Prior sun exposure and skin-specific auto-antibodies are associated with skin inflammation in systemic Lupus Erythematosus

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Almost 80% of systemic lupus erythematosus (SLE) patients manifest lupus-specific skin lesions as a result of immune dysregulation and sun exposure. We have previously demonstrated that skin-directed antibodies are present in SLE and are associated with a history of significant sun exposure. Blood was collected from three patient populations; SLE with a history of lupus-specific skin lesions as cases (n=17), SLE without a history of skin lesions (n=8) and atopic dermatitis (n=17) as controls. Serum anti-desmoglein-3 antibodies were measured by ELISA. Peripheral blood mononuclear cells were analyzed by flow cytometry. Patients completed a scored questionnaire addressing sun exposure history prior to disease onset. The questionnaire, flow cytometry and ELISA results were analyzed using Mann-Whitney U test. Questionnaire responses indicated increased sun exposure prior to disease onset in SLE patients with skin disease when compared to SLE patients without skin disease (median score=60 versus 34.5, respectively; p<0.05). Anti-desmoglein-3 auto-antibody titers were lower in SLE patients with skin disease compared to those with sun exposure consistent with the hypothesis that sun exposure is an environmental trigger for disease. The resulting immune activation of the skin may be reflected in aberrant skin-specific antibody production and heightened IL-21 secretion by TFF cells.

Single cell analysis reveals the autoantigen-reactive B cell cytokine production in systemic sclerosis

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Systemic sclerosis (SSc) is a connective tissue disease with an autoimmune background. Although the mechanism of SSc remains unknown, B cells are considered to play crucial roles. The autoreactive B cells have ability to produce several cytokines independent of the thymus. In this study, we focused on the production function using human B cells. We have previously demonstrated that the elimination of immunosuppressive signals and the enhancement of stimulatory pathways enhanced the vaccinal effect of TA99 anti-tumor antibodies in melanoma. Our data suggest that the elimination of immunosuppressive signals and the enhancement of stimulatory pathways could be used in the treatment of other malignancies. FDA-approved anti-tumor antibodies (such as rituximab and trastuzumab) have made a major impact in the treatment of other malignancies, but not yet in melanoma. These antibodies induce ADCC, and also drive antigen presentation-dependent adaptive immune responses to both neoantigens and differentiation antigens. To enhance anti-tumor antibody efficacy in melanoma, here we have explored eliminating the suppressive effects of Tregs, as well as enhancing adaptive Tcell responses using Tcells. Using the B16 melanoma model, we tested the combination of TA99 antibodies (anti-TRP1) and Treg depletion (using a single dose of anti-CD25 depleting antibodies) to cause a significant reduction and delay in tumor growth, associated with a reduced immunosuppressive environment and a strong CD137+ infiltrate, as shown by quantitative multispectral imaging. On the basis of this result, we investigated the therapeutic potential of the combination of TA99 antibodies and anti-CD137 (4-1BB) agonist antibodies in the B16 model of melanoma. Combination treatment resulted in a rapid and significant reduction of tumor growth with strikingly durable complete responses. Our data suggest that the elimination of immunosuppressive signals and the enhancement of stimulatory pathways enhanced the vaccinal effect of TA99 anti-tumor antibodies in melanoma. Furthermore, the combination of novel therapeutic strategies, including Treg depletion antibodies (such as mogamulizumab) or Tcell agonists (such as urelumab or utomilumab) with anti-tumor antibodies offers the possibility to expand the arsenal of immunotherapeutic approaches, including checkpoint inhibitors, currently in the clinic for melanoma.