UCH-L1 Expressed by Podocytes: a Potentially Therapeutic Target for Lupus Nephritis?

Ji-hong Cui¹,² and Xin Xie¹,²,³,⁴

Abstract—Systemic lupus erythematosus (SLE) is a multisystem disease affecting many organs, and the most severe complication is lupus nephritis. Podocyte injury and loss play vital roles in the pathogenesis of lupus nephritis. Studies have shown that ubiquitin carboxyl-terminal hydrolase L1 (UCH-L1) is involved in the pathogenesis and progression of many diseases, such as neurodegenerative disorders, cancers, and diabetes. Recently, numerous studies have indicated that UCH-L1 was upregulated in the podocytes in immune complex-mediated glomerulonephritis. This increase was correlated with disease aggravation. In this review, we discuss the role and mechanism of UCH-L1 in the pathogenesis of many diseases and, particularly, in lupus nephritis. Hence, we highlight the role of UCH-L1 in lupus nephritis.

KEY WORDS: UCH-L1; podocyte; lupus nephritis; NF-κB.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by loss of tolerance against self-antigens, lymphoproliferation, polyclonal autoantibody production, and immune complex deposition, leading to multi-organ injuries [1]. Lupus nephritis is the most severe complication of SLE [2]. Proteinuria is an important risk factor for the progression of renal diseases in patients with lupus nephritis [3]. Podocytes and their slit-diaphragms are vital for the integrity of the renal basement membrane, which acts as a barrier to urinary protein loss. At the early stage of lupus nephritis, podocytes were affected and correlated with the disease histological changes [4]. The loss of podocytes in the urine (also termed podocyturia) has been detected in patients with lupus nephritis, which could be useful in monitoring the disease activity [5, 6]. Recently, studies have shown that ubiquitin C-terminal hydrolase L1 (UCH-L1) is not expressed in glomerular podocytes of the normal kidney, but de novo expressed and correlated with podocyte injury in lupus nephritis [7–9]. Considering the expression of UCH-L1 in injured glomerular podocytes and the vital role of podocytes in lupus nephritis, we hypothesize that UCH-L1 may be a target for the treatment of this disease. In this review, we discussed recent development of UCH-L1 in the pathogenesis of many diseases and in particular lupus nephritis, with a view of providing insights into the pathogenesis and treatment of lupus nephritis.

LUPUS NEPHRITIS

Studies have revealed that up to 2/3 of SLE patients develop glomerular injury, which is denoted as lupus nephritis, due to immune complex deposition [10]. Approximately 60% of those patients develop a proliferative form of lupus nephritis (termed class III or IV), while 20–40%
Overview of the Pathogenesis of Lupus Nephritis

Pathogenesis | Study findings | Ref. |
---|---|---|
Adaptive immune system | Activation of B cells and their maturation to plasma cells promotes the production of autoantibodies and proinflammatory cytokines. T cells provide help for B cell production of nephritogenic autoantibodies, regulate B cell responses, and modulate T helper and effector functions and expansion. T cells infiltrate the kidney to injure parenchymal cells directly via cytotoxicity or indirectly through activation and recruitment of macrophages and NK cells | [13–17] |
Innate immune system | In the early stages of the disease, dendritic and other myeloid cells activate T cells, and produce key mediators including B cell-activating factor, which results in the activation of the adaptive immune system. The complement system, a key component of the innate immune system, is thought to play an important role in the pathogenesis of lupus nephritis, and the exact mechanism was shown in refs. [20] and [21]. Autophagy, which is involved in autoimmunity, plays a vital role in maintaining the homeostasis of T cell and B cell | [18–21] |
Autophagy | Autophagy plays critical roles in maintaining the homeostasis of T cells and B cells. Also, autophagy-relative genes such as APOL1 and MTMR3 are associated with lupus nephritis | [22–26] |
Cell death | Chromatin or nucleosomes are the driving antigens in the induction of anti-ds DNA autoantibodies. The formed immune complex is deposited within the basement membranes and the mesangial matrix of glomeruli | [27] |
Podocyte injury | Injury to the podocyte leads to a loss of interdigitating foot processes with detachment from the GBM and disruption of the glomerular sieve and charge-selective barrier resulting in massive proteinuria | [32] |

Podocytes, also called visceral glomerular epithelial cells, are highly differentiated cells that line the outside of the glomerular capillary. They comprise a cell body with extending major processes that further branch into foot processes separated by a slit-diaphragm, which is an electron-dense membrane that spans the 30-nm space between their interdigitating foot processes. The podocyte architecture is predominantly maintained by a contractile apparatus composed of microfilaments including actin, myosins, α-actinin, talin, vinculin, paxillin, and palladin. Previously, it was thought that podocytes are static cells; time-lapse imaging showed the dynamics of podocyte movement, shedding, and replacement. Podocytes are a part of the glomerular filtration barrier together with capillary endothelial cells and the glomerular basement membrane.

