Immune podocytes in the immune microenvironment of lupus nephritis (Review)

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Abstract. Systemic lupus erythematosus (SLE) is a systemic autoimmune disorder caused by the loss of tolerance to endogenous nuclear antigens such as double-stranded DNA, leading to the proliferation of T cells and subsequent activation of B cells, which results in serious organ damage and life-threatening complications such as lupus nephritis. Lupus nephritis (LN) develops as a frequent complication of SLE, accounting for >60% of SLE cases, and is characterized by proteinuria and heterogeneous histopathological findings. Glomerular injury serves a role in proteinuria as podocyte damage is the leading contributor. Numerous studies have reported that podocytes are involved in the immune response that promotes LN progression. In LN, immune complex deposition stimulates dendritic cells to secrete inflammatory cytokines that activate T cells and B cells. B cells secrete autoantibodies that attack and damage the renal podocytes, leading to renal podocyte injury. The injured podocytes trigger inflammatory cells through the expression of toll-like receptors and trigger T cells through major histocompatibility complexes and CD86, thereby participating in the local immune response and the exacerbation of podocyte injury. Based on the existing literature, the present review summarizes the research progress of podocytes in LN under the local immune microenvironment of the kidney, explores the mechanism of podocyte injury under the immune microenvironment, and evaluates podocytes as a potential therapeutic target for LN.

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Contents

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by a mild rash, joint pain and multi-organ damage. The global SLE incidence and prevalence are estimated to be 5.14 (1.4 to 15.13) per 100,000 person-years and 43.7 (15.87 to 108.92) per 100,000 individuals (1). The hallmark of SLE is the defective clearance of dead cells by the immune system and the loss of tolerance to endogenous antigens such as double-stranded (ds)DNA, resulting in the abnormal activation of the immune system. This activation leads to immune-mediated attacks on organs and tissues, including lung, gut and kidney involvement (2). In particular, the kidneys are affected, leading to the development of lupus nephritis (LN) as the most severe manifestation of SLE and the common cause of morbidity and mortality in patients with SLE. In patients with SLE, >60% suffer from LN, and 40% of them progress to end-stage renal disease (ESRD) (3,4), which endangers the lives and health of the individuals, with the exact incidence contingent upon ethnicity and sex (5). The immune system contributes to the development of SLE. The two main cell types in the adaptive immune system, B cells and T cells, are both indispensable for the development of LN. B cells are pathogenic in SLE through the autoantibodies (such as

anti-dsDNA antibodies and anti-nucleosome antibodies) and cytokines they produce. T cells drive both the systemic and intra-renal activation of B cells (6). In addition, genes for SLE also cause LN. Renal aggression during SLE is triggered by genes that undermine immune tolerance and stimulate autoantibody production. These genes may collaborate with other genetic factors to amplify innate immune signaling and type α interferon (IFN-α) production, consequently leading to the recruitment of leucocytes, inflammatory mediators and autoantibodies into end organs, notably the kidneys (7). Currently, high-doses of hormones (glucocorticosteroid) combined with immunosuppressants (methotrexate) are first line therapeutics for LN treatment. Short-term complete renal response rates are only 10-40% at 12 months, long-term outcomes have not improved further, and as many as 30% of LN patients will still progress to ESRD (8,9).

Podocyte injury is involved in the occurrence and development of LN, a disease that is associated with the progressive loss of renal function and various renal pathological features, including mesangial cell proliferation and subendothelial immune complexes. Podocytes are terminal epithelial cells that protrude into the glomerular urinary space and constitute an important component of the glomerular filtration barrier. Immune complex deposition in the renal tissues activates the complement system and thereby contributes to the failure in the efficient clearance of cellular fragments, triggering both the innate and adaptive immune systems. The production of cytokines such as IFN-α stimulates the antigen presentation and overactivation of T and B cells (7). Ultimately, additional inflammatory cytokines and chemokines promote the recruitment of inflammatory cells to the kidney and cause podocyte injury in the glomerulus (10). Numerous studies have reported the involvement of podocyte injury in LN (11-13) and have suggested that podocytes can serve as biomarkers of LN activity (14). A new concept called 'lupus podocytopathy' has been proposed (15), which refers to patients with LN with normal glomeruli but a diffuse disappearance of foot processes and podocyte damage. However, podocyte injury in patients with LN with normal glomeruli is often overlooked in clinical practice, which delays timely treatment and accelerates the deterioration of renal function. Therefore, investigating the role of podocyte injury in LN is warranted.

The immune microenvironment is considered as the environment of the local immune response. It is composed of diverse populations including infiltrating immune cells, immune molecules and humoral components. Immune complex deposition, local complement activation, along with immune cell recruitment and local intrarenal cytokine signaling account for glomerular injury in the LN immune microenvironment (10). Renal immune cells accumulate in the kidneys of the patients with LN, which involves the formation of tertiary lymphoid structures (TLS) (16). The TLS consists of immune cells, cytokines and resident renal cells in LN, and the activation of immune cells triggers a transient aggravation of resident cell injury and even the production of autoantibodies within the kidneys, exacerbating disease progression (17).

LN develops from a loss of immune balance to ubiquitous autoantigens, which is a result of inflammation and immune responses. Although the immunomolecules and immune cells in the renal immune microenvironment have important roles, the underlying mechanisms of the immune responses in the podocyte injury of LN remain unclear. The present review aimed to summarize the current understanding of the immune microenvironment of podocytes in LN, provide an update on their interaction mechanisms and offer the rationale for the podocytes as novel therapeutic targets in the treatment of LN.

