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CONNECTIVE TISSUE DISEASES

New cellular players in Sjögren syndrome pathogenesis

> "treatment of NOD mice with LTβR-Ig fusion protein affected some, but not all, CD4$^+$ T cell subsets"

Scientists have identified two novel PD1$^+$ CD4$^+$ T cell subsets in the target tissue of primary Sjögren syndrome (pSS), one corresponding to a population of regulatory T cells and the other to a pathogenic T cell subset. The findings provide new insights into the pathogenesis of the disease and could help in the design of future therapies.

To overcome the limitations of current histological methods for studying the composition of cellular infiltrates in glandular tissue, the investigators used novel techniques, combining highly dimensional flow cytometry and mass cytometry with transcriptome analyses. "This approach allowed us to identify two novel cell subsets characterized by the shared expression of PD1 and ICOS at high levels and differential levels of CD73 and CD200, which identified a pathogenic effector T cell subset and a FOXP3$^+$ effector regulatory T cell subset," states Michael Mingueneau, the study's corresponding author. Initially identified in lacrimal gland tissue of NOD mice, the presence of these T cell subsets was also verified within salivary gland tissue of patients with pSS.

Mingueneau and colleagues next examined the effects of lymphotoxin-β receptor-Ig (LTβR-Ig) fusion protein treatment on the recruitment and accumulation of these cells. "A strong body of data gathered from mouse models supported the notion that treatment with LTβR-Ig would prevent or reverse the hallmark inflammatory infiltrates in, and improve the function of, the target tissues of pSS, thereby alleviating disease symptoms," explains co-author Taylor Reynolds. However, treatment of NOD mice with LTβR-Ig fusion protein affected some, but not all, CD4$^+$ T cell subsets, an observation that could explain why a clinical trial of the LTβR-Ig fusion protein baminercept did not meet its primary end point. "Importantly, unlike naive CD4$^+$ T cells, recruitment of PD1$^+$ effector T cells to the target tissue in NOD mice was not halted by treatment with LTβR-Ig, a finding which, if also true in humans, could contribute to the lack of clinical benefit in pSS patients in the baminercept trial," Reynolds says.

These findings could help "pave the way to the development of improved therapeutic strategies that would selectively affect the cell subsets with pathogenic potential while leaving unaffected cells with immunoregulatory functions," concludes Mingueneau.

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ORIGINAL ARTICLE Haskett, S. *et al.* Identification of novel CD4$^+$ T cell subsets in the target tissue of Sjögren's syndrome and their differential regulation by the lymphotoxin/LIGHT signaling axis. *J. Immunol.* http://dx.doi.org/10.4049/jimmunol.1600407 (2016).

FURTHER READING St Clair, E. W. *et al.* The clinical efficacy and safety of baminercept, a lymphotoxin-β receptor fusion protein, in primary Sjögren's syndrome: results from a randomized, double-blind, placebo-controlled phase II trial [abstract]. *Arthritis Rheumatol.* **67** (Suppl. 10), 3203 (2015).