Figure 1. Effect of ISG15 on STAT phosphorylation and number of Treg and Tconv **Abstract THU0202 – Figure 1****REFERENCES:**

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THU0203

PROMOTER DNA METHYLATION AND HSA-MIR-424-5P REGULATE ATF6 ALPHA EXPRESSION IN SALIVARY GLANDS OF PATIENTS WITH SJÖGREN'S SYNDROME

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Background: Salivary glands (SG) from Sjögren's syndrome (SS)-patients show chronic inflammation and endoplasmic reticulum (ER) stress. To counteract ER stress, eukaryotic cells activate adaptive mechanisms referred to as the unfolded protein response via sensors present in the ER membrane, such as ATF6 α ^{1,2}. In response to ER stress, ATF6 α is translocated to the Golgi apparatus where is processed releasing ATF6f, which translocates into the nucleus as a transcription factor to activate ER-associated degradation and protein folding-related gene transcription³. The overexpression of ATF6 α observed in Labial SG (LSG) from SS-patients¹ could be modulated by epigenetic mechanisms.

Objectives: To evaluate the involvement of epigenetic mechanisms such as promoter-specific DNA methylation and microRNA (miRNA) regulation on ATF6 α expression in LSG from SS-patients and controls. The effect of IFN- γ on both mechanisms was also evaluated in a 3D-acini model.

Methods: SG biopsies from 12 SS-patients and 10 controls were analyzed. For in vitro assays 3D-acini incubated with 1 or 10 ng/mL IFN- γ for 24 h were employed. Specific DNA methylation of ATF6 α gene promoter was evaluated by methylation sensitive-high resolution melting PCR. The profile of miRNAs differentially expressed was determined by miRNA sequencing (seq), of which hsa-miR-424-5p was selected because the *in silico* analysis showed that ATF6 α mRNA is a target of this miRNA. The levels of hsa-miR-424-5p were determined by Taqman miRNA assays. Functional assays using miRNA mimic and miRNA inhibitors were also performed.

Results: LSG from SS-patients showed a significant decrease of ATF6 α promoter DNA methylation percentage (p=0.04), which was inversely correlated with high ATF6 α mRNA levels (p= 0.02). The hsa-miR-424-5p was found downregulated by miRNA-seq in LSG from SS-patients. Taqman miRNA assays validated the significant decrease of hsa-miR-424-5p levels found in LSG from SS-patients (p=0.02), which were inversely correlated with ATF6 α mRNA levels (p=0.02). Functional assays suggest that hsa-miR-424-5p regulates the mRNA levels of ATF6 α . Finally, stimulation of 3D-acini with IFN- γ induced a significant increase of ATF6 α mRNA levels together with a decrease in ATF6 α promoter DNA methylation percentage and hsa-miR-424-5p levels.

Conclusion: The results suggest that the ATF6 α overexpression is regulated by two complementary epigenetic mechanisms: the DNA hypermethylation of its promoter and the silencing of its mRNA by hsa-miR-424-5p in LSG from SS-patients. IFN- γ affects the expression of ATF6 α by modulation of epigenetic mechanisms, regulating the ability of epithelial cells to handle the chronic ER stress. Interestingly, these changes carry out under a global DNA hypomethylation condition⁴.

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THU0204

ASSOCIATION OF LILRA3 GENE WITH LYMPHOMAGENESIS RISK IN YOUNG SS PATIENTS

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Background: Primary Sjögren's Syndrome (SS) is a systemic autoimmune disease, characterized by increased risk of non-Hodgkin's lymphoma development. A functional polymorphism of the immunoreceptor LILRA3 (Leukocyte immunoglobulin-like receptor A3) has been recently identified as a potential etiopathogenic factor for both pSS susceptibility and lymphomagenesis in the general population.

Objectives: The aim of the current study was to explore the potential contribution of the LILRA3 functional polymorphism in primary SS susceptibility and SS related lymphomagenesis.

Methods: In this study, 346 primary SS patients (ACR/EULAR classification criteria, 2016) and 350 healthy controls were included. The presence of LILRA3 functional polymorphism was detected by polymerase chain reaction (PCR), whereas serum levels were measured by Enzyme-Linked Immunosorbent Assay (ELISA), respectively. Statistical analysis was performed by Graph Pad Prism.

Results: LILRA3 wild type gene variant was detected in 84% of healthy controls, 86.3% of pSS non-Lymphoma patients and 89.7% of patients complicated with lymphoma. Of interest, in pSS patients ≤ 40 years complicated by lymphoma, LILRA3 wild type variant was detected in 100% in contrast to pSS - non lymphoma patients (81.8%) and healthy controls (HC) (83.2%) [p=0.03]. In line with these results, LILRA3 protein serum levels were increased in pSS-lymphoma patients with pSS onset ≤ 40 years compared to healthy controls (p=0.009).

Conclusion: Increased LILRA3 protein levels, as a result of predominance of the LILRA3 wild type gene variant in the young pSS onset patients complicated by lymphoma, imply a potential role of the LILRA3 gene in pSS related lymphomagenesis.

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