostasis [125].

5.4 Suppressing Inflammatory Cytokine Secretion

In LN, pro-inflammatory cytokines released from macrophages are a leading contributor to renal inflammation and damage, making inhibiting cytokine release a reasonable therapeutic target. Glucocorticoids are one of the most frequently employed treatments for LN due to their strong anti-inflammatory effects by decreasing secretion of IL-1β, IL-6, TNF-α and increasing the secretion of other anti-inflammatory mediators [126]. However, chronic glucocorticoid exposure is associated with serious complications, such as chronic glomerular scarring and interstitial fibrosis, highlighting the need for alternative therapies. Synthetic compounds such as Cf-02 have demonstrated the ability to inhibit the release of inflammatory cytokines. Treatment with Cf-02 significantly inhibits NLRP3 inflammasome activation and macrophage infiltration, decreases IL-1β and IL-18 levels, and improves renal function [127], highlighting their potential as a therapeutic agent for treating LN. There are also numerous natural compounds that inhibit macrophage cytokine release. For example, paeoniflorin, luteolin, and quercitrin have all been shown to attenuate NF-κB activation, a key pathway responsible for regulating cytokine release, and reduce the secretion of TNF-α, IL-6, and IL-1β [128–130]. Their natural origins and low toxicity (at appropriate concentrations) make these natural compounds appropriate for clinical trials. In addition, inhibiting the NLRP3 inflammasome is an effective therapeutic strategy for many diseases, as inhibiting the NLRP3 inflammasome inhibits cytokine-driven inflammation. For example, the NLRP3 inhibitor MCC950 has been shown to significantly reduce IL-1β and IL-18 in preclinical models, reduce the symptoms of LN, and improve renal function [131]. Thus, targeting the NLRP3 inflammasome is a valid strategy to reduce inflammation. Likewise, MSCs and exosomes derived from MSCs strongly modulate macrophage cytokine release [132]. In the presence of MSCs, macrophages can shift from a pro-inflammatory to anti-inflammatory phenotype, which involves a reduction in pro-inflammatory cytokine production and an increase in anti-inflammatory cytokine secretion, including IL-10 [133]. MSC-derived exosomes containing miR-146a-5p and miR-16 inhibit the secretion of pro-inflammatory cytokines by directly targeting inflammatory pathways [134,135]. HMGB1 is a pro-inflammatory molecule that promotes M1-like macrophage polarization and the secretion of pro-inflammatory cytokines [136]. Preclinical studies have demonstrated that targeting HMGB1 with inhibitors and antagonists reduces the production of TNF-α and IL-1β. Targeting HMGB1 also promotes an anti-inflammatory macrophage phenotype, suggesting its

therapeutic potential in LN. Targeting the secretion of cytokines from macrophages involves a complex mechanism, suggesting that future research should focus on inhibiting macrophage cytokine secretion to reduce renal inflammation and damage in LN.

