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Letter to the Editor

The Role of Interleukin-23/Interleukin-17 Axis in Coexisting Anti-glomerular Basement Membrane Disease and Lupus Nephritis

To the Editor,

We read with great interest the contribution by Yadla et al[1] entitled, "An unusual association of anti-GBM diseases and lupus nephritis presenting as pulmonary renal syndrome," published in your esteemed journal. They reported an unusual case of coexisting lupus nephritis (LN) and anti-glomerular basement membrane (anti-GBM) disease and suggested three plausible pathogeneses of the association between the two diseases: Interstitial pneumonitis due to LN and secondary production of anti-GBM antibody, downstream molecular pathways including complement- and FcR-dependent activation of resident renal cells, and kallikrein. We would like to add another possible pathomechanism in view of immunopathology.

According to an *in vitro* experiment by Zhang et al,[2] interleukin (IL)-23–induced nephritis by lymph node cells from lupus-prone mice and the expression of IL-17 and IL-23 receptors in lymphocytes increased as the disease progressively worsened. *Ex vivo* induction of IL-17 by IL-23 from co-stimulated lymphocytes was significantly higher in systemic lupus erythematosus patients than controls (P <0.05).[3] In another animal study, IL-23R–deficient lupus-prone C57BL/6-lpr/lpr mice showed decreased number of CD3(+)CD4(−)CD8(−) double-negative T cells and IL-17–producing cells in the lymph nodes, and produced less anti-DNA antibodies.[4] These experiments indicate the importance of aberrant activation of IL-23/1L-17 axis and IL-23R–mediated signaling in the development of LN.

Recently, Ooi et al[5] demonstrated that mice deficient in IL-23 were protected from experimental autoimmune anti-GBM glomerulonephritis, but mice with IL-23 were not. IL-23–deficient strains also exhibited lower autoantibody titers, reduced cellular reactivity, diminished production of cytokines such as interferon-gamma (Th1) and IL-17A (Th17), and less renal disease and glomerular IgG deposition. It shows that autoreactivity to the Goodpasture antigen, the non-collagenous domain of alpha3 type IV collagen [alpha3(IV)NC1], is directed primarily by IL-23, absence of which results in hyporeactivity including, but extending beyond a deficient Th17 response.

Therefore, it is possible that IL-23, a heterodimer composed of IL-12p40 and IL-23p19 subunits, and IL-17A, a cytokine produced by the IL-23–maintained Th17 subset, may play a pivotal role in the pathogenesis of coexisting LN and anti-GBM disease. However, further studies are necessary to elucidate the exact molecular role and signaling transduction pathway of IL-23 and IL-17 during the disease process. The relationship between LN and Goodpasture's syndrome and the proper biological treatment should also be further evaluated in the future.

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