2. Pathogenesis of LN

LN is the most common complication of SLE, and proteinuria and hematuria are the primary clinical manifestations. The salient features of LN are associated with the deposition of immune complexes, which cause an inflammatory and immune response in the kidney (18). *In vivo* apoptosis or secondary necrosis (19) is responsible for the chromatin fragment exposure. The exposed DNA or nucleosomes bind with corresponding autoantibodies to form immune complexes and deposit onto the glomerular basement membrane. Concurrently, after associating with immune complexes in the glomeruli, nucleosomes within necrotic intrinsic glomeruli cells form *in situ* immune complexes containing both DNA and nucleosomes (20).

The nucleic acid components of the immune complexes collectively stimulate intrarenal inflammation by binding to toll-like receptors (TLRs) and Fc receptors (FcRs) or by activating immune responses through the complement cascade. Additionally, the ligation of TLRs induces the maturation of plasmacytoid dendritic cells (pDCs) and facilitates the secretion of proinflammatory cytokines and chemokines including interferon (IFN)-α (21,22). Secreted IFN-α promotes the activation of antigen-presenting dendritic cells (DCs), thereby promoting the differentiation of self-reactive B cells to plasma cells and enhancing the production of memory T cells, which form germinal center structures (23).

B-cell activating factor (BAFF) emerges as an inducer of B cell proliferation, differentiation and maturation through the CD40 ligand (CD40L) and CD28, on the surface of T cells migrating into the glomeruli, binding with CD40 and B7 on B cells, respectively (17). Subsequently, the autoantibodies produced bind to autoantigens and deposit *in situ* in the kidney. In addition to secreting antibodies, activated B cells, as a type of antigen-presenting cell (24), promotes the activation of pathogenic T cells to secrete proinflammatory cytokines such as IL-6 and TNF-α, and facilitate the recruitment of macrophages and DCs into the glomerulus and the tubulointerstitium (25). Immune cells also undergo intrarenal proliferation and activation by binding to the FcRs of immune complexes. Activated neutrophils and macrophages secrete reactive oxygen species and proteases, which directly damage the kidneys (26). In addition, immune complexes also activate the complement pathway to form membrane attack complexes, releasing anaphylatoxins to promote inflammatory reactions and accelerate the progression of LN (27) (Fig. 1).

3. Basic structure and function of podocytes

The podocyte, a terminally and highly differentiated epithelial cell located in the urinary space, consists of a foot process and an apical surface domain. Given that podocytes act as