5.5 Reprogramming Macrophage Metabolic Pathways

Macrophage metabolism is integral to defining their functional phenotype, particularly in the LN context. Metabolic reprogramming has been identified as a potential therapeutic approach. M2 macrophages rely on oxidative phosphorylation, a metabolic route that is bioenergetically favorable and allows M2 macrophage involvement in tissue repair functions [137]. One study demonstrated that inhibiting glycolysis can reduce kidney inflammation by decreasing the release of IL-1β and preventing the recruitment of inflammatory cells to the kidney [16]. Together, these data support the notion that metabolic reprogramming can be harnessed therapeutically to modulate macrophage behavior in LN. An additional metabolic route influencing macrophage polarization is fatty acid metabolism. M2 macrophages enhance fatty acid oxidation, which contributes to their anti-inflammatory function [138]. Recent data indicate that the restoration of carnitine palmitoyltransferase 1A (CPT1A) enhances phagocytic activity and improves renal inflammatory changes during LN (phagocytosis dysfunction in LN is linked to the reduced expression of CPT1A in monocytes/macrophages) [139]. Finally, amino acid metabolism also plays an important role in macrophage polarization. The mammalian target of rapamycin (mTOR) pathway is inhibited by specific amino acids and is involved in important macrophage functions [140]. The regulator of mTOR, tuberous sclerosis 1, has demonstrated increased M2 modulation and defective M1 modulation of macrophage phenotyping *in vivo* [141,142]. Thus, macrophage-mediated changes modulated by amino acid metabolism may serve as potential therapeutic targets in LN. Mitochondrial function is also an important dimension of macrophage metabolic reprogramming [143,144]. M2 macrophages, which are anti-inflammatory and promote tissue repair, exhibit higher mitochondrial function than M1 macrophages. Mitochondrial function is enhanced with PPAR-γ agonists that promote M2 polarization and inhibit the inflammatory response in LN [93]. Study has demonstrated that pioglitazone (PPAR-γ agonist) can induce M2-like macrophages and protect against renal damage in models of lupus [145]. Collectively, these data complement ongoing studies evaluating macrophage metabolic reprogramming as a therapeutic target in LN. Thus, targeting macrophage metabolism may be a powerful approach for transitioning between M1 to M2 macrophage phenotypes and developing novel therapeutic interventions. Markers of macrophage metabolism, such as CPT and mTOR activity, could serve as biomarkers for both response to treatment and disease severity [146]. Overall, our understanding of the role of macrophage metabolism (i.e., glycolysis, fatty acid metabolism, amino acid metabolism, and mitochondrial function), as well as the interactions of these pathways, define the mechanisms underlying macrophage function in LN. Continued studies into the role of macrophages in LN will require validation in clinical populations and should identify potential biomarkers to personalize treatment strategies.

5.6 Harnessing miRNA for Therapeutic Intervention

MiRNAs serve as key regulators of macrophage function in LN and are promising targets for therapeutic approaches, as they regulate gene expression at the post-transcriptional level. These small non-coding RNAs can significantly impact macrophage polarization and the inflammatory response to injury, and are well-established contributors to the pathogenesis of LN. For example, miR-181d-5p is an important contributor to renal inflammation and pyroptosis [147,148]. In exosomes that have been released from macrophages, increased expression of miR-181d-5p is a mechanism for targeting B-cell lymphoma 2 (anti-apoptotic protein) and regulating the NLRP3/caspase-1/gasdermin D pathway responsible for inducing pyroptosis [148]. Furthermore, antagonism of miR-181d-5p has been shown to diminish renal damage and inflammation, indicating that exosomal miRNAs represent potential therapeutic targets in LN [147]. Thus, the concept of utilizing miRNA therapy to treat LN by reducing inflammation mediated by macrophages is promising, specifically mi-R181d-5p and miR-13896 packaged in exosomes from MSCs, which have shown favorable therapeutic outcomes. Similar to miR-181d-5p, exosomes can mediate M2 macrophage polarization and enhance tissue repair functions through mechanisms that block macrophage activity. The miR-13896 exosomes have been shown to improve renal function and reduce renal inflammation. The use of exosomes derived from MSCs to improve LN appears promising [149]. In addition, exosomes derived from MSCs that contain miR-146a-5p and miR-16 also provide protective effects through different pathways, with miR-146a-5p downregulating the Notch 1 signaling pathway, which is associated with proliferation and inflammation [150]. The miR-16 components promote M2 macrophage polarization. Collectively, they provide a method to diminish collagen deposition in the glomeruli and decrease complement C3 levels, while promoting renal function. Other than exosome-packaged miRNAs, miR-21 and miR-155 are also related to LN pathology [151]. While miR-21 can promote fibrosis and inflammation, miR-155 can promote M1 macrophage differentiation and enhance the release of inflammatory cytokines. Thus, inhibiting miR-155 and miR-21 may lead to a shift in cytokine production towards a more anti-inflammatory M2 phenotype, ultimately leading to less inflammation and improved renal function in patients with LN. This information demonstrates the multifaceted roles of miRNAs in modulat-

Table 3. Clinical implications and biomarkers in LN.

