DYSFUNCTIONAL TELOMERASE IN NAÏVE CD4+ T-CELLS IN PRIMARY SJÖGREN'S SYNDROME

P. Fasching[1], A. Raicht[2], S. Hammerl[1], A. Lackner[1], J. Fessler[1], W. Schwinger[2], M. Stradner[1]

[1]Medical University of Graz, Div. of Rheumatology and Immunology, Graz, Austria
[2]Medical University of Graz, Div. of Paediatric Haematology and Oncology, Graz, Austria

Medical University of Graz

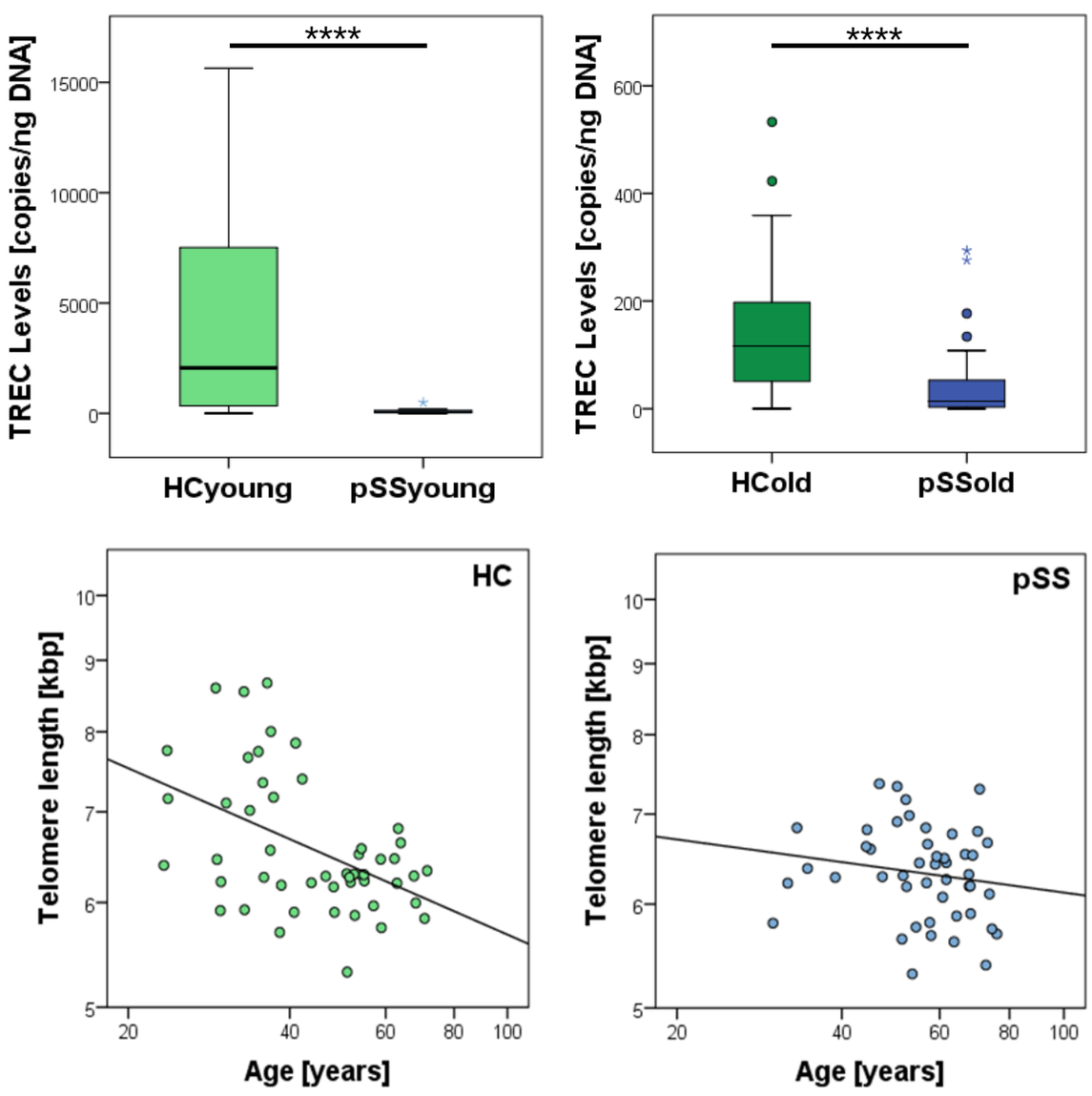
Background:

Lymphopenia is a frequent finding in primary Sjögren's syndrome (pSS) affecting mostly the $CD4^+$ T-cell polulation. In this study we aimed to examine possible underlying defects.

Methods:

We included 47 pSS patients and 50 healthy controls (HC) in a prospective, cross-sectional study. For part of the analysis, patients and HC were split into two groups to analyze data from younger (pSS_{young} 39.7 [30.0-47.3]; n=10 and HC_{young} 34.5 [23.3-46.6]; n=26) and older (pSS_{old} 61.7 [50.3-75.9]; n=37 and HC_{old} 57,6 [48.2-71.4]; n=24) individuals separately. The prevalence of total and naïve ($CD45RA^+$ $CCR7^+$) $CD4^+$ T-cells was assessed by flow cytometry according to standard surface staining protocols. Naïve $CD4^+$ T-cells were furthermore isolated by MACS technology for the assessment of telomere length and T-cell receptor excision circle (TREC) levels by real-time PCR, and telomerase activity was analyzed according to the Telomeric Repeat Amplification Protocols (TRAP).

Results:



Overall, we found lower numbers of $CD4^+$ T-cells in pSS patients compared to HC (480/µl vs. 790/µl; p<0.0001) with a reduction in the naïve subset accounting for most of this difference (130/µl vs. 313/µl; p<0.0001). The number of TRECs in naïve $CD4^+$ T-cells was already reduced in young pSS patients (58copies/ng DNA vs. 2058copies/ng DNA, p<0.0001) and was further decreased in older patients (14copies/ng DNA vs. 117copies/ng DNA, p=0.0001). To test for an increased proliferative history in the naïve subset we performed telomere length as well as telomerase activity analysis.

A decrease in telomere length correlated with increasing age in HC (r_s=-0.377, p=0.007). This correlation could not be observed in pSS patients. Instead, patients already displayed significantly shortened telomeres at young age compared to age-matched HC (6.5kbp vs. 7.0kbp, p=0.04). Moreover, the increase in age and the shortening of telomeres resulted in an elevation of telomerase activity in HC (r_s= 0,579; p<0.0001 and r_s=-0.532; p<0.0001), a finding that we could not observe in pSS patients.

Conclusion:

Our data indicate an extensive replicative history of naïve $CD4^+$ T-cells in pSS already at young age, resulting in premature shortening of telomeres. In contrast to HC, naïve $CD4^+$ T-cells from pSS patients are unable to induce telomerase activity. This telomerase deficiency may finally lead to the reduction of the naïve $CD4^+$ T-cell pool resulting in $CD4^+$ T-cell lymphopenia.