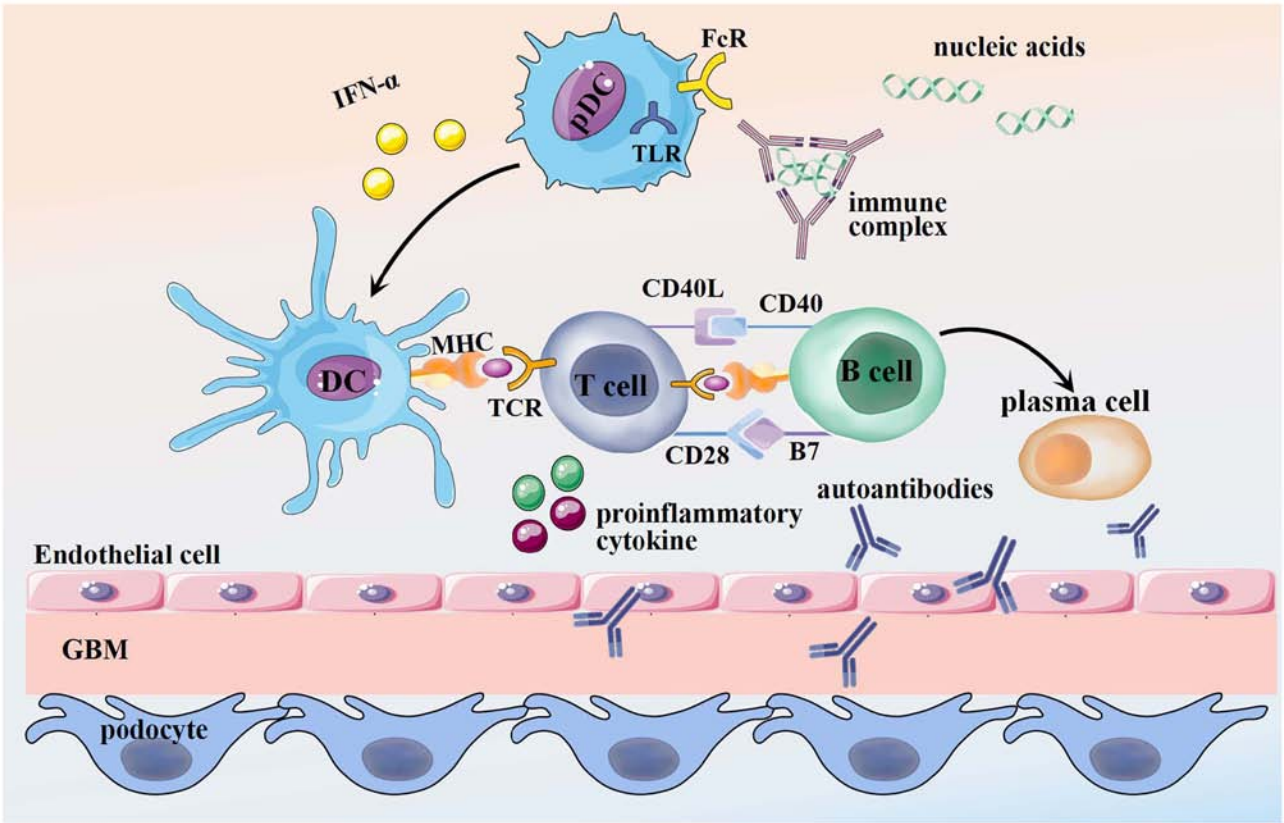

Figure 1. Pathogenesis of LN. Immune complexes, formed by the combination of autoantigens and autoantibodies, are deposited into the kidney. These immune complexes through FcR and TLR stimulate pDCs to secrete inflammatory cytokines (such as IFN-α). Inflammatory cytokines stimulate DC activation, inducing DCs to present antigens to T cells, thereby activating T cells and subsequently triggering B cell activation through CD40L and CD28 binding with CD40 and B7 respectively. B cells infiltrate the kidney in LN to secrete autoantibodies that attack and damage the renal intrinsic cells such as podocytes. FcR, Fc receptor; IFN, interferon; TLR, toll-like receptors; DC, dendritic cell; pDC, plasmacytoid DC; MHC, major histocompatibility complexes; TCR, T cell receptor; GBM, glomerular basement membrane; CD40L, CD40 ligand; LN, lupus nephritis.

essential components of the glomerular filtration barrier, the apical surface domain carries a negative charge and restricts the passage of negatively charged proteins (28). Foot processes attach to the glomerular basement membrane through integrins, syndecans, dystroglycan and other adhesion molecules (28). During podocyte development, a number of large extensions are formed by the epithelial cells, therefore, primary foot processes split into secondary and tertiary processes, which are abundant in microtubule structures (29). The foot processes are primarily composed of actin, which constitutes the cellular cytoskeleton of the podocyte. The function of actin is to connect the apical and basal membrane domains, as well as the slit diaphragm. The parallel contractile actin bundles are controlled to regulate the permeability of the filtration barrier (30). Destruction of podocyte actin leads to podocyte injury, disappearance of foot process fusion, damage to the filtration barrier and to proteinuria. Adjacent foot processes interdigitate with each other, forming slit diaphragms that anchor to the glomerular basement membrane. Nephrin, podocin, CD2-associated protein (CD2AP) and other molecules compose the slit diaphragm, participating in intracellular signaling and the formation and maintenance of the filtration barrier (Fig. 2).

Nephrin, a member of the immunoglobulin superfamily, interacts with the actin cytoskeleton through Nck adapter proteins and maintains the integrity of the podocyte structure and the filtration barrier (29). Nephrin affects the assembly of actin polymers in cell membranes. Decreased levels of nephrin leads to abnormal tertiary podocytes, loss of normal polarity and abnormal intercellular junctions, as a result of proteinuria. Neph1 is another transmembrane protein located near to nephrin in the cell membrane (31). Neph1, a major regulator of actin dynamics, is indispensable in maintaining normal slit diaphragm function. The phosphorylated nephrin-Neph1 complexes can lead to the reassembly of actin complexes, exerting irreversible effects on podocyte filtration function (32). Podocin is a membrane-associated protein that is crucial for signal transduction of the nephrin-Neph1 complex. The reduction in nephrin level caused by podocin mutations will alter the signaling of the nephrin-Nephl complex and result in an impaired podocyte slit diaphragm (33). Podocin also regulates cellular cytoskeletal dynamics through the activity of transient receptor potential cation channel subfamily C member 6 (TRPC6). TRPC6 is a non-selective, calcium-permeable cation channel in the plasma membrane of podocytes, which stabilizes the actin cytoskeleton of podocytes to sense changes in pressure, fluid flow or filtration rate (34). CD2AP is a cytoplasmic protein that interacts with nephrin and podocin and also takes part in the actin filament assembly in the slit diaphragm of podocytes through cellular signal transduction (35). The downregulation of these slit diaphragm proteins can lead to

Table I. Classification of lupus nephritis and the condition of the podocytes after damage.

Type	Disease name	Pathological manifestations	Podocyte condition after damage
Class I	Minimal mesangial lupus nephritis	Mesangial immune complexes	Unknown
Class II	Mesangial proliferative lupus nephritis	Mesangial immune complexes and a small number of subepithelial or subendothelial complexes	Extensive podocyte foot process effacement
Class III	Focal lupus nephritis	Subendothelial immune complexes	Extensive podocyte foot process effacement
Class IV	Diffuse lupus nephritis	Subendothelial immune complexes	Podocyte foot process effacement
Class V	Membranous lupus nephritis	Subepithelial immune complexes	Marked disappearance of podocytes
Class VI	Advanced sclerotic lupus nephritis	Glomerulosclerosis in ≥90% of the glomeruli	Disappearance of podocytes