Category	Key biomarkers	Clinical utility	Therapeutic implications
Cell-based biomarkers	CD11c+ macrophages in urine	Proliferative LN diagnosis	Predictive models for therapy response
	scRNA-seq-defined macrophage subsets	Monitoring treatment response	Targeting macrophage polarization
Cytokine/Chemokine	M-CSF, IL-6, TNF-α, IL-1β	Disease activity monitoring	Anti-cytokine therapies (e.g., anti-IL-6, anti-TNF-α)
		Renal involvement assessment	
Genetic/Epigenetic	Hypomethylation (IFN-induced protein with tetratricopeptide repeats 1, MX dynamin-like GTPase 1)	Risk stratification	Type I IFN inhibitors (for IFN-high patients)
	miR-150 upregulation	Renal damage progression	B-cell depletion (for plasma blast-high)
	Neutrophil/plasma blast gene signatures		
Urinary biomarkers	sCD163 (macrophage activation)	Early LN diagnosis	Tubular repair strategies (EGF)
	EGF (↓ = poor prognosis)	Chronic kidney disease progression prediction	Anti-fibrotic therapies (uPAR)
	uPAR (↑ = progression)		
Clinical/Histological integration	Proteinuria (<0.7–0.8 g/dL at 1 year)	Long-term remission prediction	-
	Tubulointerstitial inflammation/chronicity index	Renal prognosis	

EGF, epidermal growth factor; uPAR, urokinase-type plasminogen activator receptor.

ing the activity of macrophages and their potential as therapeutic targets. Thus, miRNA therapeutics that target specific mRNAs and modulate macrophage activity and renal inflammation in LN may be a novel and effective treatment in the future.

6. Clinical Implications and Biomarkers

Identifying reliable biomarkers for LN that will aid in early diagnosis, monitor disease activity, and identify personalized treatment is of great value. Some of the discoveries made in molecular and cellular studies in recent years have revealed numerous informative biomarkers for disease activity, renal involvement, and treatment response. These biomarkers provide some insights into the underlying pathophysiology of LN, and in some cases therapeutic targets (Table 3).

6.1 Cell-Based Biomarkers

In the pathophysiology of LN, macrophages, particularly their polarized states (M1 and M2), contribute to both progression and regression. CD11c+ macrophages in urine have also been identified as potential biomarkers of proliferative LN [152,153]. These urinary CD11c+ macrophages originate from circulating monocytes, and are found in increased numbers in the urine of patients with active proliferative LN. They are significantly decreased in patients with complete or partial renal response to therapy. The presence of CD11c+ macrophages is associated with elevated serum anti-dsDNA antibody levels, renal tubular atrophy, and interstitial fibrosis, all of which suggest the utility of this cell type as a marker of LN. Single-cell RNA sequencing (scRNA-seq) is a powerful tool for studying cellular heterogeneity in LN by providing unprecedented granularity in gene expression analysis at the single-cell level [154]. Specific macrophage subsets have emerged as cellular contributors to renal injury. The interplay of these subsets has led to the development of predictive models to assess individual patient responses to therapies. ScRNA-seq studies have revealed that tissue-resident macrophages exhibit a diverse range of transcriptional profiles, including both IFN and mixed anti-inflammatory signatures [155]. These data demonstrate the potential of scRNA-seq to discover novel markers and identify predictive targets for therapy.

6.2 Cytokine and Chemokine Biomarkers

Cytokines and chemokines are produced by macrophages or other immune cells may also be involved in the pathogenesis of LN. Macrophage CSF (M-CSF), predominantly produced by circulating monocytes, is elevated in patients with lupus and linked to both disease activity and renal involvement [156]. Furthermore, M-CSF is positively correlated with the number of

circulating monocytes and is likely associated with the recruitment and activation of macrophages within the kidney [157]. Elevated levels of cytokines like IL-6, TNF-α, and IL-1β, particularly during M1 macrophage activity and in the context of active LN, are strongly associated with inflammation and disease progression. Collectively, these pro-inflammatory cytokines contribute to renal injury at least in part by promoting an inflammatory response and activating local renal cells, providing rationale for these factors as therapeutic targets.

