

Tumor necrosis factor-like weak inducer of apoptosis and its potential roles in lupus nephritis

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Abstract

Introduction Tumor necrosis factor (TNF)-like weak inducer of apoptosis (TWEAK) is a recently identified proinflammatory cytokine of the TNF superfamily that functions through binding to Fn14 receptor in target cells. TWEAK has multiple biological activities. Studies show that TWEAK plays an important role in immune inflammatory diseases. Recent work has revealed that TWEAK may play an important role in the pathogenesis of kidney damage, including in systemic lupus erythematosus (SLE), where its concentration in urine was correlated with the level of activity of lupus nephritis (LN).

Objective The major focus of this review is to discuss the recent studies on TWEAK and its possible role in the pathogenesis of LN, and the therapeutic potential of modulating this pathway in LN.

Results and conclusion TWEAK plays a key role in the pathogenesis of LN through activation of multiple down-signaling pathway, inducing proinflammatory cytokines and chemokines, affecting cell proliferation/apoptosis and inducing renal IgG deposition. TWEAK blockade may be a novel therapeutic approach to reducing renal damage in SLE.

Keywords Tumor necrosis factor-like weak inducer of apoptosis · Fibroblast growth factor-inducible 14 · Systemic lupus erythematosus · Lupus nephritis

Introduction

The cytokine, tumor necrosis factor-like weak inducer of apoptosis (TWEAK), is a member of the tumor necrosis factor superfamily (TNFSF) initially described in 1997 [1]. The expression of TWEAK is relatively low in normal tissue; however, it is increased in both acute or chronic inflammatory processes in numerous tissues and peritoneal macrophages, such as collagen-induced arthritis (CIA), experimental autoimmune encephalomyelitis, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Henoch–Schönlein purpura and acute kidney injury (AKI) [2–9]. Similar to many other members of the TNFSF, TWEAK is responsible for a variety of biological activities, including stimulation of cell growth and angiogenesis, induction of inflammatory cytokines, and, under some experimental conditions, stimulation of apoptosis [9–11], many of which are associated with immune system development and function [12]. It plays a key role in the pathogenesis of disease in innate immunity and inflammatory responses, including in the progress of lupus nephritis (LN). In this report, we summarize the results of recent studies focused on TWEAK and its potential roles in LN.

TWEAK and its receptor

Structural features

The human *TWEAK* gene is located at chromosome 17 and encodes a 249-amino-acid (aa) type II transmembrane

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glycoprotein (30 kDa). The intracellular domain contains a putative serine phosphorylation site; the extracellular domain contains the receptor-binding site. TWEAK may be expressed as a membrane-bound protein (mTWEAK) and as a 156-aa, 18-kDa soluble protein (sTWEAK) that results from proteolysis of mTWEAK. mTWEAK, but not sTWEAK, may enter the cell nucleus [10–12]. Furin and poorly characterized peptidases may cleave TWEAK, giving rise to soluble proteins [7]. The mouse *TWEAK* gene is located at chromosome 11 [13] and is closely related to human *TWEAK*, with a 93% homology in the receptor-binding domain, so human TWEAK can bind to murine Fn14 and vice versa [14] (shown in Fig. 1).

Distribution

As a member of the TNF ligand superfamily, similar to TNF, TWEAK can be secreted cleaved into a circulating trimeric form that is thought to mediate its biological effects [4]. It has recently been reported that TWEAK could play a role in acute or chronic diseases [11]. TWEAK transcripts are abundant in human heart, pancreas, colon, small intestine, lung, ovary, prostate, first trimester and term placenta, and lymphoid organs including spleen, lymph node, and appendix, while kidney, testis, thymus, bone marrow and liver contain the lowest levels of TWEAK [1, 15]. The human TWEAK mRNA expression has also been detected in various tumor cell lines, peripheral blood lymphocytes, and fibroblasts [1, 16–18]. In a parallel analysis of mouse tissue, TWEAK mRNA is also abundant in heart tissue, but there are several differences from the human pattern: e.g., expression is low in the mouse spleen and high in the lung. Analyses of various mouse cell lines indicated that freshly isolated thioglycollate-induced peritoneal macrophages expressed a 1.4-kb TWEAK transcript and a limited survey suggested that some hematopoietically derived T, B, and monocytic lineages express TWEAK [1]. These have been summarized in Table 1.

