Dr. Ludvigsson, *et al* reply

To the Editor:

We thank Park, *et al* for their interest¹ in our report². We agree that the association between SLE and celiac disease (CD) is multifactorial, at both genetic and environmental levels, and merits further study. Interleukin 21 (IL-21), an important cytokine for B cell growth and differentiation, needs to be examined in systemic lupus erythematosus (SLE) and CD, but multiple cytokine pathways are associated with these diseases. The pathogenic role of this cytokine is not exclusive to these 2 diseases, and aberrations in IL-21 are described in rheumatoid arthritis, multiple sclerosis, and Crohn disease. The contribution of IL-21 to the disease process may be complex because of its dual proinflammatory and antiinflammatory effects³. IL-21 has a biphasic role in the BXSB-*Yaa* mouse model of SLE; early treatment with IL-21 receptor-Fc fusion protein led to decreased survival, whereas late treatment was beneficial, but no differences were found in the severity of nephritis between the groups⁴. The authors suspected an early beneficial effect of IL-21 in expanding CD8+ suppressor T cells, whereas the late benefit was felt to be secondary to its effect on T follicular helper cells that promote humoral immunity. In CD, IL-21 has a disease-promoting effect, but it is likely in concert with other cytokines such as IL-15⁵. *In vitro* studies show that IL-21 suppresses the maturation of dendritic cells and downregulates the expression and activation of the NKG2D receptor in human natural killer and CD8+ T cells⁵; however, these effects are overcome by IL-15. IL-15 promotes chronic intestinal inflammation through its effect on the transforming growth factor- β pathway, and blocking IL-15 may be beneficial⁶.

Although IL-21 is an attractive therapeutic target, more work is needed to understand its role in the pathogenesis of autoimmune diseases.

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