6.3 Genetic and Epigenetic Biomarkers

The presence of both genetic and epigenetic factors adds to the heterogeneity of LN and may also serve as a biomarker for risk prediction and disease progression. The hypomethylation of genes involved in the type I IFN response has been shown in the immune cells of patients with SLE. Profiling the epigenetic landscape may help identify patients at higher risk of LN. The hypomethylation of genes such as IFN-induced protein with tetratricopeptide repeats 1 and MX dynamin-like GTPase 1 correlate with increased disease activity and renal involvement [158]. miR-150 is another example of a miRNA that is upregulated in patients with LN and is involved in both fibrosis and inflammation, correlating with the severity of renal damage. miR-150 promotes renal fibrosis through the downregulation of SOCS1, a negative regulator of NF-κB, making both miR-150 and SOCS1 possible therapeutic targets and biomarkers [159]. Modular transcriptional analysis has also been utilized to elicit disparate gene expression signatures in patients with LN. One example is a 20-gene neutrophil signature that correlates with LN in pediatric patients with SLE [160]; a second example is a plasma blast signature that correlates with overall disease activity [161]. This is useful to provide an overall molecular signature in the strata of patients moving forward, thus permitting precision and individualized treatment. Patients with a strong IFN signature may benefit from targeting the underlying type I IFN signal as a therapeutic intervention [162]. However, a patient with a plasma blast signature may instead benefit from therapies that target the B-cell population over type I IFN intervention. Lastly, peripheral blood cells from patients with LN have also been subjected to modular analysis where specific gene clusters have been shown to correlate with treatment response and/or lack of response, providing another avenue to predict the therapeutic response [163].

6.4 Urinary Biomarkers and Proteomics

Urinary biomarkers are emerging as potential predictors of treatment response. Soluble CD163 (sCD163), a marker of macrophage activation, has emerged as an important biomarker in LN. In urinalysis, elevated sCD163 levels are a strong indicator of active LN and correlate with disease activity, histopathology, and treatment response [164]. sCD163 levels may begin to increase up to 6 months before an individual develops LN, suggesting its utility as a biomarker for early diagnosis. Proteomic analysis of urine will identify panels of biomarkers associated with renal outcomes. As an example, urinary epidermal growth factor (EGF) and soluble urokinase-type plasminogen activator receptor (uPAR) are independent predictors of chronic kidney disease progression in LN [165–167]. EGF plays a role in tubular repair/regeneration and decreased levels are associated with poorer renal outcomes. Similarly, uPAR is an inflammatory and fibrotic marker, and elevated levels predict disease progression. Incorporating these urinary biomarkers into clinicopathologic predictive models will improve the accuracy of predicting treatment response.

6.5 Integration of Clinical and Histological Data

The establishment of models predicting response to treatment plays an important role in a multitude of factors and approaches considered in treatment decision-making in LN. A better understanding of the clinical patient profile (e.g., class, duration of disease, and onset of LN), clinical characteristics (e.g., proteinuria, serum creatinine), and histologic characteristics (e.g., tubulointerstitial inflammation, index of chronicity) can lead to improved individualized therapy and effective treatment plans. It also provides avenues where predictive models can leverage clinical data, such as laboratory results, urine protein measures, and histopathological findings to enhance treatment response prediction. For instance, tubulointerstitial inflammatory cell infiltrates and a high chronicity index indicate worse renal outcomes [168]. Additionally, a proteinuria level of $<$0.7 to 0.8 g/dL at 1 year post-diagnosis is a strong indicator of a good long-term renal outcome and a high likelihood of remission [169]. Histologic findings such as crescents and interstitial fibrosis are clinically significant independent predictors of treatment response and renal prognosis as well [170,171]. Integrating histopathologic findings with molecular and cellular biomarkers, along with long-term clinical disease activity data (i.e., end-stage renal disease, treatment response), will lead to more accurate predictive models of disease activity and treatment outcomes. As we have identified macrophage-associated biomarkers and developed predictive models of treatment response, advancements are being made towards enhancing the care of patients with LN care. Predictive models allow for early diagnosis and individualized treatment strategies, thus improving overall outcomes. The use of biomarkers, evidence-based practices, and predictive models can be validated for larger, less homogenous patient cohort, and earlier biomarkers, such as those related to macrophages, and/or predictive models can be a reproducible effective clinical approach. In addition, the utilization of multi-omics data, such as genomics, transcriptomics, and proteomics, will increase the accuracy of associated predicted models as precision medicine becomes the norm.

