

**Investigation of immunological alterations
influencing the clinical picture of
systemic lupus erythematosus**

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PhD Thesis

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that is characterized by pathologic T cell functions, the production of autoantibodies and formation of immune complexes leading to a diverse array of clinical manifestations involving predominantly the joints, kidneys, mucocutaneous and nervous system and causing haematological abnormalities.

Although SLE usually occurs alone, many patients have symptoms characteristic of other connective tissue diseases such as Sjögren's syndrome (SS) and antiphospholipid syndrome (APS), and these overlaps greatly influence the clinical presentation of SLE. Galectin-1 (Gal-1) is an immunoregulatory protein, that induces apoptosis of activated T cells, and it's function has been implicated in the development of autoimmune diseases. Considering the Th1 and Th17 driven autoimmunity and the apoptotic dysregulation of T cells, SLE is suitable to study the function of Gal-1 in pathological conditions.

Objectives

In this work we wished to determine the antigenic epitope of m3AChR which interacts with autoantibodies from SLE, RA and SS patients. We attempted to compare the prevalence of anti-m3AChR antibodies in the studied disease groups. We also aimed to assess the various disease-specific clinical correlates of the anti-m3AChR and an overlapping SS in SLE.

We also set out to define the impacts of antiphospholipid antibody (APA) production alone, and an associated APS on the clinical presentation of SLE. Our objective was to compare the frequencies of the various non-thrombotic SLE manifestations between the APA-positive and APA-negative patients, and between the patients with and without definitive APS.

In this work, the possible pathogenetic role of Gal-1 was studied in SLE. Our aim was to analyse the sensitivity of SLE T cells to the exGal-1-mediated apoptotic signal. Furthermore we were searching for a correlation between disease activity and the Gal-1 related apoptotic disturbances of SLE T cells.

Patients and methods

The specific parameters of an overlapping SS were studied in 103 SLE patients, and compared with those on 65 patients with RA, 76 patients with pSS and 50 healthy controls. The presence of sicca complex was evaluated in the SLE and RA patients. Three immunodominant epitopes of the human m3AChR (AGSE, YNIP, TRIC) were identified and used as antigens in ELISA. By means of FACIT and SF-36 surveys we assessed the mental health of the patients.

We have assessed the risk of the development of non-thromboembolic disease manifestations of SLE with relation to the presence of APAs or APS in 224 SE patients. We studied 31 types of organ involvements, laboratory features and immunosuppressive therapy.

We investigated the Gal-1-related T cell apoptosis in a specific co-culture system. We involved 18 active (SLEDAI-2K ≥ 7) SLE patients and 20 controls. After immunosuppressive therapy the experiments were repeated in 10 inactive SLE patients (SLEDAI-2K < 7 or decrease in SLEDAI-2K ≥ 7).

Results

We revealed two distinct alterations that may contribute to the complex pathophysiology of exocrine gland dysfunction in SLE overlapping with SS: autoantibody production that directly targets m3AChR, the specific autonomic neurotransmitter receptor, and an altered mental health status that may be regarded as a central inhibitory mechanism of the parasympathetic innervation of the salivary glands.

47% of the SLE patients were found to produce at least one type of APA, and 23% fulfilled the criteria for APS. Significantly higher proportion of the APS cases developed nephritis, interstitial pulmonary involvement, pleuritis, myocarditis, organic brain syndrome or thrombopenia than in the non-APS group.

In active SLE the T cells displayed nearly zero apoptotic response to the effects of exGal-1, while control T cells exhibited a normal apoptotic reaction ($p=0,0004$). The SLE T cells' susceptibility to apoptosis increased after the disease has become quiescent to the same level as that observed in controls.

Discussion

Our results have revealed a probably polyclonal autoimmune reaction to multiple epitopes on the m3AChR in SLE, but also in RA similarly to that in pSS. The fusion of these antigenic peptides to GST may be useful in the development of a laboratory test for the diagnosis of SS. A dominant stress response and deteriorated psychosocial well-being are suggested as contributors to the pathogenesis of SS in SLE.

When SLE is associated with APA production or with APS, the risk of the development of non-thromboembolic disease manifestations is higher, in addition to APA-related symptoms. The burden of the disease is greater regarding the predisposition to more extensive organ damage and enhanced disease severity.

The analysis of activated SLE T cells shows a clear diminution in Gal-1 expression and concomitant resistance to exGal-1 triggered apoptosis. This finding is a potential novel marker to SLE pathogenesis and might contribute to the immunoregulatory dysfunction and enhanced T cell activity in SLE.