Receptor

Recently, a cDNA clone encoding a TWEAK-binding cell-surface molecule was successfully isolated, and DNA

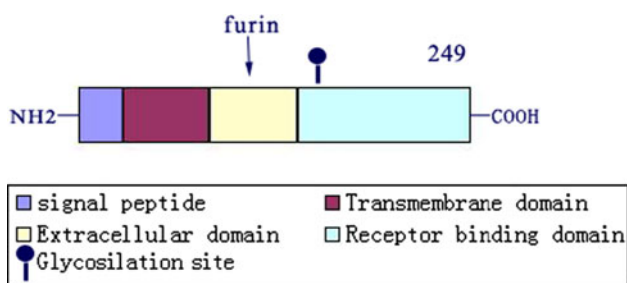


Fig. 1 Structure of TWEAK

sequence analysis revealed that the predicted protein sequence was identical to that of Fn14, a 102-aa type I transmembrane protein originally discovered during a search for growth-factor-inducible genes in mouse embryonic fibroblast cell line (NIH 3T3) fibroblasts in 2001 [24]. It is a type transmembrane protein that is referred to in the literature as either TWEAK receptor (TweakR) or fibroblast growth factor-inducible 14 (Fn14). In contrast to the other TNF ligand–receptor pairs, TWEAK and Fn14 are evidently a monogamous ligand–receptor pair. The human Fn14 homology is located on chromosome 16p13.3 and encodes a 129-aa protein with 82% sequence identity to murine protein, and has structural features characteristic of TNFR superfamily members, including an approximately 40-aa cysteine-rich region in the extracellular domain and a putative TNF receptor associated factors (TRAF)-binding site in the cytoplasmic tail [21, 24].

Fn14 is widely expressed at the RNA level in solid organs (kidney, heart, spleen, and brain), and has been reported in several cell types including endothelial and vascular smooth muscle cells, epithelial cells, monocytes/macrophages, fibroblasts, and synoviocytes [25]. Fn14 expression is relatively low in normal tissues, but is highly up-regulated during tissue stress, regeneration and repair. The expression of Fn14 on multiple microvascular cell types, fibroblasts, monocytes/macrophages, neuronal cells, astrocytes, and mesangial cells is particularly increased during systemic autoimmunity and inflammation [21, 24, 26]. In kidney, Fn14 is widely expressed by murine and human mesangial cells and by podocytes [23]. Justo et al. [25] also reported that renal tubular cells display Fn14 as well.

TWEAK and lupus nephritis

The role of TWEAK in lupus nephritis

Lupus nephritis (LN) is a major complication of systemic lupus erythematosus and is associated with high rates of morbidity and mortality. Although clinical signs of renal involvement appear in only 50–80% of patients, the disease involves the kidney in almost all patients from whom sufficient tissue can be obtained for analysis [27]. A complex interplay of genetic factors, autoantibodies (autoAbs), inflammatory responses, and aberrant apoptosis have been implicated in the pathogenesis of LN, but the actual mechanisms underlying the accelerated form remain largely unclear.

TWEAK mRNA levels were initially reported to be increased in mouse or human with both acute (induced by lipopolysaccharide) or chronic (autoimmune pathologies

Table 1 Comparison of the distribution of TWEAK in human and mouse

Species	Human	Mouse
Distribution in tissues and organs	High levels in heart, pancreas, colon, small intestine, lung, ovary, prostate, first trimester and term placenta, and lymphoid organs including spleen, lymph node, and appendix. Lower levels in kidney, testis, thymus, bone marrow, and liver [1]	Abundant in lung, heart tissue, colon, kidney, and brain, low in spleen and liver [1, 19, 20]
Cellular source	Tumor cell lines [21], peripheral blood lymphocytes, mesenchymal cells, endothelial cells, fibroblasts, and most epithelial cells [1, 16, 17]	Tumor cells, peritoneal macrophages, hematopoietically derived T, B and monocytic lineages, vascular smooth muscle cells, neurons, astrocytes, endothelial cells, and epithelial cells [1, 20–23]