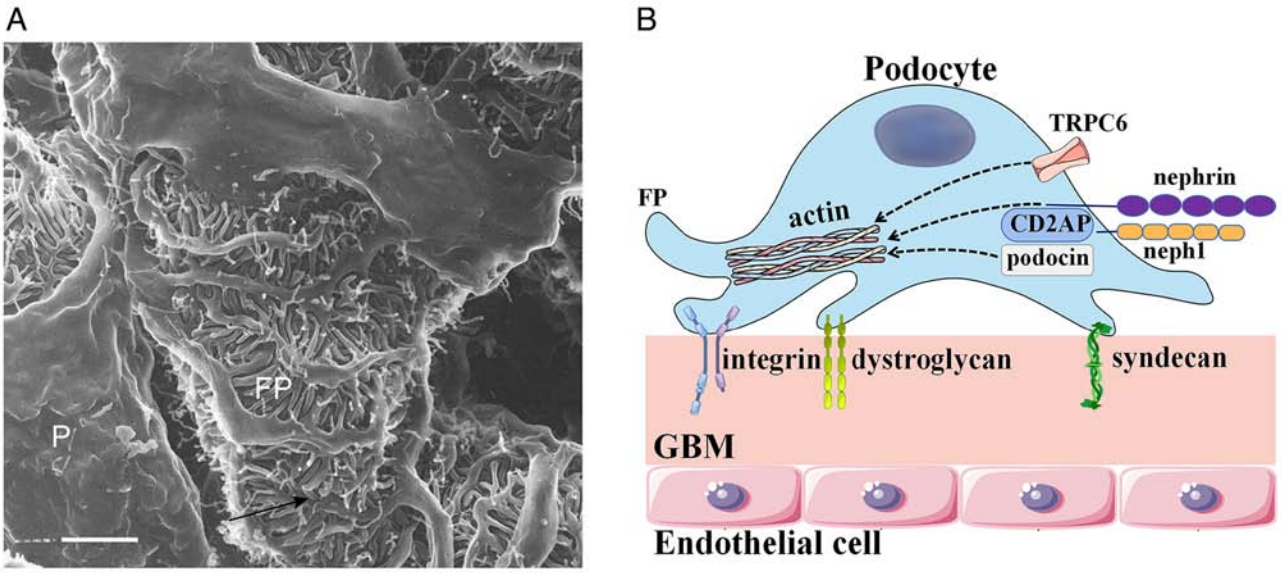

Figure 2. Podocyte basic structure. (A) Helium ion microscopy image of the glomerular podocyte structure reveals the podocytes and FP (arrow) in detail (101). (B) A schematic illustration of the basic structure of the podocyte indicates the structure and important proteins of the podocyte. P, podocyte; FP, foot process; GBM, glomerular basement membrane; TRPC6, transient receptor potential cation channel subfamily C member 6; CD2AP, CD2-associated protein.

the structural and functional damage of podocytes and the production of proteinuria.

4. Podocytes in the immune system

The occurrence and progression of LN involves multiple pathways, including abnormal cell death, autoantibody production, immune complex deposition, complement activation and the increased activation of immune cells (for example, T and B cells). Immune complex deposition predominates in the development of LN, and the majority of LN classifications by the International Society of Nephrology and the Renal Pathology Society involve immune complex deposition (Table I). Additionally, foot process fusion and podocyte injury have been observed in different classifications of LN (36). The deposition of immune complexes in the kidneys takes place by various mechanisms and activates complement components, inducing damage to podocytes through both the innate and adaptive immune responses. Furthermore, podocytes express immunomolecules and participate in immune responses (37) (Fig. 3).

Podocytes in the innate immunity

Podocytes interact with the complement system. Multiple immune pathways engage in the pathogenesis of LN. The complement system serves a positive role in maintaining tolerance against LN for the efficient clearance of cellular fragments. Increasing evidence suggests that complement can mediate podocyte injury (38-40). In membranous nephropathy, complement mediates podocyte injury by inducing cell scorch death through mitochondrial dysfunction (40). When the formation of immune complexes exceeds clearance pathways, complement components C1q, C5a and C5b-9 are released and deposited in the kidney. Subiytic C5b-9 stimulates the podocytes to release cytokines, proteases and oxidants. It can also induce DNA damage, leading to restricted podocyte proliferation (41). In LN, activated intrinsic renal cells can also promote the release

