Materials and Methods We tested, using a 5 methyl cytosine (5MeCyt) ELISA, global DNA methylation in long-term cultured salivary gland epithelial cells (SGEC), peripheral T cells and B cells from eight SS patients. DNA methylation/demethylation partners were assessed by real time quantitative PCR (DNA methyl transferase (DNMT)1, DNMT3a/b, PCNA, UHRF1, MBD2, MBD4, and Gadd45-alpha). Immunofluorescence was conducted on labial salivary gland biopsy. Co-culture experiments were performed associating the human salivary gland cell line (HSG) and B cells.

Results Global DNA methylation was reduced in SGEC from SS patients (5MeCyt: 36.3 ± 3.2% in SS *versus* 43.1 ± 3.3% in controls, $P = 0.01$), while no difference was observed in T and B cells. SGEC demethylation in SS patients was associated with a 7-fold decrease of DNMT1 and a 1.8-fold increase of Gadd45-alpha expression. The other DNA methylation/demethylation partners tested were not differently expressed when compared to controls. Interestingly, SGEC demethylation may be attributed to the B cell infiltrate as DNA methylation increased in salivary gland biopsy after rituximab (anti-CD20 antibody) treatment. Such hypothesis was confirmed using co-culture experiments (HSG cells and B cells) revealing an alteration of the PKC-delta/ERK/DNMT1 pathway. Finally, DNA methylation was associated with the overexpression of several SGEC genes such as ICAM-1 and human endogenous retrovirus (HERV).

Conclusions SGEC dysfunction in SS may be linked to epigenetic modifications and this tissue specific defect may be ascribed in part to infiltrating B cells. This observation opens new therapeutic perspectives in SS.

A7.9 DOES TELOMERE SHORTENING IN WOMEN WITH RHEUMATOID ARTHRITIS PREDICT X CHROMOSOME INACTIVATION BIAS?

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Background Rheumatoid Arthritis (RA), like most auto-immune diseases, is a female predominant disease. As a possible explanation for gender bias, we have previously shown that women with RA have non-random X chromosome inactivation (XCI) that could trigger autoimmunity (article in preparation). Intriguingly, this bias in XCI correlates with presence of the shared epitope (SE) and with disease duration.

Also associated with presence of the SE, premature immunosenescence, characterised by shorter telomere length, has been described in peripheral blood cells from patients with RA [1]. Moreover, telomeric non coding RNAs have been reported to be enriched near the inactive X chromosome in mammals [2] indicating a potential link between telomere length and XCI.

Objectives In this context, we propose to test whether women with RA have shortened telomere length and whether that could influence the epigenetic mechanism of XCI.

Methods A total of 73 women with RA and 48 healthy women with no history of autoimmune diseases, who had previously been tested for XCI and HLA-genotyped, were evaluated for telomere length. The relative telomere length was estimated by real-time PCR as originally described by Cawthon [3] with the $2^{-\Delta\Delta Ct}$ method.

Results Preliminary results show that women with RA have smaller telomere length than healthy women, although the difference is modest ($p = 0.07$) and has to be adjusted for age on a larger cohort. Contrary to expectations, shorter telomere length is not correlated with skewed XCI status, disease duration or the presence of shared epitope in our small cohort.

Conclusions This preliminary study seems to confirm that women with RA have shorter telomeres than healthy women. Further telomere length measurements have to be done on a larger group of patients with RA and healthy controls, as well as HLA-genotyping them and evaluating their XCI status. This will be a step forward in understanding the relationship between immune senescence, female predisposition and genetic risk (SE) in RA.

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A7.10 GENETIC VARIANTS IN THE *IL-4* AND *IL-4* RECEPTOR GENES IN ASSOCIATION WITH THE SEVERITY OF JOINT DAMAGE IN RHEUMATOID ARTHRITIS: A STUDY IN SEVEN COHORTS

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Objective The progression of joint destruction in rheumatoid arthritis (RA) is determined by genetic factors. Changes in *IL-4* and *IL-4R* genes have been associated with RA severity but not replicated. We studied the association between *IL-4* and *IL-4R* tagging SNPs and progression rate of joint damage in RA in a multi-cohort candidate gene study.

Methods *IL-4* and *IL-4R* tagging SNPs (8 and 39, respectively) were genotyped in 600 RA-patients of whom 2,846 sets of hands and feet X-rays were collected during 7 years follow-up. Subsequently, significantly associated SNPs were genotyped and studied in relation to 3,415 X-rays of 1,953 RA-patients; these included data-sets from Groningen (NL), Lund (SE), Sheffield (UK), NARAC (USA), Wichita (USA) and NDB (USA). The relative increase in progression rate per year in the presence of a genotype was determined in each cohort. An inverse variance weighting meta-analysis was done on the six datasets that together formed the replication-phase.

Results In the discovery-phase none of the *IL-4* SNPs and seven of the *IL-4R* SNPs were significantly associated with joint damage progression rate. In the replication-phase, two SNPs in *IL-4R* gene were significantly associated with joint damage progression rate (Rs1805011, $p = 0.02$ and Rs1119132, $p = 0.001$).

Conclusions Genetic variants in *IL-4R* were identified and independently replicated to associate with progression rate of joint damage in RA.

A7.11 GENETIC VARIATION IN PROMOTER SEQUENCE OF B-CELL-ACTIVATING FACTOR OF THE TNF FAMILY (BAFF) IN PATIENTS WITH IDIOPATHIC INFLAMMATORY MYOPATHIES (IIM)

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