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Editorial

Is Urinary Tumor Necrosis Factor-like Weak Inducer of Apoptosis a Biomarker of Lupus Nephritis?

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Lupus nephritis (LN) is usually the most serious manifestation of systemic lupus erythematosus (SLE) and develops in almost two-thirds of patients with SLE during their life-time [1]. Gluococorticoid with cyotoxic/immunosuppressive drugs including cyclophosphamide, mycophenolate mofetil, and calcineurin inhibitor are used to treat LN. These drugs for LN are usually selected based on findings of renal biopsy [2]. Yap et al. [3] reported that LN was associated with a 6-fold increase in mortality compared with the general population and major causes of death were infection, cardiovascular disease, and malignancy. Kidney biopsy is considered as a gold standard for diagnosing, classifying, and guiding the treatment of LN. Despite of clinical benefit of renal biopsy, it is an invasive procedure and possesses the possibility of drastic complication such as bleeding. Thus, it cannot be done repetitively to measure disease progression or to determine therapeutic effects. Furthermore, renal biopsy would be less objective, In this regard, novel biomarkers for LN have been reported [4].

A biomarker is a biologic, genetic or a chemical characteristic that correlates with a pathophysiological event and manifestations of a disease [5]. An ideal biomarker for LN should reflect renal disease activity, correlate with renal histology, and predict renal flares. Conventional urinary biomarkers for LN include proteinuria, urine protein to creatinine ratio, and urine active sediment. Serum biomarkers for LN are creatinine clearance, C3, C4, and anti-double stranded DNA antibody (anti-dsDNA antibody) [6]. Proteinuria itself is not specific for LN and does not reflect subclinical proteinuria. Urine active sediment, not specific for LN, cannot be quantitatively measured and does not predict renal histology [7]. Newer urine biomarkers for LN are urinary monocyte chemoattractant protein-1 (MCP-1), tumor necrosis factor-like weak inducer of apoptosis (TWEAK), transferrin, α1-acid glycoprotein, neutrophil gelatinase-associated lipocalin (NGAL), inducible protein 10 (IP-10), prostaglandin D synthetase, ceruloplasmin, lipocalin-type prostaglandin D-synthetase, hepcidin, and tumor growth factor β [6].

TWEAK is a member of the tumor necrosis factor superfamily ligands and primarily synthesized as a type II transmembrane protein [8]. Membrane bound TWEAK is expressed by immune cells including monocytes, dendritic cells, interferon (IFN)-γ stimulated NK cells, multiple sclerosis patient-derived monocytes, and cancer cells such as colonic adenocarcinoma, hepatocellular carcinoma cell lines, and the MDA-MB-231 breast cancer cell line [9]. Membrane-anchored TWEAK is cleaved by furin proteases in the stalk region that separates the transmembrane domain from the conserved extracellular C-terminal TNF homology domain into biologically active soluble TWEAK [10]. The expression of TWEAK is up-regulated by stimulation with IFN-γ or phorbol myristate acetate, tissue damage, and hypoxia [11,12].

Fibroblast growth factor inducible 14 (Fn14) is a member of type I transmembrane protein of the TNF receptor superfamily and acts as a receptor for TWEAK [9]. The expression of Fn14 is up-regulated on epithelial and mesenchymal progenitor cells by tissue damages such as hypoxia, oxidative stress, chemical and mechanical injuries, inflammation and tumor growth [9]. Binding of TWEAK to Fn14 activates the signaling pathway molecules, such as NF-κB, AP-1, and MAPKs (JNK, ERK, and p38) and

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controls several cellular responses, including proliferation, angiogenesis and induction of inflammatory cytokines [13]. TWEAK-Fn14 system has been implicated in the pathogenesis of muscle atrophy, cerebral ischemia, kidney injury, atherosclerosis, infarction, and autoimmune diseases such as rheumatoid arthritis, SLE, inflammatory bowel disease and experimental autoimmune encephalitis [9]. Fn14-knockout MRL-lpr/lpr mice demonstrated markedly lower levels of proteinuria compared with wild-type MRL-lpr/lpr mice. Fn14-knockout mice also showed significantly attenuated glomerular and tubulointerstitial inflammation [14]. It was reported that TWEAK induced mesangial cells, podocytes, and endothelial cells to secrete pro-inflammatory chemokines including MCP-1, IP-10 and RANTES (CCL5), which are crucial in the pathogenesis of LN [15]. Schwartz et al. [16] first reported that urinary TWEAK levels might be useful as a novel biomarker for LN. There are some reports dealing with serum or urinary TWEAK as a useful biomarker for LN. But, the reports showed conflicting results due to small sample sizes. Lee and Song [17] recently demonstrated that urine levels of TWEAK were significantly elevated in patients with active LN than in patients with inactive LN by meta-analysis. They also showed that level of urinary TWEAK was positively correlated with disease activity of SLE and LN measured by total SLE disease activity index (SLEDAI) or renal SLEDAI, respectively [17]. However, further longitudinal studies with larger sample size need to be conducted to confirm the clinical significance of urinary TWEAK as a novel biomarker that can reflect histological activity and determine treatment response. Brunner and colleagues reported that combinational analysis of anti-dsDNA antibody, serum C3, C4, creatinine, urinary protein creatinine ratio, and urinary biomarkers such as MCP-1, NGAL, lipocalin-type prostaglandin D-synthetase, α1-acid-glycoprotein, transferrin, and ceruloplasmin is useful in predicting activity, chronicity, and pathology of LN [18]. Therefore, it might be helpful to study the benefit of combining the urinary TWEAK and established biomarkers in LN patients. Furthermore, it will be necessary to determine the position of urinary TWEAK as a novel biomarker of LN in various ethnic groups, because ethnicity can affect SLE manifestations as well as treatment response in LN.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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