frontiers | Frontiers in Immunology

TYPE Review
PUBLISHED 14 December 2022
DOI 10.3389/fimmu.2022.1063497



OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to Autoimmune and Autoinflammatory Disorders : Autoimmune Disorders, a section of the journal Frontiers in Immunology

RECEIVED 07 October 2022
ACCEPTED 29 November 2022
PUBLISHED 14 December 2022

CITATION
Liu M, Zhang L, Wang Y, Hu W, Wang C and Wen Z (2022) Mesangial cell: A hub in lupus nephritis. *Front. Immunol.* 13:1063497. doi: 10.3389/fimmu.2022.1063497



# Mesangial cell: A hub in lupus nephritis

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Lupus nephritis (LN) is a severe renal disease caused by the massive deposition of the immune complexes (ICs) in renal tissue, acting as one of the significant organ manifestations of systemic lupus erythematosus (SLE) and a substantial cause of death in clinical patients. As mesangium is one of the primary sites for IC deposition, mesangial cells (MCs) constantly undergo severe damage, resulting in excessive proliferation and increased extracellular matrix (ECM) production. In addition to playing a role in organizational structure, MCs are closely related to *in situ* immunomodulation by phagocytosis, antigen-presenting function, and inflammatory effects, aberrantly participating in the tissue-resident immune responses and leading to immune-mediated renal lesions. Notably, such renal-resident immune responses drive a second wave of MC damage, accelerating the development of LN. This review summarized the damage mechanisms and the *in situ* immune regulation of MCs in LN, facilitating the current drug research for exploring clinical treatment strategies.

KEYWORDS

**mesangial cells, lupus nephritis, systemic lupus erythematosus, immune complex, tissue resident immunity**

## Introduction

In the 20th century, Key and Zimmermann discovered the mesangium's unique structure and defined mesangial cells (MCs) as a particular cell type (1). The mesangium comprises mononuclear stellate cells between the glomerular arteries and the glomerular basement membrane (GBM) (2). It plays a vital role in glomerular functions and is a primary site of injury in glomerular disorders (3). MCs are derived from the Foxd1$^+$ precursor cells and are estimated to account for nearly one-third of the total number of glomerular cells (1, 4). Evidence demonstrates that a single hematopoietic stem cell can differentiate into glomerular MCs (5). Notably, alpha8 integrin (Itgα8) is strongly and exclusively expressed in MCs (6), promoting cellular adhesion while inhibiting their migration and proliferation (7, 8).

MCs are damaged in renal diseases, directly or indirectly affecting the functions of the kidney when the lesions occur and eventually causing renal failure. Therefore, understanding the biological features of MCs is particularly important for treating renal diseases. In recent years, researchers have paid more attention to MCs and have acquired many impressive findings.

# MCs in glomerular homeostasis

## MCs maintain glomerular filtration

Morphologically, MCs have a low cytoplasm-to-nucleus ratio and contain fibrils in the cytoplasm (9), supporting the glomerular structure and regulating glomerular filtration (Figure 1).

In the glomeruli, endothelial cells are surrounded by GBM and podocytes (9). The regions where no direct contact occurred in the MCs and endothelial walls are called extraglomerular mesangium (10). Extraglomerular mesangium separates MCs and GBM by ECM secreted from MCs (11). These ECM components contain bulk microfibers anchored to the membrane by fibronectin, resulting in a solid structure (12). MCs can exert mechanical traction on the GBM and vascular endothelium through these fiber structures and control capillary pressure and stability, resulting in the appropriate filtration proportion and plasma ultrafiltration rate of the glomeruli (9, 13). Such a connection also provides a corresponding structural basis for the correct screening of macromolecules (14, 15). MCs show structural and functional characteristics of smooth muscle and fibroblasts; thus, they were defined as myofibroblasts (16). Besides, MCs regulate the balance of production and degradation of the mesangial matrix and signaling with other cells to maintain the normal homeostasis of the glomeruli (17–19).

## Roles of MCs in innate immunity

In addition to maintaining glomerular structure and filtration capacity, many studies have demonstrated that MCs can participate in immune responses.

With an evolutionarily conserved defense mechanism, the innate immune system acts mainly by directly disrupting the invading pathogens through phagocytosis and the production of antimicrobial peptides or proteins (20, 21). This relies on recognizing pattern recognition receptors (PRRs) to specific pathogen-associated molecule patterns (PAMPs) (22). MCs express PRRs and participate in innate immune responses. MCs mainly express Toll-like receptors (TLRs) family molecules involved in intrinsic immune regulation. TLRs activate downstream signaling pathways (e.g., interferon regulatory factors (IRF) and nuclear factor kappa-B (NF-κB) pathways) and promote the production of large numbers of adhesion factors, cytokines, and chemokines (CXCLs) (23–25). TLR1-9 mRNA levels are increased in the patients and the MRL/lpr mice as the LN progressed (26). It is shown that certain viral nucleic acids promote LN through nucleic acid-specific TLR (27). MCs express both TLR1-4 and TLR6, especially the highly expressed TLR3 (24, 26). TLR3 signaling contributes to the CXCL1 expression in MCs during the development of inflammatory kidney disease, especially the LN (28). Activation of TLR3 induces MMP-9 in cultured human MCs (HMCs), which could be enhanced by tumor necrosis factor-alpha (TNFα) (29). And, MCs highly express TLR3 to