like lupus erythematosus or hemolytic anemia) inflammatory processes in numerous tissues and peritoneal macrophages [2]. In experimental models of AKI and autoimmune injury, renal TWEAK and, more significantly, Fn14 expression are up-regulated [28]. The gene expression of TWEAK/Fn14 increased in glomeruli and tubulointerstitium of patients with lupus nephritis and increased early in kidneys of a mouse lupus model [29, 30]. In the BXSB lupus model, TWEAK mRNA is highly expressed in kidneys early in the disease process [30]. Interactions of TWEAK with its receptor are instrumental in the pathogenesis of nephritis in the chronic graft-versus-host (cGVH) induced model of lupus [3]. To support the role of TWEAK in the pathogenesis of lupus nephritis, the researchers found that deficiency of the TWEAK receptor Fn14 or anti-TWEAK Ab decreased renal damage, as indicated by significantly reduced proteinuria, glomerular immunoglobulin (Ig) deposition and kidney cytokine expression, including interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), and interferon-inducible protein-10 (IP-10) [3]. As summarized in Table 1, several basic attributes of the TWEAK/Fn14 pathway offer important clues to its involvement in mouse models of lupus.

In addition, researchers also found that urine TWEAK (uTWEAK) levels were significantly higher in LN patients than in SLE patients without renal disease and other disease control groups; uTWEAK levels peaked during flares of LN and can well represent a clinical biomarker for LN [31]. These studies further support a role for TWEAK in the pathogenesis of LN. The available data suggest that TWEAK is a new player in kidney injury both at the glomerular and tubulointerstitial levels and might be a target for therapeutic intervention (Table 2).

The possible mechanism of TWEAK in the pathogenesis of lupus nephritis

Activation of the intracellular signaling pathway

The nuclear factor κ B (NF- κ B) family of transcription factors regulates expression of various genes that participate in autoimmune disorders such as RA [34] and SLE [35], inflammatory diseases such as asthma [36], Crohn's disease, and ulcerative colitis [37], apoptotic processes such as apoptosis in serum-starved human embryonic kidney (HEK) 293 cells [38], or oncogenic processes such as cancer [36]. Mammalian cells express five NF- κ B

Table 2 Studies of TWEAK in diverse mouse models of lupus

Murine lupus model	Functional expression of TWEAK in kidney
BXSB	TWEAK mRNA is highly expressed in kidneys early in the disease process, and is down-regulated as nephritis becomes manifest [30]
cGVHD	TWEAK overexpression was found in kidneys. TWEAK stimulated mesangial cells and podocytes to release multiple chemokines and other pro-inflammatory mediators [23, 32]. Fn14 deficiency or anti-TWEAK mAb reduced proteinuria levels, renal inflammation, mesangial cell proliferation, production of chemokines, and antibody deposition in the kidney [33]. The ability of TWEAK to promote vascular permeability may be the basic mechanism [3]
MRL-lpr/lpr	TWEAK up-regulates MCP-1, RANTES, IP-10, and KC in mesangial cells derived from young lupus-prone MRL-lpr/lpr mice and induces glomerular and tubular cell proliferation, as well as renal infiltration of macrophages and T cells [22, 23]. D10 cells (an Iak-restricted cloned Th2 line) as well as AE7 (a cloned Th1 line) and freshly isolated murine T cells express TWEAK which participates in macrophage apoptosis. TWEAK is an excellent candidate for molecules mediating D10 killing of antigen-presenting syngeneic macrophage [12]
NZB \times NZW (F1)	Male NZB.Yaa mice have much lower levels of kidney TWEAK mRNA expression than female NZB mice despite having similar degrees of nephritis, suggesting that the decrease in TWEAK expression may be due to male-specific genes [3, 30]

family members: RelA, RelB, c-Rel, NF- κ B2/p100/p52, and NF- κ B1/p105/p50; the members of the family can form homologous or heterologous dimers [39–41]. In-vitro and in-vivo experimental studies of lupus nephritis (LN) found activated NF- κ B to be significantly up-regulated in renal tubular cells and interstitial cells [42]. Expression of activated NF- κ B in tubular cells correlated well with the degree of tubulointerstitial histopathological indices and/or renal function. It suggests that the transcription factor NF- κ B plays an important role in tubulointerstitial injury and/or renal function in the progression of human LN [42]. c-Rel (Rel/NF- κ B protein family) mRNA and protein expression levels were significantly higher in T lymphocytes from SLE patients than in those from healthy people [43]. By targeting *p50* gene expression with specific antisense 3'-phosphorothioate-oligodeoxynucleotides (3'PS-ODNs) into cultured splenic B cells from BXSB mice, p50 protein in the B cells was significantly inhibited; in addition the NF- κ B expression, total IgM and IgG synthesis and dsDNA antibodies were reduced [44].

