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

Results: 345 samples were obtained from patients in remission. 28.6% of the patients in *clinical remission on treatment* (requiring clinical SELENA-SLEDAI = 0, positive anti-dsDNA antibodies and/or C3 decrease and prednisone intake 1 – 5 mg/day) had an abnormal serum IFN α level, compared to 6.5% of the patients in *complete remission on treatment* (requiring clinical SELENA-SLEDAI = 0, no anti-dsDNA antibodies nor C3 decrease and prednisone intake 1 – 5 mg/day). In patients in remission, high serum IFN α levels at baseline were associated in multivariable analysis with the positivity of anti-dsDNA Abs (HR 3.4 [95%CI 1.6-7.2], $p=0.0001$) and anti-RNP Abs (HR 3.2 [95%CI 1.5-6.8], $p=0.0002$). In patients in remission, high serum IFN α level at baseline was a significant and independent risk factor of lupus flare (HR=4.8 [95%CI 2.3-9.7], $p<0.0001$). Low C3 was also associated with the risk of relapse with a HR=3.2 [95%CI 1.4-7.0], $p=0.005$, but positive anti-dsDNA Abs was not (HR=1.8 [95%CI 0.9-3.6], $p=0.1$). **Conclusion:** A large number of SLE patients in remission display abnormal levels of serum IFN α . Abnormal levels of serum IFN α in patients in remission were significantly associated with positive anti-dsDNA and anti-RNP Abs and were an independent predictive biomarker of lupus flare in the following year. Adding serum IFN α to the routine laboratory assessments perform in patient in remission could help clinicians to identify a subgroup of SLE patient clinically in remission but serologically active and at higher risk of relapse.

REFERENCES:

- [1] Mathian A, et al. Monitoring disease activity in systemic lupus erythematosus with single-molecule array digital ELISA quantification of serum interferon- α . *Arthritis Rheumatol* Hoboken NJ. 2018 Dec 3;
- [2] Vollenhoven R, et al. A framework for remission in SLE: consensus findings from a large international task force on definitions of remission in SLE (DORIS). *Ann Rheum Dis*. 2017 Mar 1;76(3):554–61.

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THU0228

EXPRESSION OF APOBEC FAMILY MEMBERS AS REGULATORS OF ENDOGENOUS RETROELEMENTS AND MALIGNANCY IN SYSTEMIC LUPUS ERYTHEMATOSUS AND SJÖGREN'S SYNDROME

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Background: Activation of type I and II interferon (IFN) pathways contributes to the pathogenesis of systemic autoimmune diseases. We have previously shown increased expression of the LINE-1 (L1) endogenous retrotransposon in systemic lupus erythematosus (SLE) kidneys and in minor salivary glands (MSG) from primary Sjögren's syndrome patients (SS) that strongly correlates with IFN α expression in the same tissues. Moreover, an imbalance between type I and II IFNs in SS salivary gland tissues has been related to non-Hodgkin's lymphoma (NHL) development. Members of a family of retroviral resistance factors (APOBECs) have been implicated in L1 control and are regulated by both type I and II IFNs.

Objectives: We investigated whether these mechanisms are involved in the response to inappropriate expression of L1 retroelements in primary SS and SLE, as well as in SS related lymphomagenesis.

Methods: MSG and kidney biopsy specimens were obtained from 41 patients with primary SS and 23 patients with SLE, respectively. Peripheral blood mononuclear cells (PBMC) and sera were also collected from 73 SLE patients. Relative mRNA expression was quantified by real-time polymerase chain reaction for full-length L1 transcripts, along with members of the APOBEC family [APOBEC3A, APOBEC3B, APOBEC3G, AID (activation-induced cytidine deaminase)] and IFN α and γ transcripts. Type I IFN activity was assessed in lupus plasma by a reporter cell assay. The induction of APOBEC3A and B by IFN α in healthy control PBMCs was also assessed.