Table 1. The Pathogenesis of Lupus Nephritis
basement membrane (GBM), which ensures the selective permeability of the glomerular capillary wall [28]. Besides the filtration barrier to protein, podocytes also possess other critical roles like a charge barrier to protein, maintaining the capillary loop shape, synthesizing and maintaining the GBM, countering the intraglomerular pressure, and producing and secreting vascular endothelial growth factor required for glomerular endothelial cell integrity [33].

Proteinuria, a common manifestation in lupus nephritis, reflects podocyte injury. Injury to the podocyte leads to a loss of interdigitating foot processes with detachment from the GBM and disruption of the glomerular sieve and charge-selective barrier resulting in massive proteinuria [34]. The proteins expressed by podocytes are vital for the integrity of the filtration barrier in lupus nephritis [4]. Synaptopodin is a proline-rich actin-associated protein. It mainly distributes the cytoplasm of glomerular podocytes and plays a role in the regulation of the actin-based shape and motility of the podocyte foot processes [37]. Glomerular epithelial protein 1 (GLEPP1) is a membrane protein tyrosine phosphatase. It acts as a cellular receptor, which is involved in regulatory mechanisms related to the foot process structure and/or function [38]. Podocalyxin, a CD34-related sialomucin, is normally located at the apical part of the foot process. The absence or the change of spatial organization both has a detrimental effect on the glomerular filtration function [39, 40]. Nephrin and podocin are the main protein components of the slit-diaphragm in podocytes. They are significantly reduced in the earlier stages of lupus nephritis and correlate with disease histology [4]. Wilms tumor protein 1 (WT1), a nuclear zinc finger transcription factor, is implicated in cell cycle regulation and cell proliferation [41].

Recently, podocyturia has been found to be involved in the progression of lupus nephritis [42, 43]. Nakamura et al. [43] showed that podocytes were present in the urine of active lupus nephritis but not in SLE patients with stable renal function or healthy controls. The number of urinary podocytes was correlated with the proteinuria and hematuria excretion scores. Also, Mansur and co-workers reported that the levels of podocyturia were higher in patients with lupus nephritis particularly in class IV than in the controls [6]. Treatment with corticosteroids, cyclophosphamide, or azathioprine significantly diminished the podocyturia in patients with lupus nephritis [44]. Renal biopsy remains the gold standard for the diagnosis and prognosis of lupus nephritis; however, it is an invasive method. Perez-Hernandez and colleagues discovered that urinary dedifferentiated podocytes were found in active lupus nephritis, and the levels of podocyte-specific protein podocalyxin, synaptopodin, podocin, nephrin, and WT-1 were significantly increased and correlated with proteinuria and histological features in lupus nephritis patients [45]. These results suggest that podocyturia could be a potentially useful non-invasive marker for evaluating the progression of glomerular disease including lupus nephritis [45].

Currently, the potential mechanisms of podocyte injury in lupus nephritis remain not fully understood. Here, we summarized the recent papers relevant to podocyte injury in lupus nephritis. Smad7, an inhibitory SMAD, is activated in injured podocytes in vitro and in human lupus nephritis. It participates in negative control of transforming growth factor-β/Smad signaling besides its pro-apoptotic activity [46]. Notch activation stimulates human renal progenitors’ entry into the S-phase of the cell cycle and cell division, whereas its downregulation is required for differentiation toward the podocyte lineage. A persistent activation of the Notch pathway would induce podocytes to cross the G2/M checkpoint, resulting in cytoskeleton disruption and cell death. In the glomeruli of healthy adult kidneys, Notch expression was almost absent, however remarkably upregulated in podocytes in patients with glomerular disorders [47]. Neonatal Fc receptor, a newly recognized molecular present on human renal podocytes, acts as an immune sensor that evokes an inflammatory response, which may lead to functional and morphological changes

