Preview

Antibodies against type I IFN: The bad guys self-restrain in systemic lupus erythematosus

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B cells and autoantibodies have well-described pathological roles in systemic lupus erythematosus (SLE). Bradford et al.[1] now provide evidence that autoantibodies can also be protective by neutralizing type I interferons (IFNs) and restraining the activation of pathogenic B cells.

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with a prevalence around 0.1% in the general population. SLE can target various organs and has heterogeneous clinical manifestations, making the appropriate therapy selection challenging. Thus, patients often experience imperfect disease control, leading to impaired quality of life and sometimes death. The development of new treatments has been frustrating with only few drugs, including belimumab and anifrolumab, receiving approval for SLE during the last 60 years. However, significant progress is being made in the understanding of its pathophysiology, and novel treatment strategies are yielding remarkable results in pilot trials, leading to the identification of key cell types and cytokines driving this disease. In this context, the study by Bradford and colleagues[1] sheds new light on the interplay between B cells, autoantibodies, and type I interferons (IFNs) in SLE, filling a gap in this puzzle that will improve patient stratification and treatment selection.

SLE is prototypically associated with a rupture of immune tolerance in the B cell compartment, manifested by elevated levels of autoantibodies against double-stranded DNA and other nuclear antigens. This B cell involvement is further highlighted by the link between SLE flares and the expansion of circulating plasmocyte numbers. This has led to a focused interest for B-cell-targeted therapies such as rituximab to deplete CD20+ B cells, belimumab to deprive B cells of the cytokine BAFF, or daratumumab targeting CD38+ B cells, as well as proteasome inhibitors to reduce antibody-secreting cells. The value of targeting B cells to stop SLE was recently highlighted through the compassionate use of T cells expressing chimeric antigen receptor (CAR) directed against CD19, which resulted in rapid and durable remission, even upon the reappearance of B cells in previously refractory patients.[2] Although CAR-T cells were applied following conditioning with the lymphodepleting agents fludarabine and cyclophosphamide that may contribute to this beneficial effect, these outstanding results leave little doubt that B cells are the "bad guys" driving SLE. It is therefore important to map the factors controlling B cell activity in SLE.

In addition to B cells, SLE pathogenesis has been associated with type I IFNs. A strong type I IFN gene signature is observed in 50%–75% of patients and correlates with disease activity.[3] Type I IFNs are important inducers of B cell differentiation into plasmocyte in SLE, and several drugs have been tested to block the IFN pathway. The monoclonal antibody anifrolumab, which blocks the type 1 IFN receptor subunit 1 to inhibit IFN-I signaling, showed beneficial effects, particularly in patients presenting with an elevated IFN gene signature,[4] and was recently approved for patients with moderate to severe disease activity.

The study by Bradford and colleagues[1] now provides a new twist in the interplay between type I IFN and B cell autoreactivity, focusing on SLE patients harboring neutralizing autoantibodies against type I IFNs. The occurrence of autoantibodies to type I IFNs was previously described in patients with autoimmune polyendocrinopathy candidiasis ecto-dermal dystrophy (APECED) that is caused by genetic loss-of-function mutations in the gene autoimmune regulator gene (*AIRE*), in patients with thymoma, and recently in a small proportion of the general population (particularly in the elderly), which is at a higher risk of developing severe COVID-19.[5] The characterization of these COVID-19 patients indicated that autoantibodies to type I IFNs did not affect the abundance of various leukocyte subsets in blood but reduced the expression of interferon-stimulated gene (ISG)-1 in dendritic cells.[6] The loss of immune tolerance to type I IFN thus appears to arise in several contexts. It was known that some SLE patients also develop such autoantibodies and that a proportion of these autoantibodies possesses neutralizing activity.[7,8] Although it had been reported that these autoantibodies could be associated with a better disease course, there was little understanding of their mode of action.

In this issue of *Cell Reports Medicine*, Bradford et al.[1] provide important information on the effect of these autoantibodies on the B cell compartment in SLE patients. The assessment of 501 SLE patients revealed that 14% displayed autoantibodies to IFN-alpha and 4.2% had neutralizing autoantibodies to IFN-alpha. These patients had lower levels of IFN alpha and anti-double-stranded DNA in serum, as

well as a lower disease activity, being less commonly affected by renal, skin, and musculoskeletal involvements. A previous study by Gupta et al. investigated 199 SLE patients and 200 healthy controls and similarly reported that anti-type I IFN antibodies could display neutralizing activity and were associated with control of the type I IFN signature.[8] Bradford and colleagues[1] now bring some insights into the immune effects of these autoantibodies, reporting that these patients have a rebalanced B cell compartment with the improvement of abnormalities seen in active SLE such as the increased abundance of plasmocytes and double-negative B cells, as well as the reduced abundance of regulatory B cells. The effect of these autoantibodies could be recapitulated *in vitro* using a culture system in which activated B cells give rise to both plasmablasts and IL-10-expressing B cells. The presence of elevated amounts of type I IFNs in this culture favored the differentiation of plasmablast at the expense of IL-10-producing B cells, which could be reverted when IgG from patients with neutralizing autoantibodies were added to the culture. These autoantibodies thus seem to improve SLE by normalizing the B cell compartment in these patients. Are SLE patients carrying such autoantibodies at a higher risk of developing severe COVID-19? This question is also relevant in a broader context since SLE patients are more susceptible to serious infections.[9] In this respect, it might also be of interest that SLE patients having anti-type I IFN autoantibodies but no neutralizing activity might actually have potentiating autoantibodies, increasing the action of this cytokine, as previously described for other cytokines such as IL-2.[10] Could such potentiating autoantibodies help to stabilize type I IFN against diseases such as COVID-19?

In conclusion, the study by Bradford et al.[1] underlines the importance of evaluating the presence of such autoantibodies, which might help to calm the B cell compartment, in the stratification of SLE patients for treatment selection, especially since the approval of anifrolumab.

DECLARATION OF INTEREST

The author declares no competing interests.

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