Medical University of Graz

Metabolism and function of naive CD4+ T-cells in primary Sjögren‘s Syndrome

Summary

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Supervisor:	Prof. Dr. Martin Stradner
Availability:	This position is available.
Offered by:	Medical University of Graz
Application deadline:	Applications are accepted between August 14, 2020 00:00 and October 10, 2020 23:59 (Europe/Zurich)

Description

Background:

Primary Sjögren’s syndrome (pSS) is a chronic, systemic autoimmune disorder characterized by lymphocyte infiltration of exocrine glands such as salivary and lachrymal glands. Glandular inflammation and tissue damage ultimately lead to secretory dysfunction and symptoms of dryness including keratoconjunctivitis sicca and xerostomia.(1) The pathophysiology of pSS is multifaceted and environmental as well as genetic factors contribute to the disease. The robust genetic association between HLA class II and pSS implies a crucial involvement of T-cells. IFNγ as well as IL-17 producing T-cells are present in inflamed salivary glands of pSS patients and are associated with tissue damage.(2) Given the importance of both T-cells in the pathogenesis of pSS, it is interesting to note that peripheral lymphopenia is a frequent finding in pSS patients and was shown to be associated with higher disease activity and mortality. In healthy individuals, T-cell production of the thymus as well as homeostatic proliferation of peripheral T-cells compensate for naturally occurring T-cell loss. In a recent study, we identified fundamental alterations in naïve T-cell homeostasis including reduced homeostatic proliferation, a history of extensive replication and signs of cellular senescence as a potential cause for lymphopenia in pSS patients.(3)

Hypothesis and Objectives:

We propose that alterations in cellular metabolism affects naïve T-cell homeostasis and proliferation thus leading to lymphopenia. We aim to identify affected metabolic pathways in T-cells of pSS patients and further want to effectively target these pathways to reverse their homeostatic phenotype. Thereby, we will establish metabolic biomarkers for the diagnosis of pSS patients.

Methodology:

We will characterize the cellular metabolism of T-cells of pSS patients using a metabolomics approach, seahorse technique as well as functional assays with conitions media. Cell culture expermenits and flow cytometric analyses will allow us to study T-cell phenotypical and functional changes in response to genetic as well as genetic perturbation of metabolic pathways. In vivo experiments will be performed in a mouse model of pSS in order to estimate the applicability of the observed findings.

References:

1. Nocturne G, Mariette X. Advances in understanding the pathogenesis of primary Sjögren’s syndrome. Nat Rev Rheumatol [Internet]. 2013 Sep 16 [cited 2018 Feb 23];9(9):544–56.

2. Nguyen CQ, Hu MH, Li Y, Stewart C, Peck AB. Salivary gland tissue expression of interleukin-23 and interleukin-17 in Sjogren’s syndrome: findings in humans and mice. Arthritis Rheum. 2008;58(3):734–43.

Medical University of Graz

3. Fessler J, Fasching P, Raicht A, Hammerl S, Weber J, Lackner A, et al. Lymphopenia in primary Sjögren's syndrome is associated with premature aging of naïve CD4+ T cells. Rheumatology (Oxford) [Internet]. 2020 Mar 30 [cited 2020 Jul 9];