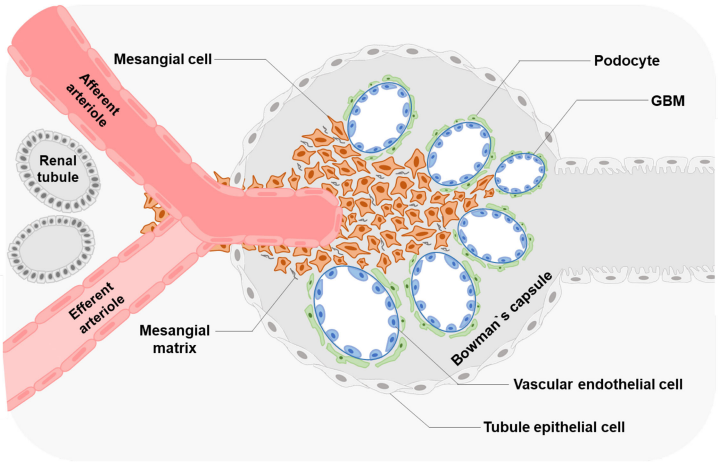


FIGURE 1
Glomerular structure and MCs' location Glomerular MCs and the mesangial matrix form a stalk that holds and organizes the multiple capillary loops together. MCs extend outside of the glomerulus to the stalk containing the afferent and efferent arterioles.

upregulate estrogen receptor alpha (ERα) expression after binding to the ligand, significantly inducing interleukin-6 (IL-6) generation in female LN patients (30). This might explain the predominance of women with lupus. In addition, MCs express NOD-like receptors (NLRs) and are related to NF-κB and transforming growth factor-beta (TGF-β)/Smad signaling pathways (31, 32). MCs also express RIG-I-like receptors (RLRs), which are upregulated upon induction by either interferon (IFN) or double-stranded RNAs (dsRNAs), regulating the generation of cytokines and chemokines (32, 33).

MCs play as non-professional phagocytes. Phagocytosis is not entirely dependent on "professional" phagocytes. There is also a group of "non-professional" phagocytes, such as epithelial cells, endothelial cells, and MCs, exerting phagocytosis function (34, 35). "Non-professional" phagocytes eliminate the deposition of apoptotic cells and matrix components as an essential mechanism for maintaining tissue homeostasis (36, 37). As early as 1962, researchers proposed the presence of phagocytic, resident infiltrating cells in the renal glomeruli (38). Later studies have found that apoptotic MCs were engulfed by neighboring healthy MCs in experimental glomerulonephritis, which contributes to restoring the integrity of glomerular tuft (38). And Itgα8-cytoskeletal interaction facilitated the phagocytosis of MCs (39). After perfusion and enzymatic digestion of the glomeruli, a class of highly adherent phagocytes expressing Fc and C3 receptors was found in the mesangium (40, 41). By injecting the macromolecule dextran, immunoglobulin, and antigen-antibody complexes, it was observed that MCs gradually removed the above substances by electron microscopy (39, 42). MCs perform phagocytosis in both extracellular and intracellular ways. Extracellular decomposition mainly depends on exosomes carrying lysosomal enzymes, and MCs also ingest substances for degradation through endocytosis (40).

MCs are non-professional antigen-presenting cells (APCs). APCs regulate T cells' activation, differentiation, and proliferation by presenting antigens when renal immune responses occur (43). T-cell activation by APCs requires major histocompatibility complex (MHC) and co-stimulatory molecules (43). The MHC gene complex encodes two major classes of molecules, MHC-I, responsible for the endogenous antigen presentation pathway, and MHC-II, involved in the exogenous antigen presentation pathway (42, 44, 45). Co-stimulatory molecules are surface molecules whose ligands transduce co-stimulatory signals essential for activating T and B lymphocytes (46). Many studies have demonstrated that MCs express both MHC-I and MHC-II molecules, like HLA-DP, HLA-DQ, and HLA-DR, for endogenous or exogenous antigen presentation and cross-presentation (47–49). MCs also express co-stimulatory molecules ICAM-1 and CD80 (B7-1) on the surface (50–52). With the stimulation of IFNγ, the expression of HLA-DP, HLA-DQ, HLA-DR, ICAM-1, and CD80 are markedly enhanced in human MCs, and the activated MCs can process antigen *in vitro*, driving the differentiation of CD4 T cells into Th1 effectors (53). IFNγ-activated mouse MCs also activate CD4 T cell differentiation and proliferation through MHC-II presentation *in vivo* and *in vitro* (52, 53).