<table>
<thead>
<tr>
<th>Podocyte markers</th>
<th>Function</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synaptopodin</td>
<td>Regulation of the actin-based shape and motility of the podocyte foot processes</td>
<td>[37]</td>
</tr>
<tr>
<td>GLEPP1</td>
<td>As a cellular receptor, which is involved in regulatory mechanisms related to the foot process structure and/or function</td>
<td>[38]</td>
</tr>
<tr>
<td>Podocalyxin</td>
<td>Located at the apical part of the foot process. The absence or the change of spatial organization both has a detrimental effect on the glomerular filtration function</td>
<td>[39, 40]</td>
</tr>
<tr>
<td>Podocin</td>
<td>The component of the slit-diaphragm in podocytes, reduced in lupus nephritis and correlates with disease histology</td>
<td>[4]</td>
</tr>
<tr>
<td>Nephrin</td>
<td>The component of the slit-diaphragm in podocytes, reduced in lupus nephritis and correlates with disease histology</td>
<td>[4]</td>
</tr>
<tr>
<td>WT1</td>
<td>It is implicated in cell cycle regulation and cell proliferation</td>
<td>[41]</td>
</tr>
</tbody>
</table>
in podocytes in glomerulonephritis [48]. Several Toll-like receptors have been found correlated with podocyte injury [49, 50]. miR-26a could regulate podocyte differentiation and cytoskeletal integrity in lupus nephritis [51]. Studies found that podocyte injury is also associated with T cells-induced intrarenal macrophage infiltration [52]. Additionally, podocytes in lupus nephritis can exert dendritic cell-like function through expression of dendritic cell-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN), which may be involved in immune and inflammatory responses of renal tissues. Blockage of DC-SIGN can inhibit immune functions of podocytes [53].

UCH-L1

The ubiquitin proteasome system (UPS), one of the major intracellular protein degradation systems, is composed of ubiquitin, ubiquitination enzymes, deubiquitination enzymes (DUBs), and proteasomes. Ubiquitin is a highly conserved 76-amino acid protein, which can be covalently attached to a target protein by ubiquitination enzymes during the ubiquitination process occurring through a three-step sequential action of ubiquitin activating enzyme (E1), ubiquitin carrier protein (E2), and ubiquitin protein ligase (E3). Initially, ubiquitin is activated by E1 through the ATP-dependent manner forming a high energy thioester linkage between the carboxy-terminal glycine residue of ubiquitin and the active cysteine of the E1 enzyme. Subsequently, activated ubiquitin is then transferred to a cysteine residue of an E2 enzyme, and then an E3 enzyme transfers ubiquitin to lysine residues of the targeted protein, forming a polyubiquitin chain (Lys48) that is recognized by the 26S proteasome leading to its degradation [54]. The action of DUBs was opposite to that of the E3 ligases. DUBs cleave the isopeptide bonds between the C-terminal glycine of ubiquitin and lysine residues of targeted proteins to allow for free ubiquitin monomers to be recycled [55].

The ubiquitin carboxyl-terminal hydrolase L1 (UCH-L1) gene, also known as neuronal-specific protein gene product 9.5, is located on chromosome 4 (4p14) and encode a peptide of 223 amino acids [56, 57]. UCH-L1 was firstly discovered as a member of the ubiquitin carboxy-terminal hydrolase family of DUBs catalyzing the hydrolysis of Lys48-linked ubiquitin chains [58]. Moreover, UCH-L1 possesses ATPase-independent dimerization-dependent ubiquitin ligase activity for the Lys63 residue of the ubiquitin molecule, forming undegradable (K63) polyubiquitin chains, which could inhibit proteasomal activity [59]. Additionally, UCH-L1 plays a role in the homeostasis of ubiquitin monomers, where UCH-L1 appears to regulate the degradation of free ubiquitin monomers in cells [58].

