

Structure-function studies on TRIM21/Ro52, a protein involved in autoimmune diseases

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Abstract

Several members of the tripartite motif (TRIM) protein family are involved in antiviral activity and immunity and have been linked to several diseases. TRIM21, the main object of this thesis, is involved in Sjögren syndrome (SS) and systemic lupus erythematosus (SLE), where patients often have autoantibodies against different epitopes on TRIM21. During the course of this study a role of TRIM21 in regulation of proinflammatory cytokines and autoimmunity emerged. The aim of this thesis is to provide a better understanding of the structure-function relationship of TRIM21. A conformational epitope in the coiled-coil domain of TRIM21 has been characterized, whose autoantibodies cause congenital heart block. A wide range of biophysical methods were employed to establish a model of the protein domain arrangement of TRIM21, and functional implications were derived. By sequence comparisons, TRIM proteins were classified into three subgroups, sharing a conserved amphipathic helix in the region, linking the conserved N-terminal Zn^{2+} -binding domains RING and B-box, called the RING-B-box linker (RBL). A structural dependence of this region on the RING has been observed and a model of the RING-RBL was derived from bioinformatics and proteolysis data. Anti-RING-RBL antibodies inhibit the E3 ligase activity of TRIM21 in ubiquitination. Interferon regulatory factors (IRFs), the substrate for TRIM21-dependent ubiquitination could therefore retain their high cellular levels after stress-induced inflammation, increasing the susceptibility to SS and SLE. According to NMR data, the antibodies bind to the Zn^{2+} -binding loop regions of the RING, which usually bind to the E2 conjugating enzyme. Antibodies against the C-terminus of the RBL region do not inhibit the E3 ligase activity.

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