Recent studies showed that TWEAK is an inducer of constitutive NF- κ B activation by interacting with Fn14 [45–47]. Upon TWEAK stimulation, I κ B α is rapidly phosphorylated, generating NF- κ B DNA-binding complexes containing p50 and RelA in a manner dependent on the canonical I κ B kinase complex. TWEAK stimulation also results in prolonged NF- κ B activation with a transition of the DNA-binding NF- κ B components from RelA- to RelB-containing complexes; this long-lasting activation is accompanied by the proteasome-mediated processing of NF- κ B2/p100, which does not depend on the NF- κ B essential modulator but requires I κ B kinase 1 and functional NF- κ B-inducing kinase activity. To further support the role of a TWEAK–NF- κ B signaling pathway in the mechanism of lupus nephritis, Gao et al. found that TWEAK induces human kidney cells to express multiple inflammatory mediators, including regulated upon activation normal T cell expressed and secreted (RANTES), MCP-1, IP-10, macrophage inflammatory protein-1a (MIP-1a), intercellular adhesion molecule 1 (ICAM-1), and vascular cell adhesion molecule 1 (VCAM-1). Cytokine production is mediated by NF- κ B activation, and is inhibited by anti-TWEAK monoclonal antibodies [32]. The data suggest that TWEAK may play a pathogenic role in tubulointerstitial injury in LN by mediating through abnormal NF- κ B activation.

Besides the NF- κ B signaling pathway, mitogen-activated protein kinase (MAPK), TGF- β activated kinase 1 (TAK1) and the serine/threonine kinase Akt are also important components of TWEAK-induced proinflammatory signaling and gene expression [47–50]. Recent studies report that TWEAK treatment of serum-deprived human umbilical vein endothelial cells (HUVECs) stimulated not only an increase in phosphorylated I κ B α (signifying

activation of the NF- κ B pathway), but also increases in phosphorylated ERK 1/2 and JNK 1/2 (but not p38 MAP kinase) [49]. Since vascular damage is frequently associated with renal damage of SLE, these intracellular signaling cascades may play important role in LN. In another study, a p38 inhibitor abrogated IL-6 and IL-8 secretion induced by TWEAK in human astrocytes [51], which may suggest that TWEAK–p38 MAPK signaling also play a part role in renal damage of lupus nephritis. Researchers also found that TAK1 is involved in TWEAK-induced activation of NF- κ B and MAPK [52]. TWEAK increased the phosphorylation and kinase activity of TAK1 in cultured myoblast and fibroblast cells. The activation of NF- κ B was significantly inhibited in TAK1-deficient (TAK1^{-/-}) mouse embryonic fibroblasts (MEF) compared with wild-type MEF. Deficiency of TAK1 also inhibited the TWEAK-induced activation of I κ B kinase and the phosphorylation and degradation of I κ B α protein. These data demonstrate that multiple intracellular signaling cascades may be involved in the biological effect of this cytokine in various cell types under different conditions.

Cytokines and chemokines induction

Lupus nephritis (LN) is a common and serious complication of SLE patients. It is characterized by the production of autoantibodies and immune complex formation production [53]. It is well known that complex interactions among different immune cell types, including both T and B lymphocytes and professional antigen-presenting cells, such as macrophages and dendritic cells, play a key role in the pathogenesis of this disease. As key elements of this communication network, cytokines and chemokines orchestrate the recruitment, survival, expansion, effector function, and contraction of autoreactive lymphocytes in autoimmunity [54]. Fn14-deficient mice or treatment with novel murine anti-TWEAK Abs have reduced renal IgG deposition, macrophage infiltration, and cytokine expression following induction of experimental lupus [3].