## Pathological injuries of MCs in LN

SLE is an autoimmune disease with various clinical manifestations, damaging many systems and organs (54). Loss of immune tolerance to endogenous nuclear material leads to the clinical symptoms (55). The progression of renal disease is the commonly used predictive source of morbidity and mortality in SLE patients (56–58). LN is one of the most severe organ manifestations and presents extensive kidney lesions, which is mainly manifested by the expansion of the glomerular mesangium and accumulation of extracellular matrix secreted from MCs.

### Excessive proliferation of MCs in LN

Excessive proliferation of MCs is one of the representative physiological changes in the progression of LN (59, 60). Self-nucleic acids and IgG anti-dsDNA antibodies can cause the abnormal activation of proliferation-related pathways in MCs (Figure 2).

Researchers have found that serum DNA levels correlate with disease activity (61, 62). High values of cell-free DNAs (cDNAs) in patients with SLE were first reported in the 1960s (61). These cDNAs induce MDM2 upregulation, thus negatively modulating both p53 and p21 in human MCs. MDM2 promotes cell cycle change from G0/G1 to the S phase in human MCs (63). However, the mechanisms of how MCs sense DNA or RNA in LN is still unclear, which might involve classic DNA sensors, including TLR9, DAI, AIM2, and the cGAS-STING pathway. Current studies on diabetic nephropathy (DN) have found that TLR9, located in the cell membrane inside, is upregulated in the kidney of experimental mice and the primary mouse MCs treated with high glucose (64). Significant activation of TLR9 is also detected in DN patient-derived MCs, associated with glucose-induced mtDNA damage (65). In the HBV-associated glomerulonephritis (HBV-GN) research, expression of AIM2 was detected by immunohistochemistry in renal biopsies from clinical patients (66). And immunostaining of nephritic kidney sections of autoimmune MRL/lpr mice revealed elevated TLR3 expression in glomerular MCs and recognized poly(I:C) RNA (67).

Anti-double strand DNA (dsDNA) antibodies and pathological IgG are critical pathogenic factors produced by aberrant activated plasma cells in SLE. They could induce the excessive proliferation of MCs. Significant cell proliferation is observed after the soluble IgG treatment in rat MCs (68). Many

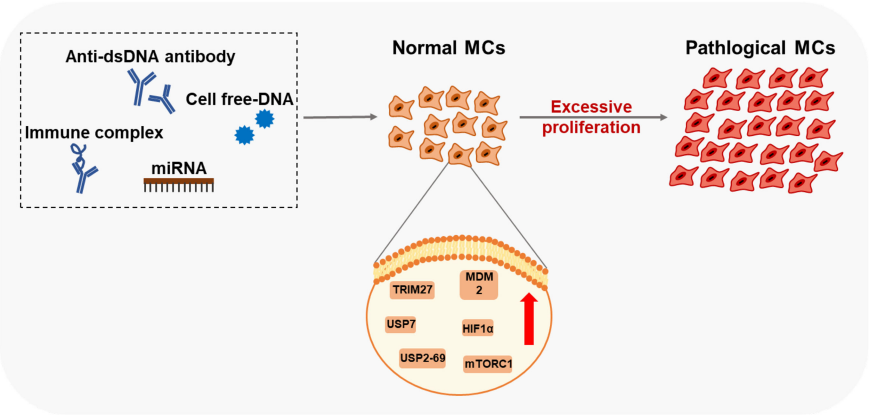


FIGURE 2
Factors and key proteins that regulate MCs proliferation in LN Anti-dsDNA antibody, cell free-DNA, Immune complex, and miRNA affect the proliferation of MCs through multiple signaling pathways. Many proteins of MCs are aberrantly expressed in LN leading to excessive proliferation.

vital proteins related to organismal regulation are aberrantly expressed in the biopsy specimens from patients with LN. Abnormal activation of mTORC1 causes mesangium expansion, and rapamycin treatment suppresses this effect in Foxd1ER(+) TSC1 mice (69). Tripartite motif-containing 27 (TRIM27), a member of the TRIM protein family, has a strong expression in the LN patients ' kidneys, lupus animal models, and human MCs stimulated by LN plasma (60). Downregulation of TRIM27 suppressed the proliferation of mouse MCs in MRL/lpr mice and cultured human MCs by regulating the FoxO1 pathway (60). Hypoxia-inducing factor 1α (HIF1α), highly expressed in LN patients and MRL/lpr mice glomeruli, promotes MC growth under LN progression (70). Deubiquitinases (DUBs) participate in the regulatory networks of plentiful substrates directly implicated in LN progression (71). Ubiquitin-Specific Peptidases7 (USP7) and USP2-69, members of DUBs, are upregulated in LN and related to the proliferation of MCs in MRL/lpr mice and mouse MCs SV40 MES13 cells (71, 72).

