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.

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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.

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