Chemokines, which are chemoattractant cytokines, play a pivotal role in inflammatory processes. Cells challenged with a pathological proinflammatory stimulus secrete a variety of different chemokines, which function to regulate and direct leukocyte migration into tissues. These leukocytes are subsequently responsible for much of the tissue injury that can be seen in the affected organ. Specifically in human inflammatory renal disease, including a variety of diseases causing acute glomerular and tubulointerstitial inflammation, chemokines are believed to be crucial in disease pathogenesis [55]. It is thought that the balance between proinflammatory and anti-inflammatory cytokines influences the clinical manifestations in many inflammatory diseases such as SLE [56].

Studies have shown that TWEAK stimulates mesangial cells, podocytes, and endothelial cells to secrete high levels of potent proinflammatory chemokines including RANTES, MCP-1, IP-10, chemokine (C-X-C motif) ligand 1 (CXCL1), mucosal addressin cell adhesion molecule-1 (MadCAM-1), and VCAM-1 [23, 57], which are pivotal in the initiation and progression of the histopathological lesions of lupus nephritis. In a GVH SLE mouse model, Zhao et al. found that anti-TWEAK neutralizing mAb treatment significantly decreased both kidney MCP-1, RANTES, IL-6, and IP-10 production and urinary total protein levels [3]. Several of these TWEAK-inducible chemokines in kidney cells, for example MCP-1 and RANTES, are instrumental in the pathogenesis of LN through local recruitment of monocytes and activated T cells. In the lupus-prone MRL-lpr/lpr mouse strain, over-expression of RANTES accelerates renal disease [58], whereas deleting MCP-1 dramatically reduces infiltration of macrophages and T cells, glomerular hypercellularity, glomerulosclerosis, crescent formation, and vasculitis [59, 60]. These studies suggest that resident kidney cells, in response to TWEAK, may secrete chemokines and cytokines which are crucial in the inflammatory cascade leading to lupus nephritis.

Cell proliferation and apoptosis

Both kidney cell proliferation and apoptosis are possible mechanisms leading to chronic progressive renal histological changes in lupus nephritis [61, 62]. Besides inducing proinflammatory cytokines and chemokines, in some studies TWEAK could also affect cell proliferation and survival [24, 63]. TWEAK treatment promotes human vascular endothelial cell (EC) and smooth muscle cell (SMC) proliferation. The mitogenic effect of TWEAK on HUVECs is comparable to that of vascular endothelial growth factor (VEGF), a well-known EC mitogen and angiogenic factor [64]. Furthermore, it has been reported that FGF-2 co-treatment can potentiate TWEAK-stimulated HUVEC proliferation [65], an effect that may be due to the ability of FGF-2 to up-regulate TWEAK R/Fn14 gene expression. Endocapillary proliferation, thickening of capillary walls and extracapillary proliferation (crescents) is frequently encountered in systemic lupus erythematosus (SLE) [66]. Over 25% of late deaths of SLE patients can clinically be attributed to the atherosclerotic process, and over 50% of autopsied SLE patients demonstrated moderate to severe generalized atherosclerosis. EC activation and proliferation of transformed SMCs are important events