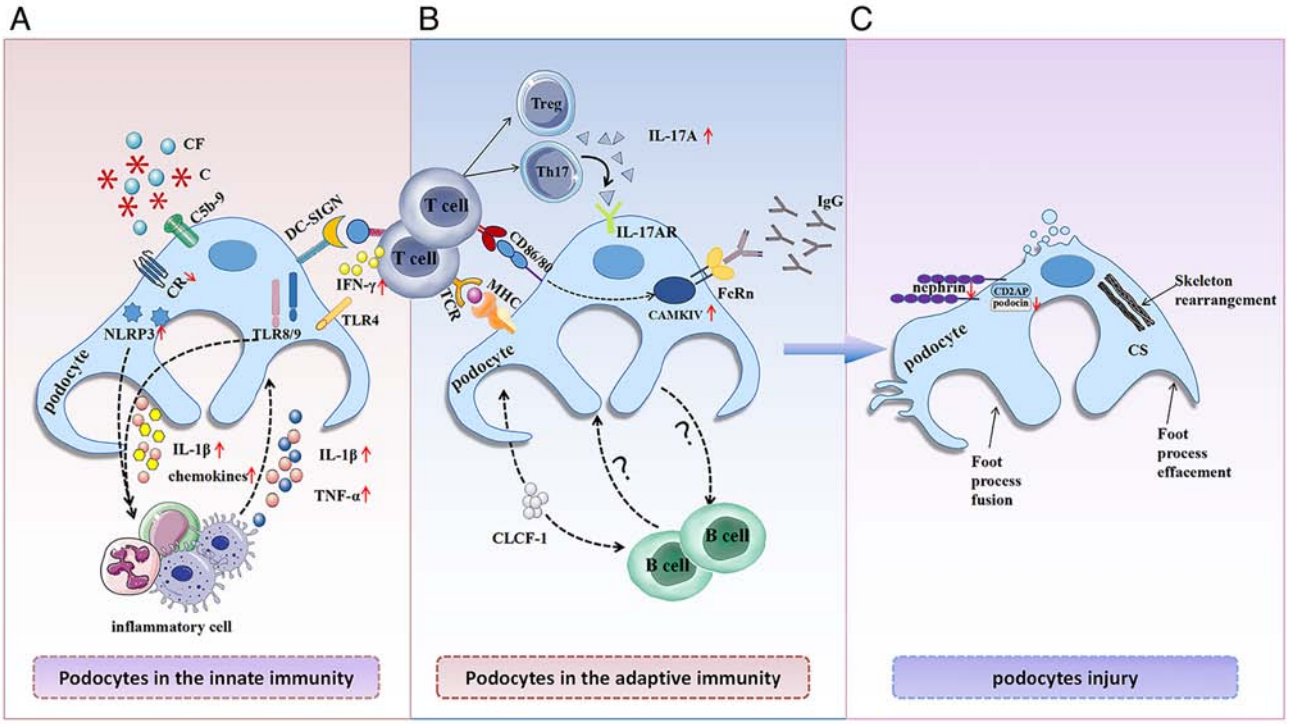

Figure 3. Immune microenvironment of lupus nephritis podocyte injury. In the immunity microenvironment, (A) innate immune components and (B) adaptive immune components stimulate (C) podocyte injury, and the damaged podocytes can interact as immune cells with inflammatory cells (such as macrophages, neutrophils and monocytes) and T cells; the specific role of podocytes with B cells is unclear. C, complement; CF, complement factor; CR, complement receptor; TLR, toll-like receptor; DC-SIGN, dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin; NLRP3, NOD-like receptor thermal protein domain associated protein 3; TNF-α, tumor necrosis factor-α; Treg, regulatory T cell; Th17, $CD4^+$ T helper-17 cell; IFN, interferon; IL-17AR, IL-17A receptor; MHC, major histocompatibility complexes; TCR, T cell receptor; FcRn, neonatal Fc receptor; CAMKIV, Ca^{2+}/calmodulin-dependent protein kinase IV; CLCF-1, cardiotrophin-like cytokine factor 1; CS, cytoskeletal; CD2AP, CD2-associated protein.

of proinflammatory mediators (IL-1β), and express multiple complement components.

Complement receptor 1 (CR1), which is exclusively expressed on podocytes, is reduced in severe glomerular lesions (42,43). Reduced expression levels of CR1 are considered to result from decreased synthesis due to podocyte injury rather than excessive depletion. The decrease in CR1 synthesis increases the sensitivity of podocytes to complement attack, further exacerbating podocyte injury (44). In Murphy Roths Large/lymphoproliferative (MRL/lpr) lupus mice, complement factor H (CFH) deficiency leads to immune complex deposition in the subendothelial and subepithelial regions of the kidney, disappearance of podocyte foot processes, and accelerated progression of LN (45). Podocytes were revealed as the targets and sources of kidney injury due to their production of complement components. Therefore, complement pathway inhibition has been considered as a potential treatment strategy for LN in clinical trials (46,47).

Podocytes interact with the TLRs. TLRs are expressed in innate immune cells (such as monocytes, macrophages and dendritic cells), which recognize pathogen-associated molecular patterns (PAMPs) and can also be activated by endogenous ligands. Studies have revealed that TLRs are expressed in mouse glomeruli and perform different physiological functions (48,49). TLR4 upregulated in podocytes in mice with membranoproliferative glomerulonephritis (MPGN) can destroy the kidney by directly releasing the chemokines, which may promote the recruitment of inflammatory cells and exacerbate glomerular injury (37).

TLR8 and TLR9 are overexpressed in BXSB/Yaa (a genetic mutation located on the Y chromosome, namely, Y-linked autoimmune acceleration) SLE mice models (49). TLR8 is mainly located in podocytes and its expression level is negatively correlated with nephrin expression and positively correlated with proteinuria levels in glomerulonephritis, suggesting that excessive levels of TLR8 are associated with podocyte injury progression (50). Therefore, it is important to monitor the changes of the TLR8 mRNA levels in the urine of patients, which reflects the podocyte injury status. In human LN pDCs recognize single-stranded RNA, 5'-C-phosphate-G-3' DNA from bacteria and viruses as well as altered eukaryotic nucleic acids via TLR9 (51), which induces the release of type I IFNs and promotes local and systemic immune responses via increased expression levels of costimulatory molecules (52). TLR9 coexists with injury podocyte proteins, and its expression is associated with podocyte injury and the development of MPGN. TLR9 is only expressed in damaged podocytes during active LN while it is not detected in healthy human kidneys. This expression may be associated with increased levels of dsDNA antibodies and may be involved in the process of podocyte injury in LN (53,54).

In summary, TLRs can combine podocytes with the innate immunity, induce podocyte injury and mediate LN. Future research could focus on the role of TLRs in LN podocyte injury in order to inhibit the TLR-induced podocyte injury and prevent the progression of LN.

