

# Autoantibodies as Biomarkers of Systemic Lupus Erythematosus

Chan Hong Jeon

Division of Rheumatology, Department of Internal Medicine, Soon Chun Hyang University Bucheon Hospital, Bucheon, Korea

Biomarkers are defined as measurements whose alterations correlate with the manifestations of diseases, can be evaluated qualitatively or quantitatively, and include genetic, biological and biochemical tests [1].

Systemic lupus erythematosus (SLE) is a complex autoimmune disease with diverse manifestations. SLE patients experience recurrent flares and remissions, and damages accumulate over time. There are lasting needs for SLE biomarkers for several reasons [2-4]. First, SLE presents with nonspecific symptoms, and diagnosis is difficult. There is no single test that is sufficiently sensitive and specific for diagnosis. Second, SLE treatment strategy should be modified according to the disease activity, but there is no reliable tool to measure such activity. Third, SLE involves many organs, and the type and severity of involvement influences the patient prognosis, but there is no efficient test to predict or calculate risk of organ damages [3].

The hallmarks of SLE are production of autoantibodies and organ damage due to immune complex deposition. Autoantibodies have been used to assess SLE for more than 50 years [5]. Over 180 autoantibodies are identified, and some are considered indicators of disease activity and prognosis [6].

Anti-U1 ribonucleoprotein (RNP) antibodies react with proteins (70 kDa, A, C) that are associated with U1 RNA, forming U1 small nuclear ribonucleoprotein, and usually accompany anti-Sm [7]. They are positive in 25%~47% of SLE patients and in nearly all patients with mixed connective tissue disease (MCTD) [8,9]. In a study that investigated detection of autoantibodies before the onset of

clinical symptoms and diagnosis of SLE, anti-RNP was detectable later than other antibodies, close to onset of clinical symptoms of disease, and the authors suggested anti-RNP as a pathogenic auto-immunity along with anti-ds DNA and anti-Sm [10]. Anti-U1 RNP antibodies are associated with milder renal involvement [11], are more prevalent in patients with Raynaud's phenomenon [12], and associated with photosensitivity [13]. In a longitudinal study of MCTD that investigated titer of autoantibody against RNP and U1-70kDa, the presence of anti-U1 and disease activity were associated, with antibodies disappearing during prolonged remission or improvement [14]. However, in patients with SLE, the utility of measuring titer of anti-U1 RNP for monitoring disease activity or treatment response is unclear [2,15].

In the previous issue of *The Journal of Rheumatic Diseases*, Kim et al. [16] described an interesting relationship between the presence of anti-RNP at diagnosis and clinical manifestations of SLE. In this study, SLE patients with anti-RNP at the time of diagnosis had a higher SLE Disease Activity Index (SLEDAI) score and eight-fold higher risk of disease flare-up than patients without anti-RNP did during the first year of follow-up. In addition, patients with anti-RNP more frequently developed oral ulcer, skin rash, and arthritis. However, a limitation of this study, as authors admitted, was the short observation period and the small number of patients. As features of MCTD occur sequentially over years, and MCTD can evolve into other diseases [17], some patients with MCTD might have been included and affect the result.

Apart from conventional autoantibodies such as anti-ds

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**Corresponding to :** Chan Hong Jeon, Division of Rheumatology, Department of Internal Medicine, Soon Chun Hyang University Bucheon Hospital, 170 Jomaru-ro, Wonmi-gu, Bucheon 14584, Korea. E-mail : [chjeon@gmail.com](mailto:chjeon@gmail.com)

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DNA and anti-Sm, there are some novel autoantibodies that have potential in monitoring of clinical activity and prediction of organ specific involvement in SLE. In SLE, major T and B cell immune responses are directed against nucleosomes that are composed primarily of DNA complexed with histone proteins [5]. Anti-nucleosome antibodies are positive in 70% to 100% of SLE patients with a high specificity (up to 97%) and are frequently present in patients with lupus nephritis [18]. They are strongly associated with lupus disease activity, and are thought to be useful in predicting flares in stable lupus [11].

Complement (C) 1q is the first component of the classical pathway, a key for activation of complement cascade, and its main function is clearing immune complexes [19,20]. Anti-c1q is closely associated with SLE activity, especially renal involvement. Anti-C1q antibodies are found in 30% to 60% of SLE patients [4] and are more common in patients with active nephritis than in those with no renal disease [21].

N-methyl-D-aspartate receptor is a glutamate receptor subtype consisting of subunits (NR1, NR2, and NR3) crucial in synaptic transmission [19]. Ant-NR2 are detected in sera of 30% of SLE patients, and are positively associated with central nervous system symptoms or neuropsychiatric dysfunction [4]. Moreover, cerebrospinal fluid level of anti-NR2 is also positively associated with neurological or psychologic symptoms, suggesting utility in neuropsychiatric SLE diagnosis [4,19].