IgG anti-dsDNA also drive the expansion of MCs through microRNAs, which are short non-coding RNAs that act as guide molecules in RNA silencing by inducing mRNA degradation or blocking protein translation (73). Research has demonstrated that diverse miRNAs are downregulated in LN induced by anti-dsDNA antibodies and could inhibit MCs' proliferation through multiple signaling pathways, including miR-10a, miR-16, miR-124, miR-133, miR-155, miR-98-5p, miR-146b-5p, and hsa–miR–371–5p (74–81). Further, some miRNAs exert positive regulatory effects on the proliferation of MCs. As such, miR-148a-3p expression is significantly higher in the glomeruli, and overexpression of miR-148a-3p accelerates MMCs' expansion (82).

## Increased matrix production of MCs in LN

Another landmark event in the progression of LN is the ECM expansion in the mesangium, derived from an aberrant increasing matrix generation of MCs. Anti-dsDNA antibodies enhance the synthesis of fibronectin (FN), alpha-smooth muscle actin (α-SMA), and TGF-β in cultured human MCs through PKC activation, thus giving rise to the occurrence of kidney fibrosis (83). Oligonucleosomes (ON) are abundant in the circulation and renal biopsies of patients with LN. Rat and mouse MCs stimulated by ON significantly increase the total matrix protein and collagen synthesis (84). The raised expression of TLR2 is observed in glomeruli of LN patients and MRL/lpr mice. TLR2 facilitates glomerular mesangial matrix deposition by activating the MyD88/NF-κB pathway in LN (85).

Excessive proliferation and increased matrix production of MCs are not the only typical features of LN. Still, they are also observed in many other types of nephropathy, such as DN, IgAN, and HBV-GN. High glucose, the most critical risk factor in DN, can drive MCs' proliferation and secretion of ECM components *via* multiple signal pathways (86–88). IgA immune complexes can induce MC activation and proliferation in IgAN (89, 90). And many viruses have been demonstrated to promote MCs' proliferation, leading to renal lesions. In addition, factors such as hypoxia also contribute to the proliferation of MCs and the subsequent fibrosis in DN (91, 92). This suggests that different and similar mechanisms exist in various kidney diseases. Although these are pathogenic factors in other conditions, we cannot rule out their possible roles in LN.

# Pathologic MCs shape tissue-resident immunity in LN

## Pathologic MCs produce a mass of inflammatory mediators

Many inflammatory mediators have been implicated in the development and progression of LN, including cytokines, chemokines, and glycosaminoglycans (59). Contents of IFN-α, TNFα, IL-6, and hyaluronan (HA) are increased in serum and renal parenchyma of patients and mice with active LN. Some endogenously inflammatory signaling pathways (e.g., NF–κB, MAPK, JNK, and AKT) induce hyperactivity in renal stromal cells and immune cells by LN pathogenic factors. MCs are one of the essential sources of these inflammatory mediators during the progression of LN (Table 1).

Anti-dsDNA antibodies could enhance the inflammation of MCs. They deposit in the glomerular mesangium and bind to MCs surface in both human and murine LN (94, 95). The intracellular inflammatory-related pathways in injured MCs are activated to produce inflammatory mediators induced by pathological anti-dsDNA antibodies (106). Anti-DNA antibodies could also induce hyaluronan synthetase II (HASII) transcription, leading to overexpression of hyaluronan in human MCs (96). Some researchers have reported that anti-dsDNA antibodies isolated from SLE patients caused the activation of the PERK/ER stress pathway, activating NF-κB, a crucial transcription factor in regulating inflammatory processes, leading to the secretion of inflammatory cytokines in HMCs (97, 98). *In vivo* experiments in rats also show that antibodies result in a time- and dose-dependent increase of IL-1β and IL-6 in MCs (97). IL-6, IL-1β, TNFα, MCP-1, and hyaluronan are highly produced in MCs and secreted to the glomeruli. They play crucial roles in the recruitment and retention of lymphocytes at sites of inflammatory renal tissue by binding or inducing chemokines/cytokines synthesis and upregulating the expression of adhesion molecules (96).

Pathological metabolic alterations affect the inflammatory factors production in MCs. Glycosphingolipid (GSL) catabolic pathway is elevated in the kidneys of MRL/lpr mice and human LN patients (102). Neuraminidase (NEU), a key enzyme in the catabolic pathway of GSL, is observed robust activity and expression in LN. High NEU1 activity mediates IL-6 production in the MRL/lpr lupus-prone MCs (102).

In addition to affecting the proliferation and matrix generation, miRNAs also regulate the inflammatory responses of MCs. Many decreased circulating miRNAs might be candidate diagnostic biomarkers for active human LN. MiR-146b, miR-124, and miR-203 attenuate the inflammatory response of MCs by inhibiting the expression levels of TNF receptor-associated factor 6 (TRAF6) in LN (74, 75, 107, 108). MiR-98-5p inhibits the secretion of TNF-α and IL-6 by targeting BACH1 in human MCs (80). Blocking hsa-miR-127-3p could promote the expression of JAK1 and leads to the excessive activation of the IFN-I signaling pathway in LN (109). TLRs activate downstream pathways and stimulate the production of many adhesion factors, cytokines, and chemokines (e.g., TNF-α, IL-12, IL-6) (110). TLR2 upregulation in MCs of LN patients and MRL/lpr mice could also induce inflammatory responses (85).

