Nature Reviews Rheumatology **8**, 564 (2012); published online 4 September 2012; doi:10.1038/nrrheum.2012.146

CONNECTIVE TISSUE DISEASES

Role for STIM proteins in Sjögren's syndrome pathogenesis

Researchers at the National Institute of Dental and Craniofacial Research at the NIH have shown, for the first time, that deficiency in stromal interaction molecules Stim1 and Stim2 in T cells results in a Sjögren's-like disease in mice. In addition, expression of STIM proteins is reduced in T cells from patients with Sjögren's syndrome, underlining a role for these proteins in the pathogenesis of this disease.

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"Our lab is interested in two major areas of research—Sjögren's syndrome pathogenesis and Ca^{2+} signalling—which came together in this exciting study", explains Indu Ambudkar, the lead author of a report published in the *Proceedings of the National Academy of Sciences*. "STIM proteins are the primary regulators of Ca^{2+} channels involved in store-operated calcium entry", says Ambudkar; this process is known to regulate the functions of many cell types including those of the immune system. Prompted by their interest in the pathogenesis of Sjögren's syndrome and the findings of other researchers in patients with *STIM1* mutations, Ambudkar and colleagues used previously generated double-knockout (DKO) mice that lack T-cell-expression of Stim1 and Stim2 (*Stim1*/*Stim2* DKO mice) to investigate a possible role for these proteins in salivary gland pathology.

First, the authors induced saliva production in the mice: salivary flow was reduced by a third in the *Stim1*/*Stim2* DKO mice compared with control mice. Next, they studied the levels of Sjögren's syndrome-specific antibodies (SSA/Ro and SSB/La). Levels of both antibodies were considerably higher in the *Stim1*/*Stim2* DKO mice than the controls. Finally, unlike in the control mice, moderate lymphocytic infiltration of the submandibular glands was seen at 6 weeks of age in the *Stim1*/*Stim2* DKO mice, which progressed to extensive infiltration, severe inflammation and destruction of salivary gland structure by 12 weeks. The *Stim1*/*Stim2* DKO mice, therefore, displayed the major features of Sjögren's syndrome.

The investigators also examined peripheral blood mononucelar cells and lymphocytic infiltrates from submandibular glands from patients with Sjögren's syndrome: these cells were found to have reduced levels of STIM1 and STIM2 and compromised Ca^{2+} influx compared with those from healthy controls. "There are no data regarding STIM proteins and Sjögren's syndrome, so this is an entirely new finding in this disease", concludes Ambudkar.

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Original article Cheng, K. T. *et al.* STIM1 and STIM2 protein deficiency in T lymphocytes underlies development of the exocrine gland autoimmune disease, Sjögren's syndrome. *Proc. Natl Acad. Sci. USA* doi:10.1073/pnas.1207354109