A159 TARGET SILENCING OF DISEASE-ASSOCIATED B LYMPHOCYTES BY CHIMERIC MOLECULES IN SCID MODEL OF PRISTANE-INDUCED AUTOIMMUNITY

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Systemic lupus erythemathosus (SLE) is a polygenic autoimmune disease characterised by B cell hyperactivity that leads to the generation of autoantibodies, formation of immune complexes and clinical involvement of multiple organs. The current therapies of the disease are non-specific and more precise approaches targeting the disease-associated B lymphocytes, are urgently needed for clinical practice.

Experimental therapy in humans is limited by technical and ethical restrictions. In contrast, studies in humanised mouse models can circumvent some of these limitations. Severe combined immunodeficiency (SCID) mice, which lack both T and B lymphocytes and readily accept xenogenic cells, have been used widely for transfer of lymphocytes from SLE patients or from lupus-prone mice.

Autoreactive B cells have a prominent role in the pathogenesis of autoimmune diseases, not only as forerunners of autoantibody producing plasma cells, but also as antigen presenting cells. The co-ligation of Fcγ receptor (FcγRIIb) with B cell receptor (BCR) inhibits the BCR-induced cellular proliferation and other downstream biological responses. These functions make FcγRIIb an attractive target for downregulation of autoimmune B cell activity.

The authors constructed a chimeric antibody by coupling the dsDNA-mimicking peptides to a rat antimouse FcγRIIb monoclonal antibody to target disease-associated B lymphocytes only. Intravenous Ig (IVIg) preparations are known to modulate autoimmune diseases via several $F(ab')_2$- and Fc-dependent mechanisms. In the present study the authors test the effect of treatment with IVIg to pristane-induced autoreactive B cells and how this treatment affects the FcγRIIb expression. This study describes also a newly developed pristane-induced transferred SCID model of autoimmunity. This model allows the combination of pristane-induced autoimmune B or T cells from Balb/c mice with normal B or T cells from the same strain and modulation of the generated autoimmune response by a protein-engineered antibody.

Using the chimeric molecules in B (pristane) + T (pristane) transferred SCID model resulted in low level of IgG anti-DNA antibodies and of proteinuria during the treatment. In contrast, an increase in the urine protein concentration, anti-DNA antibodies and deposition of IgG-containing immune complexes in the glomeruli were observed in the phosphate-buffered saline-injected controls during the same period. No pathologic kidney histology was detected in DNA-like chimera injected animals.

The treatment of autoimmune-prone and healthy mice with therapeutic IVIg has been shown to upregulate the expression of the FcγIIb inhibitory BCRs. In contrast of lupus-prone mice pristane-induced autoimmunity is a result of different regulatory mechanism which acts opposite and the administration of IVIg downregulated FcγIIb B cell expression.

In the present study the authors report a possible way to limit the interaction between autoimmune B and T cells, resulting in suppression of the lupus syndrome in pristane-induced cell-transferred SCID mice. The elimination of autoantigen-specific B cells could leave autoreactive T cells without potency of prolonged pathogenetic effects and restricts the progress of lupus disease in pristan-induced SCID model of autoimmunity.