Podocytes interact with the innate immune cells. Macrophages are antigen-presenting cells that have the capacity to process and present antigens to T cells. Cytokines, such as TNF-α and IL-1β, produced by activated macrophages can directly inhibit the expression of the podocyte-specific protein nephrin, leading to podocyte injury and the induction of glomerulonephritis and proteinuria (55). The polarization of macrophages from a proinflammatory phenotype to an anti-inflammatory phenotype can prevent podocyte injury (55,56). Sung and Fu (57) revealed that infiltrating macrophages in the glomerulus can activate T cells and interact with podocytes through cytokines. Subsequently, the injured podocytes and mesangial cells produce the inflammatory cytokines IL-1β and IL-6, leading to an upregulation of adhesion molecules and chemokines from podocytes and thereby promoting the recruitment of macrophages to the glomerulus (58). After migrating to the glomerulus, macrophages are stimulated by immune complexes, complement and cytokines in the local glomerular environment to produce TNF-α and induce podocyte injury. This process represents a cascade amplification reaction that ultimately leads to severe glomerular damage in LN. Thus, inhibiting the process of macrophage-induced podocyte injury is necessary to prevent the progression of LN.

Podocytes interact with innate immune molecules. Nucleotide oligomerization domain (NOD)-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome is a multimeric protein that is associated with the secretion of inflammatory factors such as IL-1β (59). Previous studies have revealed that patients and mice with LN demonstrate NLRP3 activation in podocytes, which induces the secretion of IL-1β and inhibits the expression of the podocyte-specific protein nephrin, thereby disrupting the integrity of the podocyte filtration barrier, leading to proteinuria (60,61). Thus, inhibiting NLRP3 has been demonstrated to prevent the loss of foot processes in podocytes and prevent renal tissue damage, thereby reducing proteinuria (61).

DC-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN) is an innate immune molecule with immune recognition functions that can be expressed on podocytes in LN. When podocytes are exposed *in vitro* to serum from mice with LN, the expression levels of DC-SIGN are upregulated, which promotes T cell proliferation and increases secretion of IFN-γ from $CD4^+$ T cells. Therefore, it seems that DC-SIGN-expressing podocytes may share similar functions with DCs, stimulating T cell proliferation and exerting corresponding effects (62). In summary, the interaction between podocyte injury and the local innate immune responses in the kidney are both involved in the progression of LN.

Podocytes in the adaptive immunity

Podocytes interact with autoantibodies. In LN, IgG-based autoantibodies bind to antigens to form immune complexes that deposit in the kidneys, subsequently causing glomerular injury and proteinuria. Simultaneously, rearrangement of cytoskeletal components in podocytes induced by IgG reduces the expression levels of podocyte proteins (nephrin and synaptopodin) with structural podocyte damage in patients with LN. As the Fc receptor (FcR) is overexpressed in LN podocytes, IgG bound with FcR is endocytosed by the podocytes (63). Furthermore, endocytosed IgG upregulates Ca^{2+}/calmodulin-dependent kinase IV in podocytes, which inhibits the expression of nephrin and results in podocyte injury. Additionally, the expression levels of CD86 on podocytes is increased by endocytosed IgG (64,65). CD86 is one of the co-stimulatory molecules in T cell activation, implying the potential engagement of podocytes in the initiation of renal T cell activation.

Bruschi *et al* (66) reported that patients with LN have antibodies that directly target podocytes, which are associated with high proteinuria in these patients. dsDNA antibodies are present at increased concentrations in renal tissue compared with that of the systemic circulation. It forms immune complexes and deposits them in the glomerulus, exhibiting podocyte injury and local immune reactions. These antibodies can also cross-react with -actinin-4 on podocytes, causing cytoskeletal rearrangement and complement activation, which directly leads to podocyte injury (67,68). Therefore, in addition to immune complex formation, the direct binding of podocyte-targeting autoantibodies present in the serum of patients can aggravate LN-associated proteinuria, leading to podocyte injury.

Overall, podocytes may provide antigenic targets for autoantibodies. Furthermore, podocyte injury is generated when autoantibodies form immune complexes that deposit *in situ* within the kidney in LN. In future studies, it will be important to identify other relevant antibodies that directly target intrinsic renal cells, such as podocytes, mesangial cells and the basement membrane, to further elucidate new mechanisms of kidney injury in LN.

Podocytes interact with adaptive immune cells. In addition to reacting with autoantibodies in the immune microenvironment, podocytes can also interact with immune cells. In crescentic glomerulonephritis, rupture of Bowman's capsule can release $CD8^+$ T cells into the glomerulus, leading to podocyte injury (69). Compared with healthy mice and people, the podocytes of lupus mice and patients with LN have high expression levels of CD80 and CD86, which may promote T cell expansion and aggregation within the renal parenchyma. Increases in CD80 levels are positively associated with the severity of proteinuria (70). *In vitro* experiments have revealed that CD80 activation leads to the reorganization of slit diaphragm proteins, nephrin and podocin, and the disruption of actin filaments, and also leads to integrin inactivation to promote podocyte migration and damage (71,72). CD80 and CD86 expressed in podocytes are a potentially rich source of biomarkers that may capture various aspects of the renal injury.

Coers *et al* (73) and Goldwich *et al* (74) demonstrated that podocytes can express major histocompatibility complex (MHC) I and II, as well as macrophage markers (CD68, F4/80, and CD206) and co-stimulatory molecules (CD80). In the inflammatory environment, podocytes came into close contact with glomerular infiltrating T cells (74), which can activate $CD4^+$ T cells and $CD8^+$ T cells (74). Podocytes can cross-present endocytosed IgG to local infiltrating T cells via MHC, activating T cells to induce podocyte injury and apoptosis (75). Therefore, these findings suggest that podocytes in LN participate in the local immune response, which is identical to the role of antigen-presenting cells, contributing to the pathogenesis of LN.

