Another Possible Underlying Mechanism for the Positive Association Between Celiac Disease and Systemic Lupus Erythematosus: The Role of Interleukin 21

To the Editor:

We read with great interest the recent contribution by Ludvigsson, *et al*[1]. They reported the increased risk of systemic lupus erythematosus (SLE) in 29,000 patients with biopsy-verified celiac disease (CD) and suggested that the association of CD and SLE could be part of the spectrum of "shared autoimmunity." We would like to add another pathomechanism of the association between the 2 diseases.

SLE is a complex autoimmune disease characterized by dysregulated interactions between autoreactive T and B lymphocytes and the development of antinuclear antibodies[2]. The novel cytokine interleukin 21 (IL-21) has been found to have a central role in the differentiation and function of B cells[3], raising the possibility that IL-21 may contribute to the pathology of B cell-mediated autoimmune disease. Herber, *et al* studied the effect of blocking IL-21 on disease in the SLE-prone MRL-Fas (lpr) mouse model[4]. Mice treated for 10 weeks with IL-21 receptor(R)-Fc fusion protein had reduced proteinuria, fewer IgG glomerular deposits, no glomerular basement membrane thickening, reduced levels of circulating dsDNA autoantibodies, total sera IgG1 and IgG2a, and reduced skin lesions and lymphadenopathy, compared with control mice[4].

Nakou, *et al* reported that patients with active SLE had 4-fold higher IL-21 mRNA and increased levels of intracellular IL-21 in peripheral blood CD4+ T cells, and addition of IL-21 to lupus autologous mixed lymphocyte cultures induced significant IgG production[5]. Treatment with IL-21R-Fc to block IL-21/IL-21R interaction reduced the proportion of plasma cells[5]. They concluded that increased IL-21 may synergize with Toll-like receptor–9 signaling and contribute to generation of plasma cells in patients with active SLE[5].

Fina, *et al* also demonstrated that IL-21 RNA and protein expression were enhanced in duodenal samples from patients with untreated CD, and blockade of IL-21 activity in biopsies of these patients reduced T-bet and interferon-γ secretion[6]. Further, a recent study showed that CD risk was increased when serum levels of IL-21 were elevated in both untreated and treated CD, compared to controls[7].

Therefore, increased IL-21 in CD may be one of the underlying mechanisms for the positive association with SLE, although Ludvigsson, *et al* did not measure IL-21 levels. Further studies should be performed to determine whether IL-21 might be related to the development of the 2 diseases at the same time.

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REFERENCES

1. Ludvigsson JF, Rubio-Tapia A, Chowdhary V, Murray JA, Simard JF. Increased risk of systemic lupus erythematosus in 29,000 patients with biopsy-verified celiac disease. J Rheumatol 2012;39:1964-70.
2. Goldblatt F, Isenberg DA. New therapies for systemic lupus erythematosus. Clin Exp Immunol 2005;140:205-12.
3. Leonard WJ, Spolski R. Interleukin-21: A modulator of lymphoid proliferation, apoptosis and differentiation. Nat Rev Immunol 2005;5:688-98.
4. Herber D, Brown TP, Liang S, Young DA, Collins M, Dunussi-Joannopoulos K. IL-21 has a pathogenic role in a lupus-prone mouse model and its blockade with IL-21R.Fc reduces disease progression. J Immunol 2007;178:3822-30.
5. Nakou M, Papadimitraki ED, Fanouriakis A, Bertsias GK, Choulaki C, Goulidaki N, et al. Interleukin-21 is increased in active systemic lupus erythematosus patients and contributes to the generation of plasma B cells. Clin Exp Rheumatol 2013;31:172-9.
6. Fina D, Sarra M, Caruso R, Del Vecchio Blanco G, Pallone F, MacDonald TT, et al. Interleukin 21 contributes to the mucosal T helper cell type 1 response in coeliac disease. Gut 2008;57:887-92.
7. Einarsdottir E, Koskinen LL, de Kauwe AL, Dukes E, Mustalahti K, Balogh M, et al. Genome-wide analysis of extended pedigrees confirms IL2-IL21 linkage and shows additional regions of interest potentially influencing coeliac disease risk. Tissue Antigens 2011;78:428-37.

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