Studies have found that UCH-L1 is implicated in the pathogenesis of many diseases. Previously, studies showed that UCH-L1 is exclusively expressed in neurons [58]. Dysfunction of the UPS has been implicated in the pathogenesis of neurodegenerative disorders. Downregulation and extensive oxidative modification of UCH-L1 have been detected in the brains of patients with Alzheimer’s disease (AD) as well as Parkinson’s disease (PD) [60]. In AD brains, UCH-L1 was negatively related to neurofibrillary tangles whose major component is hyperphosphorylated tau protein, and inhibition of the activity and expression of UCH-L1 decreased microtubule-binding ability and increased the phosphorylation of tau protein, induced the abnormal aggregation and ubiquitination of tau protein [61]. The administration of UCH-L1 was shown to alleviate β-amyloid-induced synaptic dysfunction and memory loss in AD mouse models, demonstrating that UCH-L1 is associated with the proteasomal degradation of PKA-regulatory subunit IHex. The freed catalytic subunit is then activated and can phosphorylate cAMP response element binding protein (CREB) and initiate transcription [62]. In PD, UCH-L1 was found to co-aggregate with α-synuclein, the major component of Lewy bodies. Cartier et al. [63] revealed that suppression of UCH-L1 activity induced its ligase activity increasing α-synuclein levels and resulted in a concomitant accumulation of presynaptic α-synuclein in neurons. These results suggest that the downregulation of UCH-L1 could result in the accumulation of regulators or key materials in neurodegenerative diseases.

Studies also showed that UCH-L1 is associated with the pathogenesis of cancers. Proteomic screens have revealed that UCH-L1 is expressed in many human tumors. It not only functions as a positive regulator in the growth and development of some tumors but also acts as a putative tumor suppressor in certain cancer subtypes (for a recent review, see [64]). Studies indicated that the disruption of UPS function is involved in cancer pathogenesis and progression [65]. The abnormal expression of UCH-L1 may indirectly alter both the poly- and mono-ubiquitination of oncogenes and tumor suppressors, leading to aberrant protein degradation and/or altered protein function and subsequent tumorigenesis [64].

Additionally, studies found that UCH-L1 was abundantly expressed in rat and human β cells, while accumulation of polyubiquinated proteins and UCH-L1 deficiency was found in β cells of humans with type 2 diabetes [66].
Increased expression of human islet amyloid polypeptide (h-IAPP) can lead to the formation of h-IAPP toxic oligomers and accumulation of polyubiquitinated proteins associated with decreased UCH-L1 availability. Downregulation of UCH-L1 expression and activity in \( \beta \) cells-induced endoplasmic reticulum stress leading to cell apoptosis [67]. This indicates that defective protein degradation in \( \beta \) cells in type 2 diabetes can be attributed, at least in part, to the misfolded islet amyloid polypeptide, leading to UCH-L1 deficiency. This further decreases free monomeric ubiquitin to initiate the accumulation and aggregation of proteins, causing \( \beta \) cell injury.

**UCH-L1 AND PODOCYTES**

Recently, much attention has been drawn to the expression and role of UCH-L1 in glomerular diseases. Normal kidney podocytes did not express UCH-L1. In 2008, Liu et al. [68] firstly found that UCH-L1 was obvious in the cytoplasm and processes of podocytes in the specimens of human IgA nephropathy and lupus nephritis via preembedding immunoelectron microscopy technique with gold and horseradish peroxidase labeling. Subsequently, Meyer-Schwesinger and colleagues also discovered that a subset of human glomerulopathies involved in podocyte foot process effacement (membranous glomerulonephritis (GN), SLE class V, focal segmental glomerular sclerosis (FSGS)) de novo strongly expressed UCH-L1 in podocyte cell bodies, nuclei, and processes. The expression of UCH-L1 is correlated with internalization of the podocyte-specific proteins nephrin and \( \alpha \)-actinin-4 [8]. In contrast, glomerular diseases typically not associated with foot process effacement (SLE class IV, ANCA + necrotizing glomerulonephritis, amyloidosis, IgA nephropathy) expressed low levels of UCH-L1 [8]. Moreover, UCH-L1 expression in podocytes is inversely correlated with podocyte differentiation in cultured human podocytes: higher in undifferentiated cells, lower in differentiated and arborized cells, where expression is accompanied by an increase in podocyte-specific actin-binding protein \( \alpha \)-actinin-4, nephrin, and synaptopodin [8]. LDN57444, a specific inhibitor of UCH-L1, led to a time- and concentration-dependent process formation with podocyte-specific protein \( \alpha \)-actinin-4 distribution to the cell membrane and processes, suggesting that UCH-L1 plays a role in podocyte differentiation and injury [8]. Additionally, Liu and co-workers reported that UCH-L1 was expressed in podocytes and its expression was remarkably higher in acute proliferative glomerulonephritis (APGN), lupus nephritis, membranous GN, and IgA nephropathy than that in FSGS, minimal change disease (MCD), minor abnormality, and normal kidney tissues. The percentage of PCNA-positive podocytes in lupus nephritis, APGN, and IgA