In conclusion, because SLE symptoms are protean, a single biomarker is unlikely to be sufficient. Rather, different markers may be needed to measure activity of differing clinical symptoms and predict differing organ involvement [4]. In this respect, the result of the study by Kim et al. [16] may contribute to more understanding of autoantibodies as biomarkers of SLE.

## CONFLICT OF INTEREST

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

## REFERENCES

- Liu CC, Kao AH, Manzi S, Ahearn JM. Biomarkers in systemic lupus erythematosus: challenges and prospects for the future. *Ther Adv Musculoskelet Dis* 2013;5:210-33.
- Reveille JD. Predictive value of autoantibodies for activity of systemic lupus erythematosus. *Lupus* 2004;13:290-7.
- Lateef A, Petri M. Unmet medical needs in systemic lupus erythematosus. *Arthritis Res Ther* 2012;14 Suppl 4:S4.
- Ahearn JM, Liu CC, Kao AH, Manzi S. Biomarkers for systemic lupus erythematosus. *Transl Res* 2012;159:326-42.
- Biesen R, Rose T, Hoyer BF, Alexander T, Hiepe F. Autoantibodies, complement and type I interferon as biomarkers for personalized medicine in SLE. *Lupus* 2016;25:823-9.
- Yaniv G, Twig G, Shor DB, Furer A, Sherer Y, Mozes O, et al. A volcanic explosion of autoantibodies in systemic lupus erythematosus: a diversity of 180 different antibodies found in SLE patients. *Autoimmun Rev* 2015;14:75-9.
- Keith MP, Moratz C, Tsokos GC. Anti-RNP immunity: implications for tissue injury and the pathogenesis of connective tissue disease. *Autoimmun Rev* 2007;6:232-6.
- Kattah NH, Kattah MG, Utz PJ. The U1-snRNP complex: structural properties relating to autoimmune pathogenesis in rheumatic diseases. *Immunol Rev* 2010;233:126-45.
- Migliorini P, Baldini C, Rocchi V, Bombardieri S. Anti-Sm and anti-RNP antibodies. *Autoimmunity* 2005;38:47-54.
- Arbuckle MR, McClain MT, Rubertone MV, Scofield RH, Dennis GJ, James JA, et al. Development of autoantibodies before the clinical onset of systemic lupus erythematosus. *N Engl J Med* 2003;349:1526-33.
- Cozzani E, Drosera M, Gasparini G, Parodi A. Serology of lupus erythematosus: correlation between immunopathological features and clinical aspects. *Autoimmune Dis* 2014;2014:321359.
- Reichlin M, Van Venrooij WJ. Autoantibodies to the URNP particles: relationship to clinical diagnosis and nephritis. *Clin Exp Immunol* 1991;83:286-90.
- Tang X, Huang Y, Deng W, Tang L, Weng W, Zhang X. Clinical and serologic correlations and autoantibody clusters in systemic lupus erythematosus: a retrospective review of 917 patients in South China. *Medicine (Baltimore)* 2010;89:62-7.
- Burdett MA, Hoffman RW, Deutscher SL, Wang GS, Johnson JC, Sharp GC. Long-term outcome in mixed connective tissue disease: longitudinal clinical and serologic findings. *Arthritis Rheum* 1999;42:899-909.
- Mohan C, Assassi S. Biomarkers in rheumatic diseases: how can they facilitate diagnosis and assessment of disease activity? *BMJ* 2015;351:h5079.
- Kim DS, Pyo JY, Byun SJ, Ahn SS, Song J, Park YB, et al. The presence of anti-ribonucleoprotein at diagnosis is associated with the flare during the first follow-up year in Korean patients with systemic lupus erythematosus. *J Rheumatic Dis* 2016;23:154-60.
- Cappelli S, Bellando Randone S, Martinović D, Tamas MM, Pasalić K, Allanore Y, et al. "To be or not to be," ten years after: evidence for mixed connective tissue disease as a distinct entity. *Semin Arthritis Rheum* 2012;41:589-98.
- Ravirajan CT, Rowse L, MacGowan JR, Isenberg DA. An analysis of clinical disease activity and nephritis-associated serum autoantibody profiles in patients with systemic lupus erythematosus: a cross-sectional study. *Rheumatology (Oxford)* 2001;40:1405-12.
- Su D, Liu R, Li X, Sun L. Possible novel biomarkers of organ involvement in systemic lupus erythematosus. *Clin Rheumatol* 2014;33:1025-31.
- Katsumata Y, Miyake K, Kawaguchi Y, Okamoto Y, Kawamoto M, Gono T, et al. Anti-C1q antibodies are asso-

- ciated with systemic lupus erythematosus global activity but not specifically with nephritis: a controlled study of 126 consecutive patients. *Arthritis Care Res* 2011;63:2436-44.
21. Marto N, Bertolaccini ML, Calabuig E, Hughes GR, Khamashta MA. Anti-C1q antibodies in nephritis: correlation between titres and renal disease activity and positive predictive value in systemic lupus erythematosus. *Ann Rheum Dis* 2005;64:444-8.