Editorial

Targeting the extracellular scavenger DNASE1L3 on SLE

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Systemic lupus erythematosus (SLE) is characterized by breakdown of immune tolerance to self-antigens, production of large amount of anti-nuclear antibodies (ANA) and immune-mediated injury in multiple organs. Anti-dsDNA antibody is one of the major components of ANA and has been proven to play major pathogenic role in the tissue damage of SLE. The production of anti-DNA antibodies in SLE has long been associated with defective clearance of apoptotic nuclear debris, which when entering the circulation, may form microparticles (MP) containing DNA and other nuclear components (1). The investigation of the underlying mechanism for impaired clearance of apoptotic cells has been focused on an endonuclease, DNASE1, which can degrade chromatin into low molecular weight fragments, and is associated with disposal of apoptotic nuclear debris. The role of DNASE1 has been implicated in the pathogenesis of SLE for several decades (2). For example, an earlier study in a murine model for DNASE1-deficiency demonstrated that the presence of ANA, and deposition of immune complex in glomeruli developed full-blown glomerulonephritis. Reduced serum DNASE1 activity was found to be linked to the development of autoantibodies and active SLE disease in patients and lupus-prone mice (3). However, the reasons for such an association, as well as the basis for increased concentration of DNA in the serum were not well understood.

A recent study published on *Cell* by Sisirak and colleagues has uncovered the novel function of DNASE1 as a scavenger of DNA in MP and its association with the autoantibody production in SLE (4). The authors reported that the deficiency of DNASE1L3, a homolog of DNASE1, resulted in production of autoantibodies to DNA and chromatin and the development of SLE-like disease. Sisirak *et al.* also unveiled that the autoimmunity is repressed by circulating DANSE1L3. DNASE1L3 belongs to the family of DNASE1-like proteins which are divalent cation-dependent endonucleases, including DNASE1L1, 2 and 3. Compared to DNASE1, DNASE1L3 has been shown to be more efficient in the cleavage of internucleosome genomic DNA in isolated cell nuclei.

Null mutation of DNASE1L3 is an extreme form of homogeneity in SLE that represents a single gene etiology and follows Mendelian inheritance. A rare autosomal recessive form of SLE has been identified as null mutation of DNASE1L3 in seven Arabian families (5). All the patients manifested with pediatric onset of SLE and increased prevalence of lupus nephritis. In this study, the authors established a mouse model reflecting familial SLE with DNASE1L3 deficiency. The DNASE1L3-deficient model by knocking out DNASE1L3 gene recapitulated clinical features of SLE as seen in the patients, including early development of antibodies to dsDNA and chromatin, late onset of immune activation via IFN-α pathway, splenomegaly and renal damage. According to the apoptotic clearance deficiency hypothesis, MPs and other apoptotic debris are cleared extracellularly. Then how does the endogenous DNASE1L3 work on the DNA clearance? By detecting the circulating DNASE1L3 in serum, the authors proved the secreting nature of this enzyme. They also identified the mononuclear phagocytes, including cytoplasmic dendritic cells (cDC) and tissue macrophages as the major source of secreting DNASE1L3, further confirmed that the enzyme works extracellularly. Most importantly, they demonstrated that DNASE1L3 has the greatest potency in digesting genomic DNA, specifically the DNA within MP derived

from apoptotic cells. Quantification of DNA by qPCR showed that the amount of DNA in MP was significantly reduced in the presence of DNASE1L3 in wild type mouse, indicating DNASE1L3 targets on circulating DNA in MP and is responsible for defective clearance of apoptotic cells in SLE patient and DNASE1L3-dificient mouse. This study reassured the previous observation that DNASE activity is inversely related with SLE disease index. The findings by Sisirak and colleagues revealed that the enzyme DNASE1L3 is the key player in the clearance of circulating DNA in MP and provided direct evidence that aberrant apoptotic clearance predisposes to lupus in a monogenic form of SLE.

Formation of autoantibody in SLE indicates B cells play a role in the pathogenesis and the loss of immunotolerance. To restore immunotolerance, a great deal of efforts have been focused on agents which deplete B cells (anti-CD20, anti-CD22), block cytokines (TNF α, Il 6), inhibit B/T cells interaction (CTLA-4Ig, anti-CD40L) etc. For instance, Belimumab, a human mAb binds to BAFF (B-cell activating factor) receptor on mature B cells to decrease their activation, was found to be beneficial in SLE patients with dermatitis, mucositis and arthritis, but was not evaluated in lupus nephritis (6). Sisirak and colleagues discovered that the microparticles are targeted by autoantibodies present in the sera of DNASE1L3-deficient mice and humans, and from patients with sporadic SLE. The treatment of microparticles with exogenous DNASE1L3 abolished antibody binding. These findings suggested a distinct mechanism of tolerance regulated by a secreting DNA-cleaving enzyme, thus highlighting the role of DNASE1L3 as the major player in the regulation of autoimmunity in SLE, such as the formation of the hallmark antibodies of SLE, anti-dsDNA, and induction of tolerance to genomic DNA.

The DNASE1 gene has long been considered as one of the susceptible genes for SLE, but its role in the pathogenesis of the disease has not been fully elucidated. A critical observation made by these investigators was the detection of DNASE1L3 in mouse serum and demonstrated that DNASE1L3 works on its substrate in a cell-extrinsic manner. This property of the enzyme has made it possible for the intervention of SLE by manipulation of DANSE1L3. Although previous experimental attempts using DNASE1 replacement therapy in mice were encouraging, for example, the treatment of recombinant DNASE1 in NZB/NZW F1 hybrid mice resulted in deceleration of SLE progression and reduction of severity of renal histopathology (1), however, the clinical trials of DNASE1 in SLE patients have not been sufficiently efficacious or successful. Intravenously administration of human DNASE1 in patients of SLE did not cause a change in serum marker and improvement of disease activity, which can be explained by lower digestive activity of DNASE1 on MP. By testing the digestive activities of DNASE1 and several variants of DNASE1L3 on different forms of DNA, the authors demonstrated that DNASE1L3 has much higher efficiency and specificity in digesting liposomal debris DNA and nucleosomal genomic DNA. The specificity and activity of this enzyme can be attributed to its positively charged c-terminal peptide, which facilitates the membrane penetration and the displacement of DNA from bound histones. The remarkable properties of DNASE1L3 on clearance of MP warrant a prospective investigation for its *in vivo* efficacy in SLE.

SLE remains a challenging disorder for clinicians and researchers. The study by Sisirak and colleagues has provided a novel mechanistic explanation for impaired apoptotic clearance in SLE. DNASE1L3, a highly active DNA enzyme, scavenges the MP-associated chromatin, which is a major source of self-antigen for autoimmunity. Deficiency in DNASE1L3 has led to breakdown of tolerance and autoimmune response to self-antigens, autoantibody production and development of SLE. Replenishment of high efficient DNASE1L3 might be a promising therapeutic strategy in SLE by restoring immune tolerance.

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