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Expression</th>
<th>Mechanism</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurodegenerative disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AD</td>
<td>Down</td>
<td>Decreased UCH-L1 induced the abnormal aggregation and ubiquitination of tau protein, and suppressed the proteasomal degradation of the PKA-regulatory subunit II( \alpha )</td>
<td>[60–62]</td>
</tr>
<tr>
<td>PD</td>
<td>Down</td>
<td>Suppression of UCH-L1 activity induced its ligase activity increasing a-synuclein accumulation in Lewy bodies</td>
<td>[60, 63]</td>
</tr>
<tr>
<td>Cancers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma/pancreatic ductal carcinoma/squamous cell carcinoma/breast cancer/medullary thyroid carcinoma (oncogenesis)</td>
<td>Up</td>
<td>UCH-L1 stimulates Akt, leading to increased MAPK signaling; decreases poly-ubiquitination and proteasomal degradation of ( \beta )-catenin, resulting in enhanced ( \beta )-catenin-mediated transcription, promotes the proteasomal degradation of the cell cycle inhibitor p27 and p53</td>
<td>[64]</td>
</tr>
<tr>
<td>Prostate cancer/breast cancer/esophageal cancer/pancreatic cancer/hepatocellular carcinoma (tumor suppressor)</td>
<td>Down</td>
<td>UCH-L1 promotes deubiquitination of p53 and inhibits its proteasomal degradation</td>
<td>[56, 64]</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Down</td>
<td>The misfolded islet amyloid polypeptide leads to UCH-L1 deficiency, which further decreases free monomeric ubiquitin to initiate the accumulation of and aggregation of proteins causing ( \beta ) cell injury</td>
<td>[67]</td>
</tr>
<tr>
<td>Immune complex-mediated GN</td>
<td>Up</td>
<td>UCH-L1 is upregulated by NF-( \kappa )B signaling. The increased UCH-L1 expression in podocyte decreases the mono-ubiquitin pool and impaired UPS, causing the accumulation of total proteins and further resulting to podocyte injury</td>
<td>[9, 69–71]</td>
</tr>
</tbody>
</table>
nephropathy was much higher than that in MCD, FSGS, and normal control [7]. These studies showed that the expression of UCH-L1 was contradictory in FSGS and IgA nephropathy, this may be attributed to the small samples or geographical limitations. In any case, UCH-L1 expression in the kidney podocytes of lupus nephritis is significantly higher than normal kidney tissues, and the increased UCH-L1 is apparently responsible for disease aggravation.

Ubiquitin expression was very low in podocytes from normal kidney biopsies; increased expression correlated with UCH-L1 in glomerular diseases [8]. Further studies found that the increased UCH-L1 expression coincided with decreased glomerular mono-ubiquitin content and impaired the UPS in membranous GN. Inhibition of UCH-L1 with LDN57444 reduced UPS impairment and ameliorated proteinuria, whereas inhibition of proteasomal activity enhanced UPS impairment, leading to increased proteinuria [69]. In cultured podocytes, stable overexpression of UCH-L1 resulted in the accumulation of mono-ubiquitin and poly-ubiquitin proteins, while knock-down of UCH-L1 reduced mono-ubiquitin and poly-ubiquitin proteins and notably increased proteasomal activity [69]. These results indicate that UCH-L1 regulates the mono-ubiquitin pool and induces the accumulation and aggregation of poly-ubiquitinated proteins in injured podocytes in membranous GN. Additionally, Lohmann et al. [70] revealed that UCH-L1 enhanced podocyte cytoplasmic p27Kip1 levels by nuclear export and decreased poly-ubiquitination and proteasomal degradation of p27Kip1 to increase the total protein content, leading to podocyte hypertrophy in membranous GN. In lupus nephritis, the increased UCH-L1 expression in podocytes decreases the mono-ubiquitin pool and impairs UPS, causing the accumulation of total protein and resulting in podocyte injury.