7. Future Directions

The study of macrophage polarization has revealed possible avenues for future research and therapeutic development, especially as we learn more about the complex functions of M1 and M2 macrophages in the pathophysiology of LN. One key area of interest is selective modulation of the macrophage polarization state to restore the balance between the pro-inflammatory M1 phenotype and anti-inflammatory M2 phenotype. Recently, there has been interested in developing therapeutics that target specific macrophage signaling cascades, including those involving molecules like HMGB1, IL-33, and miRNAs. The development and application of accurate biomarker assessment for macrophage polarization states, such as CD163, CD206, and specific cytokines, would be useful for early diagnostic and follow-up assessments of LN if the biomarkers could be assessed through non-invasive methods such as urine or blood samples. Lastly, we should look beyond the modulation of cytokines in macrophage polarization and consider examining novel potential therapeutic targets in the macrophage signaling network as well as the roles of extracellular vesicles and microparticles in macrophage polarization and the progression of LN. The M1/M2 classification is an oversimplification of macrophage behavior in LN, as real-world macrophages exhibit hybrid phenotypes and dynamic plasticity. Murine studies are limited by species-specific differences, whereas human LN involves IFN-driven and metabolic influences. Spatial heterogeneity and unreliable biomarkers further complicate the M1/M2 framework. Future research should integrate advanced models (organoids, spatial omics) and target specific dysfunctional pathways rather than broad polarization shifts.

The implementation of single-cell omics technologies (e.g., transcriptomics, proteomics, and metabolomics) could generate significant insights into the molecular pathways that drive macrophage polarization in LN, as well as identify new pathways and molecular signatures that may serve as therapeutic targets. However, translating macrophage-targeted therapies from preclinical studies to clinical practice in LN settings present significant challenges due to differences between animal models and human disease, dynamic macrophage behavior, and patient heterogeneity. Biomarkers for monitoring macrophage activity in patients remain underdeveloped, and immunomodulators can have off-target effects. In addition, the complexity of LN suggests a need for multifaceted approaches that provide opportunities to modulate macrophage polarization while at the same time targeting the inhibition of pro-inflammatory cytokines or enhancing anti-inflammatory responses. Future research should focus on humanized models, combination therapies, advanced imaging, and personalized approaches to improve clinical translation. Characterization of these biomarkers in preclinical and clinical studies are needed to validate our observations, and based on these findings, establish protocols to evaluate the appropriate safety and efficacy of macrophage-targeted therapy for patients with LN, and establish best-practice assessment protocols in the clinic for conducting standard measurements. The goal for the treatment of LN is personalized medicine, which aims to tailor therapies based on individual patient factors like macrophage polarization, cytokine profiles, and genetic predispositions to attain the best possible outcomes with minimal side effects/discontinuation of therapy.

8. Conclusion

This review focuses on the key aspects of macrophage polarization in LN pathogenesis and management, highlighting the opposing roles of M1 macrophages, which promote inflammation, and M2 macrophages, which promote tissue repair and anti-inflammatory responses. Macrophage functions and LN are modulated through a dynamic process involving numerous microenvironment components. Furthermore, new strategies implicated in ameliorating renal inflammation and improving clinical outcomes target macrophage polarization and signaling pathways. The identification of biomarkers to facilitate early diagnosis in conjunction with therapies that alter macrophage function, such as M2 macrophage transfusions, represent promising approaches for the more effective treatment of LN. While current treatments for LN have variable efficacy, furthering our understanding of the context-dependent contributions of macrophage function is critical to advancing therapeutics that will reduce inflammation but also improve tissue repair and restore immune homeostasis.

Author Contributions

LZ: Writing-original draft and Visualization. JS: Substantial contributions to the conception and supervision; TL: Writing-review & editing and Conceptualization. LZ conceived the study, designed the methodology. JS participated in manuscript review and editing. TL oversaw project administration. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

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Conflict of Interest

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