## Pathologic MCs promote regional immune cell infiltration

MCs could regulate various immune cells *in situ* of LN, but the current understanding of the interactions between MCs and immune cells is still indefinable.

MCs promote the infiltration of macrophages, monocytes, and T cells in the glomerular mesangium through the activation of the NF-κB signaling pathway and the NF-κB-regulated proinflammatory mediators, including IL-6, IL-1β, TNF-α, MCP-1 (111, 112). *De novo* macrophage migration inhibitory factor (MIF) expression is evident in LN MCs examined by *in situ* hybridization and immunohistochemistry staining of biopsies (101). Increased MIF expression is significantly correlated with the reduction of creatinine clearance, immune cells' accumulation, and the severity of histologic lesions (101). In addition to cytokines, some cell surface proteins of MCs can also induce the infiltration of immune cells through cell-cell contacts. CD40L is a transiently expressed T-cell surface molecule interacting with CD40 on target cells (113). The expression of CD40 is markedly upregulated in MCs with LN and promotes T-cell infiltration in the patients' glomeruli biopsies (103, 114). The adhesion molecules ICAM-1 and VCAM-1 are upregulated in the MCs of murine models with LN (104). ICAM-1 and VCAM-1 could act as renal adhesion molecules that bind T cells to MHC-II positive cells, thus promoting antigen recognition and renal injury (52, 105).

## Pathologic MCs regulate the differentiation of immune cells in LN

Aside from promoting the infiltration of immune cells in the glomerular mesangium, MCs are also related to the differentiations of immune cells under pathological states (Figure 3). Resting human MCs constitutively express IL-6 and chemokine ligand 2 (CCL-2), inducing M2 macrophages polarization under a co-culture system (99). In LN, PDGF-BB-stimulated human MCs rather than resting MCs attenuate classical macrophage activation and drive macrophages into M2 type (99). Human MCs also promote B-cell survival by upregulating APRIL and BLyS, essential for B-cell maturation

TABLE 1 Molecule features of MCs in LN.

| ITEM | SLE Patients | Lupus-Prone Mice | Other treatment Related to LN | Other Information |
|---|---|---|---|---|
| CXCL1 | ↑ (protein level) (28) | | ↑ HMCs are treated with poly IC. (protein and mRNA levels) (28) | Regulated by TLR3 signaling (28) |
| MDM2 | ↑ (protein level) (63) | | ↑ HMCs are treated with poly Ic or LN serum. (protein level) (63, 93) | |
| IFI35 | ↑ (mRNA and protein levels) (93) | | ↑ HMCs culture with LN serum. (mRNA and protein levels) (93) | Hypomethylated by MBD2 (93) |
| IFNγR | ↑ (mRNA level) (93) | | ↑ HMCs culture with LN serum. (mRNA and protein levels) (93) | Hypomethylated by MBD2 (93) |
| STAT1 | ↑ (mRNA level) (93) | ↑ (MRL/lpr mice, protein level) (93) | ↑ HMCs culture with LN serum. (mRNA and protein levels) (93) | Hypomethylated by MBD2. Phosphorylation by IFN-α and IFN-γ (93). |
| p53 | | | ↑ HMCs are treated with poly IC. (protein level) (63) | |
| p21 | | | ↑ HMCs are treated with poly IC. (protein level) (63) | |
| mTORC1-S6 kinase | ↑ (LN-II, protein level) (69) | | | |
| TRIM27 | ↑ (LN-III, IV, protein level) (60) | ↑ (MRL/lpr mice, protein level) (60) | | Regulated by FoxO1 pathway (60) |
| HIF1α | ↑ (protein level) (70) | ↑ (MRL/lpr mice, protein level) (70) | | |
| USP7 | ↑ (protein level) (71) | ↑ (MRL/lpr mice, mRNA and protein levels) (71) | | |
| JMJD3 | ↑ (protein level) (71) | ↑ (MRL/lpr mice, protein level) (71) | | USP7 promote the stability of JMJD3 by deubiquitination (71) |
| p-NF-kB p65 | | ↑ (MRL/lpr mice, protein level) (71) | | JMJD3 stabilize NF-kB p65 expression through demethylation (71) |
| USP2-69 | ↑ (LN-IV, protein level) (72) | | ↑ Rat MCs are stimulated with IL-1 and anti-thymocyte serum (ATS). (mRNA and protein levels) (72) | |
| TLR2 | ↑ (protein level) (85) | ↑ (MRL/lpr mice, protein level) (85) | ↑ HMCs culture with LN plasma. (mRNA and protein levels) (85) | |
| Col IV | ↑ (protein level) (85) | ↑ (MRL/lpr mice, protein level) (85) | | |
| Annexin II | ↑ (protein level) (94, 95) | ↑ ( (NZB*NZW)F1/J mice, protein level) (94, 95) | | |
| FN | ↑ (protein level) (83) | ↑ ( (NZB*NZW)F1/J mice, protein level) (83) | ↑ HMCs are stimulated with anti-DNA antibodies. (protein level) (83) | Regulated by PKC (83) |
| HAS II | | | ↑ HMCs are stimulated with anti-DNA antibodies isolated from LN patients. (mRNA level) (96) | |
| ER stress pathway | | | ↑ HMCs are stimulated with anti-DNA antibodies isolated from LN patients. (protein level) (97, 98) | |
| TGF-β | ↑ (protein level) (83) | ↑ ( (NZB*NZW)F1/J mice, protein level) (83) | ↑ HMCs are stimulated with anti-DNA antibodies. (protein level) (83) | Regulated by PKC (83) |
| IL-1β | | | ↑ HMCs are stimulated with anti-DNA antibodies isolated from LN patients or PDGF-BB. (mRNA and protein levels) (97, 99) | |
| TNFα | | | ↑ HMCs are stimulated with anti-DNA antibodies isolated from LN patients. (mRNA and protein levels) (97) | |
| MCP-1 | | | ↑ HMCs are stimulated with anti-DNA antibodies isolated from LN patients. (mRNA and protein levels) (97) | |
| CCL-2 | | | ↑ HMCs are stimulated with PDGF-BB (mRNA and protein levels) (99) | |

