Driving forces of inflammatory diseases: Th9 in allergic rhinitis and estrogen in SLE

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Destructive immune-mediated diseases are often accompanied with microenvironments that drive the vicious cycles of inflammation and pathological conditions. In this issue, two reports on allergic rhinitis and SLE revealed the association of IL-9 producing helper T cells and estrogen as enhancers of allergic rhinitis (AR) and lupus, respectively.

IL-9-producing helper T cell (Th9) was first thought as a Th2-associated helper T cell subset but detailed analysis of gene expression and cytokine profiles cemented this newly characterized helper T cell subset as a unique distinctive helper T cell.[1] Key cytokines shaping Th9 differentiation include IL-4, TGF□, which activate multiple transcription factors downstream, including STAT6, SMAD, PU.1 and IRF4, all of which are crucial for differentiation of Th9.[2] IL-9, a signature cytokine produced by Th9, is pleiotropic in functions. It promotes mast cell proliferation and tissue accumulation, enhances IgE class switch in B cell.[3] Therefore, it is not surprising to find association of Th9 with allergic diseases and asthmas. In fact, multiple lines of evidence suggested increased Th9 or IL-9 in allergic and asthma patients and animal models.[2] In this issue, Wang et al. extend the role of Th9 in AR, an upper airway inflammatory conditions induced by exposure to allergen.[4] They conducted their study in Chinese population and found increased IL-9$^+$ Th cells in PBMC of AR patients. The mRNA level of key transcription factors, including *irf4* and *PU.1*, increased in PBMC of AR patients. The correlation of Th9 frequency and disease severity was observed. Previously, it was reported that AR patients with pollen allergy have higher serum IL-9 than healthy controls, consistent with the report here.[5] In contrast, another study comparing the frequency of Th9 from PBMC of patients with AR and allergic asthma found that allergic asthma patients have the higher percentages of Th9, while AR and healthy control showed no difference.[6] Beyond the discrepancy among these studies, IL-9-producing Th9 emerges as one of the key players in driving airway inflammation and presents a novel target for therapeutic application.

Systemic lupus erythematosus (SLE) is an autoimmune disease involving multiple organs. Both genetic and environmental factors are believed to play a key role in driving the disease. Sex hormone, estrogen, has long been considered as one of the aggravating factors of SLE because of much higher incidence of diseases in female.[7] In this issue, a role of estrogen in SLE was examined in a mouse model with complement component deficiency. Deficiency of the classical pathway components of the complement system, C1 and C4, is associated with SLE in human and in a mouse model.[8] Extending on the observation that C4 deficiency in mice resulted in lupus-like phenotypes, and impaired regulatory T cells, Boonsoongnern et al. reported here that ovariectomized mice receiving 17-β estradiol gradually exhibited increased immune complex deposition in glomeruli and proximal convoluted tubules.[9] Furthermore, increasing reactivity of autoantibodies against dsDNA was observed in a dose- and time-dependent manner of 17-β estradiol treatment. This study further confirmed the role of estrogen as a factor that worsen the progression of SLE in this C4-deficiency model. Interestingly, the ovariectomy did not reduce the severity of disease, suggesting that estrogen plays a role in aggravating SLE disease progression.

Both studies highlighted here show complexity of immune-mediated diseases and the results open up the opportunity for a more targeted treatment.

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