Local infiltration of $CD4^+$ T cells in the kidney promotes the progression of nephritis (76). Lipopolysaccharide (LPS)-induced podocytes polarize naive $CD4^+$ T cells into T helper-17 (Th17) and regulatory T (Treg) cells, affecting the Th17/Treg balance and producing large amounts of proinflammatory cytokines. Th17 cells can secrete IL-17A, which has the potential to promote podocyte cytoskeletal rearrangement (77), and is probably the reason for the positive correlation between IL-17A levels and proteinuria in patients with LN (78,79). Following the stimulation of IL-17A secretion by Th17 cells, podocytes can express IL-17A receptors and produce the NLRP3 inflammasome, resulting in increased secretion of IL-1β. Additionally, IL-17A can disrupt podocyte morphology and induce podocyte injury (80). Preventing $CD4^+$ T cell activation in the renal immune microenvironment and maintaining Th17/Treg balance may provide a new potential therapeutic strategy for LN. However, further research is required for *in vivo* validation and investigation of the mechanisms of action (81).

In LN, intrarenal B cells can form germinal center-like structures and locally produce pathogenic antibodies (82,83). Kolovou *et al* (84) described that oligoclonal B cells are associated with podocyte injury and glomerulosclerosis in LN, but oligoclonal expansion of B cells failed to be detected in the peripheral blood of patients with LN. This is possibly due to the inflammatory stimulus promoting B cell proliferation in the local renal environment. The interaction between B cells and podocytes in the immune microenvironment leads to podocyte injury, but the specific mechanism is unclear and further research is needed to elucidate the role of intrarenal B cells in podocyte injury. Cardiotrophin-like cytokine factor 1 (CLCF-1), also known as B cell-stimulating factor, can regulate B cell differentiation and Ig class switching when overexpressed (85). Moreover, CLCF-1 is currently considered as a potential therapeutic target as it can affect kidney development (86), and activate the Janus kinase (JAK)/STAT pathway and change podocyte morphology in focal segmental glomerulosclerosis, leading to renal dysfunction and proteinuria (87).

Therefore, the progression of LN may be caused by the interaction between substances in the immune microenvironment and podocytes and it is necessary to explore this interaction.

5. Immune microenvironment of podocytes in animal models

Previously, four lupus mouse models have been established, including spontaneous lupus mouse models, induced lupus mouse models, genetically modified lupus mouse models and humanized lupus mouse models. Currently, the spontaneous lupus mouse model is commonly used to study the interaction between podocytes and the immune microenvironment. The spontaneous lupus mouse models include New Zealand Black (NZB), NZB x New Zealand White (NZB/W) first filial generation (F1), MRL/lpr and BXSB/Mp (BXSB/Yaa). These models produce SLE-like autoimmunity, with the production of autoantibodies including anti-nuclear, anti-dsDNA and anti-histone. Clinical manifestations of SLE have also been observed, such as immune complex-mediated glomerulonephritis and polyclonal hypergammaglobulinemia and foot process effacement (88) (Table II).

NZB/W F1 mice are a model for studying renal lesions in SLE. These mice have a susceptibility to autoimmunity and exhibit podocyte damage, reduced nephrin and podocin expression levels and proteinuria production. Immune complex deposition and crescent formation can be observed in the glomeruli, with mild mesangial hyperplasia in the early stages of murine development and focal and diffuse proliferative histological forms in the late stages of murine development, culminating in renal failure (89).

MRL/lpr mice are a model of spontaneous recessive mutant lymphocyte proliferation that can present with immune complex deposition-mediated glomerulonephritis, with a proliferative LN histological pattern characterized by endothelial and mesangial cell proliferation and thickening of the basement membrane (90). MRL/lpr mice are commonly used to investigate the mechanisms of podocyte injury and specific pathogenic mechanisms in diseases affecting the kidneys. CFH deficiency in this mouse model leads to immune complex deposition, loss of podocyte foot processes, accelerated renal injury and LN progression (45). When MRL/lpr mice are stimulated with LPS, levels of proinflammatory cytokines increase in the serum, and there is damage to the podocytes in the kidney, as well as increased urinary albumin (91).

BXSB/Yaa mice are a male lupus-like autoimmune disease model (92) that develops severe immune complex-mediated glomerulonephritis with podocyte injury and foot process effacement. This model also develops membranoproliferative LN with IgG and C3 deposition in the mesangium (46). The overexpression of the TLR was correlated with urinary albumin levels and mRNA levels of the nephrin in the BXSB-Yaa mice, which are commonly used to investigate the interaction between TLRs and podocytes. The BXSB/Yaa mouse model is the result of a gene mutation that causes translocation of the terminal region of the X chromosome to the Y chromosome, leading to TLR7 gene duplication, which increases TLR7 expression levels (93). Additionally, BXSB/Yaa mice demonstrate overexpression of the TLR8 in the glomerulus, which is negatively correlated with podocyte markers (nephrin, podocin and synaptopodin), inducing autoimmune responses. The mRNA expression level of TLR8 is positively correlated with urinary albumin, suggesting the involvement of TLR8 in the process of podocyte injury (50).

New animal models are expected to be established to explore the specific pathogenic mechanisms of renal intrinsic cell autoantibodies in kidney disease. This will shed light on novel pathways leading to renal damage in LN.