*(Continued)*

TABLE 1 Continued

| ITEM | SLE Patients | Lupus-Prone Mice | Other treatment Related to LN | Other Information |
|---|---|---|---|---|
| IL-6 | | | ↑ HMCs are stimulated with PDGF-BB (mRNA and protein levels) (99) | |
| APRIL | ↑ (LN-III, IV, mRNA and protein levels) (100) | | | |
| BLyS | ↑ (LN-III, IV, mRNA and protein levels) (100) | | | |
| MIF | ↑ (mRNA and protein levels) (101) | | | |
| NEU1 | | ↑ (MRL/lpr mice and NZM2410 mice, protein level) (102) | ↑ Primary MRL/*lpr* lupus-prone MCs are stimulated with HA-IgG (mRNA and protein levels) (102) | |
| CD40 | ↑ (markly regulated in LN-III, IV, protein level) (103) | | | |
| ICAM-1 | ↑ (in all LN patients, protein level) (104) | | | |
| VCAM-1 | ↑ (markly regulated in LN-III, M compared to LN- II protein level) (104) | ↑ (MRL/lpr mice, protein level) (105) | | |

and activation of plasma cells, facilitating human autoimmune disease progression (100).

## Renal-resident immunity drives a second wave of MC damage in LN

MCs regulate *in situ* immunity through paracrine inflammatory mediators or cell-cell contacts. Meanwhile, many cytokines and autoantibodies produced by immune cells further aggravate MCs' damage in LN (Figure 4).

Cytokines, such as PDGF, IL-6, IL-1, and IFN-γ, are accumulated in the kidneys of the mice models and patient biopsies under LN progression (Table 1). Several LN-associated cytokines have been shown to contribute to MC proliferation. B cell-activating factor (BAFF), a member of the TNF family, promotes the expansion of human MCs, which is mediated *via* the BAFF-receptor (BAFF-R) (115). CXCL13 accelerates the proliferation of human MCs by triggering extracellular signal-regulated kinase (ERK) tyrosine phosphorylation (116). Contents of IFN-γ and HMGB1 in serum are raised in patients or experimental animal models with LN (93, 117). It has been observed that lots of the IFN-γ/STAT1 pathway-regulated genes are hypomethylated and related to the pathogenesis of LN (118). IFN-induced 35-kDa protein (IFI35) is responsible for these changes in LN (93). IFI35 is regulated by methyl-CpG binding domain protein 2 (MBD2), which could enhance the proliferation of human MCs (93). The researchers have found that HMGB1 expression is specifically increased in lupus patients compared with other renal disease patients (119). HMGB1 promotes the cell cycle transition from G1 to the S phase by the cyclin D1/CDK4/p16 pathway in mouse MCs (117, 120). Furthermore, HMGB1 could mediate mouse MCs' proliferation through the PTEN/PI3K/Akt/NF-κB signaling pathway and exhibit a synergistic pro-inflammatory effect in MRL/lpr mice (119, 121). Urinary samples of patients with LN and MRL-1pr/1pr mice contain significant IL-6 activity, and the high level of IL-6 is associated with MC proliferation (122, 123). MRL/lpr mice exert enhanced proliferating cell nuclear antigen (PCNA) in MCs mediated by PI3K/Akt/periostin signaling pathway induced with PDGF (124). Tumor necrosis factor-related weak inducer of apoptosis (TWEAK), a member of the TNF-ligand superfamily, is elevated in the blood and urine of patients with LN (125), enhancing NF-κB transcriptional activity and promoting human MC proliferation (125).