Results: APOBEC3A, previously implicated in control of endogenous retroelements, was increased in SS MSG and lupus nephritis kidney tissues and in SLE PBMC and strongly correlated with L1 retroelement expression in both SS and SLE tissues. APOBEC3A was also associated with IFN α mRNA expression in SS MSG tissues and lupus kidneys and with type I IFN activity in lupus plasma. While APOBEC3A expression was induced by IFN α , such a relationship was not observed with APOBEC3B. Moreover, a strong correlation was detected between AID and APOBEC3G with IFN γ expression in SS MSG tissue, a relationship particularly relevant to development of NHL.

Conclusion: Increased expression of APOBEC3A reflects a host-intrinsic and IFN α -dependent mechanism regulating potentially harmful L1 retroelements in patients with SS and SLE. Moreover, IFN γ -related induction of APOBEC3G, together with AID, might contribute to SS-related lymphomagenesis by increasing mutational load or epigenetic alterations. These data reveal a previously unappreciated role of APOBEC family proteins in the pathogenesis of autoimmune disorders.

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THU0229

AMPHIREGULIN ATTENUATES LUPUS NEPHRITIS VIA SUPPRESSION OF PRO-INFLAMMATORY T-CELL FUNCTIONS IN AN ANIMAL MODEL OF SLE

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Background: Amphiregulin (AREG) is a member of the epidermal growth factor (EGF) family and plays a role in development, tissue homeostasis and tumorigenesis. Recently, however, AREG has also emerged as novel player in immunity. Interestingly, AREG expression was shown to be one of the most highly upregulated transcripts in peripheral blood leukocytes of patient with systemic lupus erythematosus (SLE) [1]. The functional role of AREG in SLE, and inflammation in general, remains unclear to date and both, pro- and anti-inflammatory functions have been postulated [2, 3].

Objectives: Our aim was to investigate the role of AREG in the mouse model of pristane induced lupus (PIL) with particular focus on lupus nephritis (LN). We further wanted to identify target cells and mechanisms by which AREG exerts its immunomodulatory effects.

Methods: PIL was induced in AREG knock-out (KO) mice and wild type controls. Animals were sacrificed at pre-specified time points. Renal histology, immune complex deposition, leukocyte influx and mRNA expression levels were analyzed. Furthermore, broad in vivo and in vitro analyses of renal and systemic immune responses were carried out.

Results: Renal AREG mRNA expression significantly increased during development of LN, indicating functional relevance. Indeed, lupus nephritis was significantly aggravated in AREG-KO mice both at early (9 months) and later (12 months) stages after PIL induction. In line with this, we noted an increased deposition of immune complexes and renal influx of pro-inflammatory leukocytes (CD3⁺ T-cells, macrophages and neutrophils). In addition, we found the CD4⁺ T-cells of AREG-KO mice to have a more pro-inflammatory phenotype with significantly increased production of pro-inflammatory cytokines (IFN γ and IL-17A) both in ex-vivo culture, as well as FACS-analyses of nephritic kidneys. Mechanistically, we found that AREG treatment of spleen cell cultures potently suppressed cytokine production. More detailed evaluation by further in-vitro studies indicated, that AREG can directly suppress cytokine production by effector CD4⁺ T-cells as well as enhance the suppressive capacity of FoxP3⁺ regulatory T-cells (Tregs).

Conclusion: These data show that AREG has a protective role on development of LN induced by pristane, which might be therapeutically exploited. Our results further suggest, that direct effects on CD4⁺ T-effector cells, as well as indirect effects via Tregs, are two mechanisms by which AREG exerts its protective role.

REFERENCES:

- [1] Ishii, T., et al., *Isolation and expression profiling of genes upregulated in the peripheral blood cells of systemic lupus erythematosus patients*. *DNA Res*, 2005. 12(6): p. 429-39.
- [2] Kefaloyianni, E., et al., *ADAM17 substrate release in proximal tubule drives kidney fibrosis*. *JCI Insight*, 2016. 1(13).
- [3] Zaiss, D.M., et al., *Amphiregulin enhances regulatory T cell-suppressive function via the epidermal growth factor receptor*. *Immunity*, 2013. 38(2): p. 275-84.