Conclusion: Our data revealed that adrenergic receptors are differentially expressed by salivary epithelium of SS patients compared to control tissues. This finding was further substantiated by the increased levels of cAMP, indicating a profound sympathetic stimulation of this secretory tissue. The dilated ER lumen of the salivary gland epithelial cells from SS patients confirmed the occurrence of ER stress. Moreover, the finding that catecholamines induce severe ER stress *in vitro* in SGEc under conditions resembling chronic stress suggests a causal relationship between sympathetic tone and ER stress. Deciphering the role of chronic stress in ER machinery will provide important insights that may lead to novel therapeutic targets for SS.

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THU0224 THE HEPATITIS VIRUS PRE S1 PROTEIN RETARDS THE ONSET OF LUPUS-LIKE GLOMERULONEPHRITIS IN NZB/W F1 MICE

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Background: Infection can trigger autoimmunity but the nature of the pathogen could enhance or inhibit the onset of the disease. In this study we tested the tolerogenic effect of the surface Hepatitis B Virus capsid protein preS1 in a lupus mouse model.

Objectives: To evaluate the effect of administration of Hepatitis B virus preS1 subunit to NZB/WF1 mice

Methods: Mice (10 each group) were injected with a total volume of 200µl of 32.5 µg PreS1 in 200µl PBS (group 1), 200µl PBS (group 2), 3 times at 11th, 14th and 17th weeks of age. Urine samples were collected weekly to evaluate proteinuria by reactive strips. Blood samples were collected before every injection, at 22th and 28th weeks, and at death to evaluate levels of anti-C1q and anti-dsDNA by home-made ELISA tests. Tissues were harvested for histological analyses. Proteinuria free and survival rates were analyzed by Kaplan-Meier method using Mantel-Cox test for comparisons. Neurocognitive functions were evaluated with Staircase, Y-Maze and Forced Swim Test.

Abstract THU0224 – Figure 1

Results: Anti-dsDNA and Anti-C1q levels (OD±SD) were significantly higher in PBS than in preS1 treated mice (Figure 1). Mean proteinuria levels (mg/dl±SD) were higher in PBS than in preS1 treated mice. Proteinuria free survival rate (<300 mg/dl) was lower in group 2 than group 1 (p=0.016; Figure 2). Also survival rate was significantly lower in PBS than in preS1 injected mice (p=0.033). Memory deficits (p<0.01) and anxiety-like behavior was pronounced in PBS treated mice. Severe segmental and focal glomerulonephritis in both groups with large proliferation of mesangial and endothelial cells and Russell bodies were found by histological analysis. Mice treated with preS1 had more chronic inflammation in the kidneys and extramedullary hematopoiesis in the spleen and liver. Notably, in salivary glands, severe acute inflammation was observed in group 1 and chronic inflammation in group 2.

Conclusion: HBV capsid protein preS1 causes a delay in the onset of lupus-like glomerulonephritis and ameliorates behavioral disorders in NZB/BF1 mice. This peptide seems to induce a tolerizing rather than a pathogenic effect in these autoimmune prone mice models.

Abstract THU0224 – Figure 2

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THU0225 THE MOLECULAR PROFILING OF MONOCYTES FROM PATIENTS WITH PRIMARY ANTIPHOSPHOLIPID SYNDROME IDENTIFIES SEVERAL NETWORKS RELATED TO THEIR ATHEROTHROMBOTIC STATUS. ROLE OF ANTIPHOSPHOLIPID ANTIBODIES ON MONOCYTE MIRNA SECRETION

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Objectives: 1. To characterize the mRNAs and microRNAs transcriptomes of monocytes, key immune cells in the atherothrombotic pathology of Antiphospholipid Syndrome patients (APS). 2. To evaluate the role of antiphospholipid antibodies (aPL) in the regulation of these processes. 3. To identify and characterize circulating microRNAs secreted by activated monocytes.

Methods: Monocytes from peripheral blood of 40 APS patients and 40 healthy donors were purified by negative immunomagnetic selection. Gene expression microarray (Agilent G4112F platform) and nCounter microRNA expression array (Nanostring) were performed on purified RNA. Functional categorization of altered genes and miRNAs was made using IPA software, and miRNA-mRNA interaction networks showing inverse correlation expression were identified. Genes and miRNAs integrating the networks were validated in the whole APS cohort by RT-PCR, as well as on a set of thrombotic non-autoimmune patients. Predicted miRNA-mRNA interactions were tested by microRNA transfection experiments.

In parallel, a miRNA array in the plasma of those patients was performed, and common deregulated miRNAs between monocytes and plasma were identified. Monocytes isolated from HD were treated *in vitro* with purified aPLs and the altered gene/miRNA expression induced in monocytes was evaluated. Moreover, the effects of aPLs on the secretion of common deregulated microRNAs in the supernatant of cultured cells were assessed.

Results: Microarray identified 518 altered genes in APS monocytes. Relevant biofunctions on which these genes were involved included hematological and cardiovascular system development and function, inflammatory response, and embryonic development, among others. Gene alterations were validated in the whole cohort, demonstrated to be stable along the time, divergent of the gene profile in monocytes from non-autoimmune thrombotic patients, and associated to thrombotic recurrences and early atherosclerosis. Analysis of miRNA profiles showed altered expression of 22 miRNAs in APS monocytes. Fifty-four genes were inversely correlated and predicted as CVD-related target genes of 19 differentially expressed miRNAs in monocytes. Association of these genes and miRNAs with the

occurrence and type of thrombotic events, obstetric complications and presence of atheroma plaques were demonstrated. Transfection studies further confirmed the relationship between specific miRNAs and their identified target genes. In vitro studies demonstrated the specific modulation of several genes/miRNAs by aPLs. Furthermore, those autoantibodies promoted the increase in several secreted miRNAs, found simultaneously altered in plasma and monocytes, and deeply involved in the development of inflammation and cardiovascular disease.