## The contribution of MC-related therapeutics to clinical treatment

To achieve rapid remission of active disease, control the progression of chronic kidney disease (CKD), restrain renal flares, alleviate morbidity and mortality, minimize treatment-related toxicity, and preserve fertility, researchers have developed a variety of drugs and therapeutic regimens for LN over the years (126). The present treatment options mainly involve steroids, immunosuppressants, and adjuvant therapies. First-line treatments for LN include steroids, cyclophosphamide (CTX), azathioprine, and mycophenolate mofetil (MMF) (127). Although these medications do not specifically target MCs, inhibition of MCs proliferation is one of their pharmacological effects in controlling the progression of kidney deterioration.

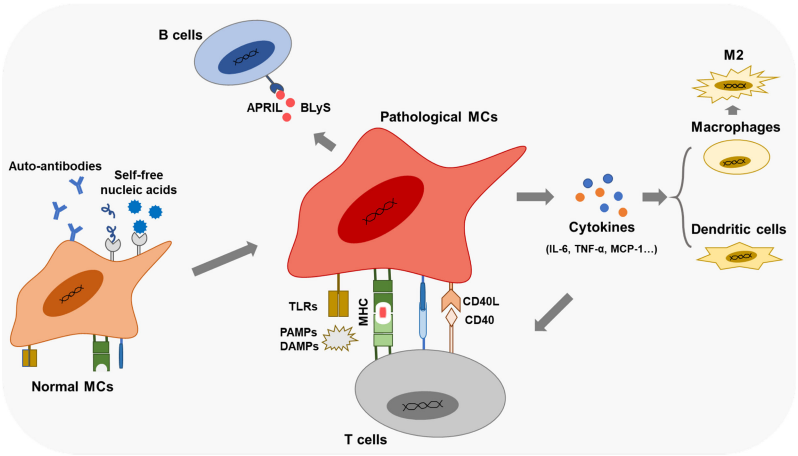


FIGURE 3
Immune functions of the pathological MCs Pathological MCs with aberrant phagocytic function exert robust expressions of APCs markers (TLRs, MHC, co- stimulators). They secret inflammatory cytokines and chemokines, participate in the renal inflammation effect, and regulate immune cells' infiltration and differentiation by cytokines and cell-cell contacts.

The mechanisms of how CTX and MMF inhibit the proliferation of MCs have been validated. CTX arrests the cell cycle in the G1 phase through cell cycle regulators in human MCs (128). MMF is one of the immunosuppressive agents, blocking purine biosynthesis and thereby damaging cell proliferation (129). Besides, recent research has demonstrated that the combination of MMF and tacrolimus (TAC) at the half dose is more therapeutic than monotherapy in inhibiting MC proliferation *in vitro* and *in vivo* (130). TAC is a valid treatment option for SLE patients with renal involvement (131). TAC targets the Smad2 signaling pathway, and MMF targets the p38 signaling pathway, both of which could inhibit MC proliferation (130). The combination of TAC and MMF could significantly benefit patients with LN and shows no severe adverse effects.

Several non-SLE classic drugs developed to attenuate the condition in patients with LN show effective inhibition against MC lesions. The researchers have conducted extensive *in vitro* and *in vivo* studies to verify these medicines' curative effects and mechanisms. Trifluoperazine (TFP), a calmodulin inhibitor and

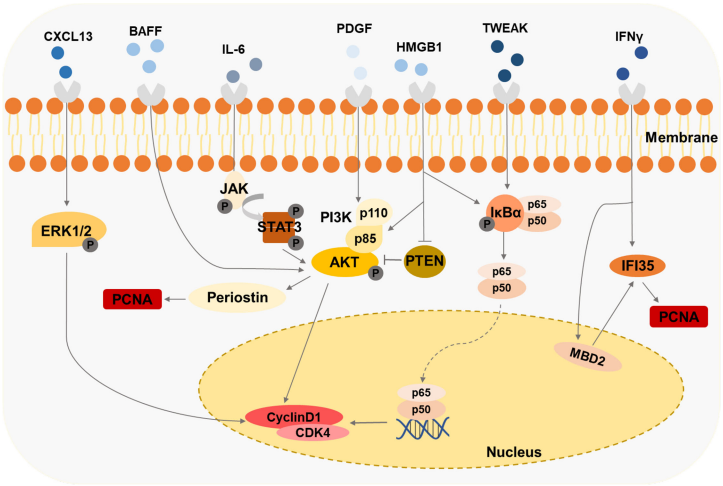


FIGURE 4
Immune cells-derived cytokines drive the second damage to MCs Cytokines like HMGB1, IFNγ, and BAFF induce the proliferation of MCs through various signaling pathways.