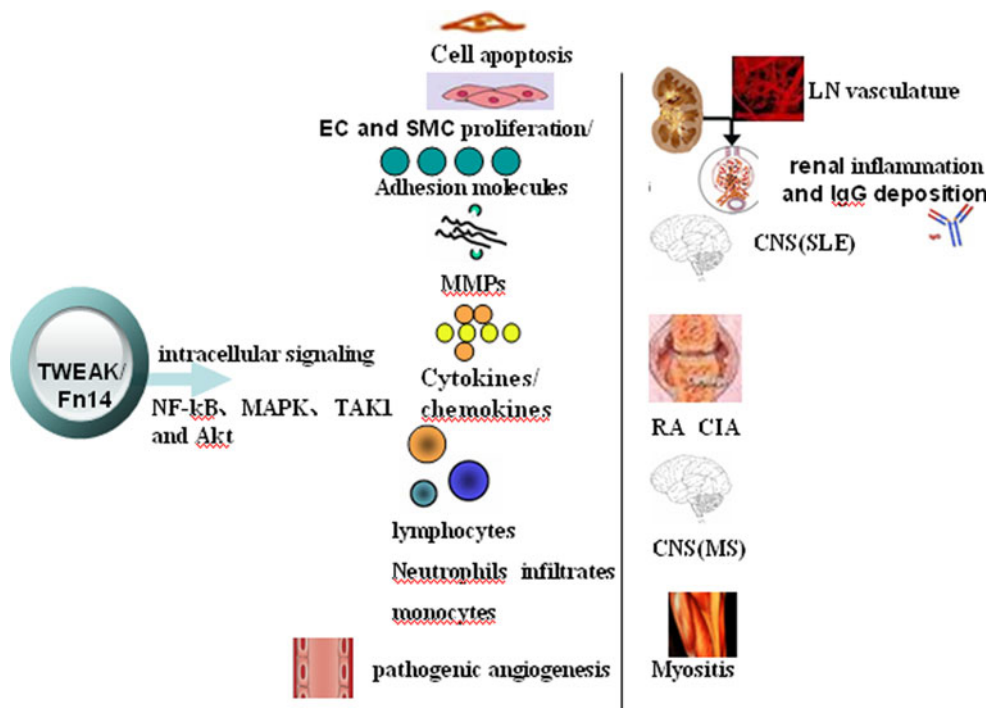


Fig. 2 TWEAK/Fn14 activation in LN and other autoimmunity diseases. TWEAK/Fn14 activation is involved in activation of NF- κ B, MAP-kinases JNK, ERK, p38, TAK1 and Akt signaling pathway and has several pro-inflammatory effects which may be important in the pathogenesis of systemic lupus erythematosus, and perhaps other systemic autoimmune rheumatic diseases. TWEAK induces secretion of multiple chemokines which are pivotal in the pathogenesis of lupus

nephritis, as well as CNS lupus. An additional biological effect of TWEAK is the induction of apoptosis and proliferation. Increased apoptosis and/or decreased clearance of apoptotic material are responsible for the breakdown of tolerance to nuclear antigens in several genetic models of murine lupus. *MS* multiple sclerosis, *RA* rheumatoid arthritis, *SLE* systemic lupus erythematosus, *CIA* collagen-induced arthritis, *CNS* central nervous system

which may be shared in the pathogenesis of vasculitis, thrombotic microangiopathy and premature and arteriosclerosis [67]. Therefore, the role of the TWEAK-Fn14 pathway in vascular EC and SMC proliferation may also be strongly implicated in the pathogenesis of SLE.

Studies have also revealed that individuals with SLE showed evidence of a significant increase in monocyte apoptosis. This process is mediated, at least in part, by an autoreactive T-cell subset that kills autologous monocytes in the absence of nominal antigen. TWEAK expression in T cells (CD4+ and CD8+) in SLE patients was significantly increased and pronounced on autologous monocyte death [12, 67]. What is the other mechanism of TWEAK-induced cell death? It has been reported that TWEAK produced by interferon- γ -stimulated monocytes could induce multiple pathways of cell death, including caspase-dependent apoptosis, cathepsin B-dependent necrosis, and endogenous TNF-mediated cell death, in a cell-type-specific manner [25].

Renal IgG deposition

IgG deposition in renal tissues was detected in patients with LN; the researchers found that patients positive for IgG deposition showed higher SLEDAI score than IgG-negative ones [68, 69]. Mice with lupus nephritis also showed significantly elevated glomerular IgG deposition. Glomerular IgG deposition is a major manifestation of cGVH-induced lupus, and glomerular immune complexes were believed to be the primary mediators of renal disease. Recent studies make it apparent that although Fn14 deficiency or treatment with anti-TWEAK Abs has no effect on the autoantibody titers (serum anti-ssDNA, anti-dsDNA, anti-chromatin, and anti-histone) in cGVH-induced lupus, kidney IgG deposition was significantly decreased in Fn14-deficient mice and the group treated with an anti-TWEAK neutralizing mAb [3]. One explanation for this might be that TWEAK itself may have led to increased vascular permeability, resulting in a nonspecific rise in the amount of deposited Ig [3, 69, 70].

Conclusion

In conclusion, after years of major contributions by studies of B and T lymphocytes that led to innovative therapies in lupus, TWEAK might be an important local mediator of kidney damage in the pathogenesis of LN. TWEAK blockade may be a novel therapeutic approach to reducing renal damage in SLE, and possibly other forms of immune glomerulonephritis as well. It may be helpful to open new fields of lupus research and may finally change pathogenic and therapeutic concepts (shown in Fig. 2).

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