To further investigate the regulation mechanism of UCH-L1 in injured podocytes in glomerulonephritis. Zhang et al. [71] firstly found that stimulation of podocytes with the cytokines TNF-α and IL-1β upregulated UCH-L1 expression, while inhibited by the transcription factor nuclear factor-κB (NF-κB) specific inhibitor pyrrolidine dithiocarbamate. The electrophoretic mobility shift assay showed that NF-κB upregulates UCH-L1 via binding the −300- and −109-bp sites of its promoter. Moreover, the expression of NF-κB and UCH-L1 increased and was positively correlated in the renal biopsy from lupus nephritis patients. Activation of NF-κB upregulates UCH-L1 expression following changing of other podocytes molecules like nephrin and snail [71]. This group further revealed that the increases in levels of NF-κB and UCH-L1 were positively correlated with the number of diseased podocytes in human renal biopsies from several cases of immune complex-mediated GN, including lupus nephritis [9]. In contrast, no clear activation of NF-κB and increase of UCH-L1 expression was observed in non-immune complex-mediated GN [9]. In cultured murine podocytes, immune stimulation also led to the upregulation of UCH-L1 through the NF-κB signaling [9]. Collectively, these results indicate that UCH-L1 is upregulated by NF-κB and correlated with podocyte injury in lupus nephritis.

*Fig. 1.* NF-κB/UCH-L1 signaling in lupus nephritis. Various stimulations including TNF-α could induce the activation of NF-κB signaling pathway. NF-κB upregulates UCH-L1 expression via binding the −300- and −109-bp sites of its promoter, leading to the injury of podocytes that further contributes to lupus nephritis.
UCH-L1: Potential Therapeutic Target for Lupus Nephritis

CONCLUSIONS AND PERSPECTIVES

Podocytes, which are terminally differentiated cells, respond to injury with foot-process retraction, hypertrophy, hyperplasia, and loss, which ultimately results in proteinuria in lupus nephritis. The urinary dedifferentiated podocytes were detected and correlated with proteinuria and histological features of lupus nephritis, indicating that it may be a potential non-invasive marker for evaluating the progression of lupus nephritis. UCH-L1, an important DUB, has been found to relate with the progression of neurodegenerative diseases, cancers, and type 2 diabetes. Recently, the role of UCH-L1 in the glomerular diseases has been found. UCH-L1 is not expressed in normal kidney podocytes, but de novo expressed in podocytes of many glomerular diseases including lupus nephritis. The expression is correlated with the number of diseased podocytes, which is responsible for the disease aggravation. So far, no specific marker protein except UCH-L1 has been identified that is absent in healthy but upregulated in diseased podocytes in lupus nephritis. Thus, UCH-L1 could be a marker of histological differentiation between healthy and diseased podocytes or a prediction about prognosis or the degree of podocyte damage [8]. NF-κB, a fundamental intracellular transcription factor, is induced in response to various sources of extracellular stimulation such as proinflammatory cytokine TNF-α (Fig. 1). It is upregulated and correlated with proteinuria and proinflammatory cytokines expression in podocytes of lupus nephritis [72, 73]. Additionally, Brahler and co-workers found that proinflammatory activity of NF-κB in podocytes aggravates proteinuria in experimental GN in mice, suggesting that podocytes may be considered as major regulators of glomerular homeostasis [74]. Thus, UCH-L1, an important downstream target gene of NF-κB, could also provide a specific therapeutic target for lupus nephritis. However, considering the abundantly expression of UCH-L1 in human neurons and β cells, to avoid patients suffering more from AD, PD, or diabetes, the target reduction of UCH-L1 in kidney is of importance in patients with lupus nephritis. Hence, any use of UCH-L1 as a therapeutic in lupus nephritis should be with caution.

ACKNOWLEDGEMENTS

This work was supported by the National Natural Science Foundation of China (No. 31300797, 31670996) and Natural Science Basic Research Plan in Shaanxi Province of China (No. 2013JC2-03).

COMPLIANCE WITH ETHICAL STANDARDS

Conflicts of Interest. The authors declare that they have no potential conflicts of interest.

REFERENCES


UCH-L1: Potential Therapeutic Target for Lupus Nephritis

43: 4842–4890.


665