Conclusion: 1. Gene and microRNA expression profiles allowed the identification of relevant genes and pathways altered in monocytes and plasma of APS patients, associated with the pathogenesis of the disease and modulated, at least partially, by aPLs. 2. Specific microRNA-miRNA regulatory networks control the biological processes and factors related to the CV pathology in APS. 3. aPL antibodies induce the secretion by monocytes of specific microRNAs that might act as messengers in the bloodstream to propagate their deleterious effects.

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THU0226

DOES THE PRESENCE OF CLASSIC AND NOVEL ANTIPHOSPHOLIPID ANTIBODIES INFLUENCE THE RISK OF THROMBOSIS DEVELOPMENT IN PATIENTS WITH UTERINE MALIGNANCIES?

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Background: Patients with uterine malignancies (UM) are at a higher risk of venous thromboembolism (VTE) than the general population. The malignancy itself, the treatment modalities including medication, surgery and also increased levels of leukocytes, platelets, and tissue factor-positive microvesicles contribute to the risk of developing VTE.

Objectives: Several authors have shown that the antiphospholipid antibodies (aPLs) can be detected in peripheral blood of patients (pts) with malignancies. However, whether or not the aPLs could induce thrombosis in pts with UM is not yet known.

The aim of our study was to determine whether the presence of aPLs in patients with **uterine malignancies** is associated with higher VTE risk than in pts with **non-cancer gynecological disorders (NCGD)**.

Methods: The study involved 151 female pts scheduled for gynecological surgery divided into two groups:

Group I with UM (70 pts) confirmed by histopathological examination after surgery; group II with non-cancer gynecological disorders (NCGD) (81pts). The presence of aPLs was detected in patients' serum before surgery using the commercially available test aPL-immunodot assay Anti-Phospholipid 10 Dot, for the qualitative detection of IgG or IgM antibodies. The statistical data analysis was performed using Statistica v13.0.

The following aPLs were assessed in the study groups: IgM and IgG of a- cardiolipin; a-phosphatidic acid; a-phosphatidylcholine; a-phosphatidylethanolamine; a- phosphatidylglycerol; a-phosphatidylinositol; a-phosphatidylserine; a-annexin V; a-β 2-GP I and a-prothrombin.

Results: The VTE occurred significantly more frequently in pts with UM, compared to pts with NCGD.

In UM group VTE was diagnosed before surgery in 9/70 (12.9%) pts; in NCGD group VTE was diagnosed in 3/81 (3.7%) pts, $p=0.0001$.

We have obtained positive test results for classic and novel aPLs significantly more frequently in group I pts with UM (mainly a-β 2-GP I IgM and IgG; a-prothrombin IgM, a-annexin V IgM) than in group-II NCGD pts. The positive test for classic or novel aPLs was detected in 17/70 pts with UM (24.3%) and in 6/81 pts with NCGD (7.4%). The differences were statistically significant ($p=0.003$). All pts with thrombosis in group I (9 pts UM) were positive for at least 3 aPLs (a-β 2-GP I IgM and IgG; a-prothrombin IgM, a-annexin V IgM).

Conclusion: The classic and novel aPLs are found more frequently in pts with uterine malignancies than in pts with **non-cancer gynecological disorders**. The higher risk of thrombosis is connected with malignancy and the presence of classic and novel aPLs.

The better understanding of the relationships between thrombosis in cancer patients and its immunological determinants (presence of aPLs) may lead to reducing the morbidity and mortality associated with thrombosis in cancer and non-cancer **gynecological disorders**. We suggest that aPLs could be a novel biomarker of thrombosis risk in gynecological malignancies.

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THU0227

BIOLOGICAL MONITORING OF REMISSION IN SYSTEMIC LUPUS ERYTHEMATOSUS: ABNORMAL SERUM INTERFERON-ALPHA LEVELS PREDICT RELAPSE

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Background: Remission and relapses prevention are the main objectives of the treatment of Systemic Lupus Erythematosus (SLE). Interferon alpha (IFNα) is a key cytokine in SLE, but its usefulness for the definition of remission and for the prediction of flare has not been validated in clinical practice.

Objectives: To study the association between serum IFNα level, remission and risk of relapse.

Methods: 502 SLE patients were assessed for serum IFNα level using a biological functional assay(1). Remission was defined by the absence of clinical manifestation of lupus activity (clinical SELENA-SLEDAI = 0) and a prednisone intake ≤ 5 mg/day(2). Patients in remission were subsequently followed for one year. The SELENA-SLEDAI Flare Index was used to identify SLE flare. Uni- and multivariable analyses were performed to define disease parameters associated with serum IFNα positivity in patients in remission at baseline. Survival curve analysis, log-rank tests and Hazard Ratios (HR) were calculated to evaluate the risk of flare depending on IFNα, dsDNA Abs and C3 levels at baseline.

Abstract THU0227 – Figure 1