a classic anxiolytic and antipsychotic drug (132), inhibit human MC proliferation in a dose– and time–dependent manner. By downregulating the Bcl–2 expression and upregulating the Bax expression, TFP promotes cell apoptosis (133). And TFP targets also inhibit the activation of the PI3K/AKT signaling pathway (133, 134). Thus, TFP treatment significantly reduced blood urea nitrogen and serum creatinine levels in lupus mice without apparent side effects (134). Mizoribine (MZR) is a selective inhibitor of the inosine monophosphate dehydrogenase and a key enzyme in the *de novo* pathway of guanine nucleotides (135). MZR downregulates MCP-1 at both mRNA and protein levels in human MCs treated with poly (I:C), which is associated with the pathogenesis of LN (135). ALW (ALWPPNLHAWVP), a peptide with 12 amino acids, inhibits the binding of polyclonal anti-dsDNA antibodies to MCs. ALW attenuates LN lesions, including MC proliferation and inflammatory infiltration in renal tissues of MRL/lpr mice (136). Quercetin is a polyphenol extracted from plants and has many biological activities (137). Quercetin treatment could reduce the expression of pentraxin3 (PTX3) and inhibit the excessive proliferation of human MCs by blocking the NF-κB signaling pathway (138).

## Summary

MCs are stromal cells that are fatal for renal glomerular homeostasis and the glomerular responses to injury. In LN, the aberrant self-nucleic acids, auto-antibodies, and ICs lead to the first wave of pathogenic damage to MCs. The pathologic MCs proliferate and secrete excess ECM, resulting in kidney dysfunction. In the glomerular microenvironment, MCs not only commit self-injury but also play an essential role in regulating the formation and function of tertiary lymphoid organs in tissues, promoting the abnormal physiological processes of the immune cells by generating massive inflammatory mediators and facilitating immune infiltrations. Such renal-resident immune responses drive the second wave of pathogenic damage to MCs, accelerating kidney dysfunction (Figure 5). This might be a universal immunopathological paradigm underpinning the immune-mediated organ damage in human diseases.

Although MCs' intra-regional immune-related activity has been demonstrated (Table 1), precise mechanisms underlying how MCs regulate immune cells in the glomerular region are largely unknown. The immune effects of immune cells activated or amplified by MCs can also affect the morphology and functions of glomerular stromal cells, causing more significant damage to the glomeruli in which MC acts as a critical hub. Precise mechanisms underpinning how MCs maintain homeostasis and how to interfere with pathological MC-immune cell interactions to benefit clinical patients are far less clear. More significant insights into the immunological effects of MCs and their roles in tissue-resident immunity could uncover new treatment strategies to target MCs, revolutionizing the treatment of LN.

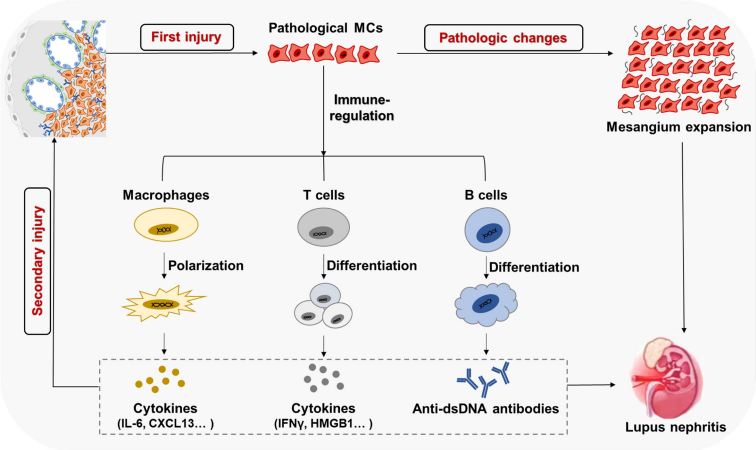


FIGURE 5
MCs with immune cells form a positive feedback loop to amplify kidney parenchyma in LN ICs' deposition in the mesangium results in the first wave of pathological damage and activation of MCs, causing excessive proliferation and ECM secretion. The activated and pathological MCs participate in local immune regulation, inducing immune cell infiltration and abnormal differentiation. Such renal-resident immune responses increases glomerular local inflammatory mediators and autoantibodies, which drive the second wave of pathological damage to MCs and other stroma cells in the kidney, eventually causing the progress of LN.

## Author contributions

ZW and ML lead the conception and design of the manuscript. ML, LZ, YW, and WH collected and interpreted the relevant literature. ML and LZ drafted the manuscript, while ZW and CW made critical revisions with input from all authors. All authors contributed to the article and approved the submitted version.

## Funding

This work was supported by grants from the National Natural Science Foundation of China (82071826, 82271841), the National Natural Science Foundation of Jiangsu Province (BK20211542, BK20201407), Jiangsu Specially-Appointed Professor Program, Suzhou Municipal Science and Technology Bureau (ZXL2022460), Major Project of Natural Science Research in Jiangsu Higher Education Institutions (22KJA310005), and Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD). The sponsors were not involved in study design, data collection and analysis, manuscript preparation, and the decision to submit the manuscript for publication.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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