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# Anti-topoisomerase I autoantibodies in systemic sclerosis ☆

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ABSTRACT

Systemic sclerosis (SSc) is an autoimmune disease characterized by fibrosis of the skin, vascular abnormalities and activation of the immune system. The majority of SSc patients have autoantibodies against nuclear antigens. Among these antibodies against topoisomerase I (topo I) are frequently detected in sera of SSc patients. Since the discovery of these antibodies as immunoglobulins reacting with a 70 kDa nuclear protein (Scl-70), a massive body of clinical and experimental data has been generated. In this review we summarize accumulated evidence about anti-topo I autoantibodies in SSc, including results of epitope mapping studies and investigations on the possible pathogenic role of these antibodies.



**Contents**



## 1. Introduction

Systemic sclerosis (SSc) is a systemic autoimmune disorder characterized by immune activation, vascular injury, inflammation, fibrosis of the skin and various internal organs. Activation of the immune system leads to production of disease specific autoantibodies, lymphocyte activation and secretion of various cytokines [1]. Patients with SSc could be classified into two clinically distinct subsets. Diffuse cutaneous SSc (dcSSc) is characterized by rapid fibrosis of the skin, lungs and other organs, while in limited cutaneous SSc (lcSSc) vascular abnormalities are dominating and fibrosis is limited predominantly to the acral regions [2]. However, possible limitations of this two subset based classification system has been identified by a recent analysis of the EUSTAR database which indicated that a subset classification distinguishing anti-topoisomerase I and anti-centromere antibody positive subsets may even be clinically more relevant [3].

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Moreover, introduction of additional subsets reflecting integrated clinical parameters has also been proposed (reviewed in [4]).

The vast majority of SSc patients have antinuclear antibodies, which predominantly recognize DNA topoisomerase I (topo I), RNA polymerases, centromere proteins, and Th/To [5,6]. In addition antibodies against several other structures (including U3RNP, PM/Scl, B23, Ku, snRNP, mitochondrial components, defined or undefined cell surface antigens present on endothelial cells and fibroblasts, and extracellular antigens) could also be detected in sera of SSc patients (reviewed in [7]). However, the role of these antibodies in the pathogenesis of SSc is not clearly demonstrated.

In this review we summarize accumulated evidence about anti-topo I autoantibodies in SSc, including results of epitope mapping studies and investigations on the possible pathogenic role of these antibodies.

## 2. The family of topoisomerases

Topoisomerases change the tertiary structure of the DNA molecule either by relaxing supercoiled DNA through breaking and rejoining one strand at a time (type I enzymes) or by catalyzing catenation/decatenation, knotting/unknotting of DNA rings through breaking and rejoining DNA in a double-stranded fashion (type II enzymes) [8,9]. Type I enzymes are further classified to type IA subfamily if the enzyme forms a covalent link with the 5′ end of broken DNA, or type IB subfamily when the enzyme binds covalently to the 3′ phosphate. Topoisomerase activity has been detected in a variety of species from bacteria through mammals. In humans six distinct topoisomerase enzymes have been identified: topoisomerase I (topo I) a type IB enzyme, topoisomerase II a type II enzyme with two isoforms (topo IIα and topo IIβ), topoisomerase III a type IA enzyme with two isoforms (topo IIIα and topo IIIβ), and mitochondrial topoisomerase I which is a type IB enzyme. Topo I has a significant homology with mitochondrial topoisomerase I (52% identity, 64% similarity), while the other human topoisomerases have primary sequences showing no homology with topo I.

## 3. Identification of antibodies against topoisomerases

Anti-topo I autoantibodies were first identified by immunoblotting in sera of SSc patients as immunoglobulins reacting with a 70 kDa nuclear protein, and were termed anti-Scl-70 antibodies [10]. Since then it has been shown that Scl-70 is the breakdown product of topo I [11]. In addition to SSc the presence of anti-topo I antibodies has been demonstrated in systemic lupus erythematosus (SLE) patients showing no clinical signs and symptoms of systemic sclerosis [12,13].

While anti-topo I antibodies considered to be present almost exclusively in SSc, the presence of anti-topo IIα autoantibodies has been demonstrated in a number of autoimmune disorders including SSc [14], localized scleroderma [15], idiopathic pulmonary fibrosis [16], systemic lupus erythematosus [17], juvenile rheumatoid arthritis [18], and insulin dependent diabetes mellitus [19]. To date the presence of autoantibodies against other members of the topoisomerase family has not been demonstrated. Since anti-topo I autoantibodies are considered to have a high specificity for SSc in further parts of this review we will address anti-topo I antibodies.

## 4. Anti-topoisomerase I autoantibodies: isotype, prevalence, and association with clinical parameters

Anti-topo I antibodies are most frequently detected with IgG isotype, although the presence of anti-topo I antibodies with IgA and IgM isotype has also been demonstrated [20]. The mean frequency of anti-topo I autoantibodies among SSc patients is around 20%, with a high specificity for SSc [21]. Anti-topo I autoantibodies are considered to be associated with dcSSc [22,23]. However, the presence of anti-topo I autoantibodies may not be entirely restricted to this subset, since a subgroup of lcSSc patients was also found to be positive [3,22]. Anti-topo I autoantibody is found to be associated with increased mortality, pulmonary fibrosis,

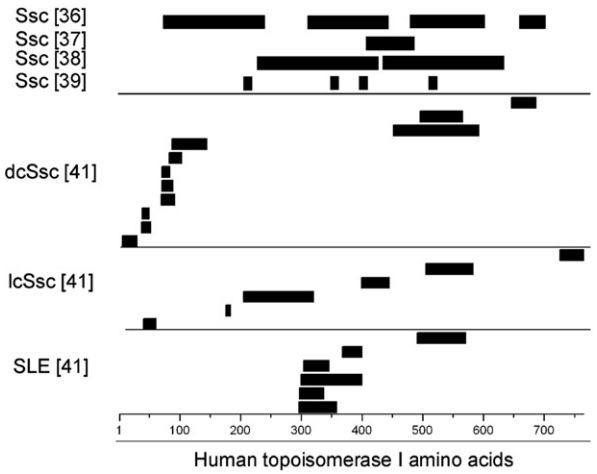


**Fig. 1.** Results of epitope mapping studies performed with topoisomerase I. Identified epitope regions are indicated by black boxes. Abbreviations on the left indicate the investigated diseases or disease subsets. SSc: systemic sclerosis, dcSSc: diffuse cutaneous systemic sclerosis, lcSSc: limited cutaneous systemic sclerosis, SLE: systemic lupus erythematosus. Numbers in square brackets indicate references cited.