Institutionen för Medicin

TRIM21/ Ro52 in B cell pathology

AKADEMISK AVHANDLING
som för avläggande av medicine doktorsexamen vid Karolinska
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ABSTRACT

Primary Sjögren’s syndrome (pSS) is a systemic autoimmune disease affecting 0.2% of the population. Several B cell aberrances have been linked to pSS, such as autoantibody production, hypergammaglobulinemia and B cell associated genetic polymorphisms. In addition, pSS patients display a 16 fold increased risk to develop B cell lymphomas. Autoantibodies to TRIM21/ Ro52 are detected in approximately 70% of patients with pSS. The cellular role of TRIM21 was largely unknown when this thesis was initiated. However, TRIM21 had been implicated to belong to the TRIpartite Motif (TRIM) family, of which many proteins are E3 ligases, mediating ubiquitination. The aims of this thesis were to characterize the role of B cells in primary Sjögren’s syndrome pathogenesis and to elucidate the cellular role of the autoantigen TRIM21.

By using vaccination as a tool to study immune responses pSS in vivo, we detected a vigorous B cell hyperreactivity, specifically in IgG producing cells. Further, in vitro induction of IgG class switch revealed an increased response to endosomal Toll-like receptor (TLR) stimulation in B cells from patients. This phenomenon may explain the hypergammaglobulinemia observed in pSS patients, and possibly also the high autoantibody titers.

In both in vivo and in vitro ubiquitination assays, we could show that TRIM21 is an E3 ligase. To better understand its role in immunity, a TRIM21−/− IRES-GFP mouse was generated. Studies revealed a hyperresponsive immune system. Mild immune activation induced Th17-dependent dermatitis and subsequently systemic autoimmunity with hypergammaglobulinemia, anti-nuclear antibodies and glomerulonephritis. We observed that TRIM21 regulates several interferon regulatory factors (IRFs), central transcription factors of pro-inflammatory responses, by ubiquitination. The loss of TRIM21 expression therefore resulted in loss of negative regulation of the transcription factors, and thereby accentuated immune responses.

By using GFP as a reporter in the TRIM21-deficient-IRES-GFP mice, we observed that TRIM21 protein is almost exclusively expressed in hematopoietic cells. Further, overexpression of TRIM21 in a B cell lymphoma cell line resulted in markedly reduced proliferation and increased apoptosis. These findings prompted us to study the role of TRIM21 in lymphomagenesis. In three independent cohorts of diffuse large B cell lymphomas (DLBCL), a strong correlation between low TRIM21 expression and short overall and progression-free survival was demonstrated.

In conclusion, these studies show that endosomal TLR hyperreactivity underlie hypergammaglobulinemia in primary Sjögren’s syndrome. Further, the major autoantigen TRIM21 is an E3 ligase, negatively regulating interferon and TLR responses. Loss of TRIM21 expression is associated both to aggravated immune responses and poor outcome in lymphoma development, implicating a central role for TRIM21 in the development of both systemic autoimmune diseases and lymphomas.