6. Application of drug-targeted podocytes

In the last decade, prominent advances have been made in studying the structure and function of podocytes. Anifrolumab is a human monoclonal antibody targeting the type I IFN receptor subunit 1 and is the first type I IFN receptor antagonist approved by the US Food and Drug Administration for the treatment of SLE in adult patients. Meanwhile, anifrolumab has been investigated as a promising strategy for the treatment of LN in clinical trials (94-96). A large randomized placebo-controlled trial suggested that neutralizing type I IFN receptors expressed

Table II. Summary of LN mouse models.

Mouse model	Autoantibodies	Main clinical features	Age of mice at mortality	Main research area	(Refs.)
NZB	Anti-dsDNA, anti-RBC and anti-gp70	LN, IC-type GN, autoimmune hemolytic anemia and hypocomplementemia	15 and 18 months because of autoimmune hemolytic anemia	Inflammatory factors and immune complex deposition	(60,61,102,103)
NZB/WF1	ANA, anti-dsDNA, anti-Ro, anti-La, anti-Sm, anti-RBC and anti-RNA	LN, lymphadenopathy, splenomegaly, mild vasculitis, lymphadenopathy and hemolytic anemia	10 and 12 months because of renal failure	Inflammatory factors, podocyte injury and immune complex deposition	(89)
MRL/lpr	ANA, anti-dsDNA, anti-ssDNA, anti-Sm, anti-Ro, anti-La, rheumatoid factor, anti-RBC and snRNP	LN, hypergammaglobulinemia, high titers of autoantibodies, circulating ICs, lymphadenopathy, polyarthritis, vasculitis and splenomegaly	5 and 12 months due to renal failure	Immune complex deposition, complement system, podocyte injury and specific pathogenic mechanisms involved in kidney disease	(45,90,91)
BXSB/Yaa	ANA, anti-dsDNA and anti-RBC	LN, IC-mediated GN, secondary lymphoid node hyperplasia, hypergammaglobulinemia and monocytosis	5-8 months for BXSB/Yaa male mice and ~15 months for BXSB female mice complex because of	Expression levels of the TLR, podocyte injury and immune deposition renal failure	(46,50,54,93)

NZB, New Zealand Black; NZB/W, NZB x New Zealand White; F1, first filial generation; MRL/lpr, Murphy Roths Large/lymphoproliferative, a mouse strain with the lymphoproliferation (lpr) mutation; BXSB/Yaa,a mouse strain with the Y-linked autoimmune accelerator mutation; RBC, red blood cell; gp70, 70 kDa glycoprotein; ANA, anti-nuclear antibodies; dsDNA, double-stranded DNA; Sm, Smith; Ro, a nuclear protein; La, a nuclear protein; ssDNA, single-stranded DNA; snRNP, small nuclear ribonucleoproteins; IC, immune complex; GN, glomerulonephritis; TLR, toll-like receptor; LN, lupus nephritis.

by podocytes can effectively reduce proteinuria in patients with LN (97). Tacrolimus, a calcineurin inhibitor, can reduce proteinuria and improve kidney function in mice with lupus and patients with LN (98), while stabilizing the podocyte cytoskeleton and suppressing podocyte apoptosis, partially protecting podocytes from injury in LN (99). Baricitinib, a selective inhibitor of JAK1 and JAK2, is commonly used for rheumatoid arthritis treatment. Recent a study has revealed that baricitinib demonstrates benefits in inhibiting systemic autoimmunity in MRL/lpr mice and improves the lupus-like phenotype. It has been identified that baricitinib can inhibit the JAK/STAT pathway in podocytes, restore the abnormal podocyte structure caused by inflammation, and thus prevent renal damage (100). Greka *et al* (71) revealed that abatacept, a co-stimulatory blocker of B7-1, suppresses T cell activation and promotes integrin activation in podocytes. It also inhibits podocyte migration and prevents podocyte damage, which improves proteinuria in patients with LN.

Podocyte damage is reversible in LN, and actin is able to restore foot processes and reorganize the podocyte cytoskeleton. These studies illustrate a therapeutic target of podocytes in the glomerulus and immune cells in the immune microenvironment for precise treatment of LN, as they reduce systemic side effects of drugs, relieve proteinuria symptoms and improve disease progression.

7. Conclusion and future perspectives

Podocytes are glomerular epithelial cells, and the majority of all kidney diseases lead to podocyte injury. There is evidence that podocytes are important intrinsic cells of the kidney, which confer immune cell functions to promote the occurrence and development of LN. The manifestation and pathology of SLE in murine models, especially NZB/W F1 and MRL/lpr mice, are identical to that in patients with LN and have similar immune mechanisms. These help to further investigate the interaction mechanisms between podocytes and the renal immune microenvironment in LN. Recently, a number of studies have revealed that current therapies used to treat autoimmune diseases exhibit a direct protective effect on podocytes, alleviating the occurrence of proteinuria. These findings provide insights into targeted therapy for kidney diseases. Numerous studies have confirmed that LN podocytes participate in the innate and adaptive immune processes

and interact directly with cells and molecules in the immune microenvironment. However, the mechanism of their interaction has not been thoroughly investigated. Therefore, further studies are needed to elucidate the interactions between LN podocytes and the local immune cells of the kidney, especially T and B cells. Targeting these pathogenic pathways might enable a more personalized approach to the treatment of LN and lead to improved outcomes for patients with LN.

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Availability of data and materials

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Authors' contributions

RL and XP wrote the manuscript. MZ acquired and interpreted the data. LM and JL conceptualized and designed the manuscript. XW and KX reviewed and revised the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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