a few T-cells within the infiltrates and strikingly by epithelial cells. Furthermore, RANK-L expression by SGEs in primary cultures was increased after INF- α or IL-1b stimulation.

Conclusions: To our knowledge, this is the first report of a RANK-L contribution to primary Sjögren's syndrome. These results suggest that RANK-L could be an important actor of ectopic lymphoid neogenesis. RANK-L inhibition might represent, in the future, a relevant immuno-modulatory strategy in primary Sjögren's syndrome.

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FRI0287 SEROLOGIC EVIDENCE OF VIRAL REACTIVATION AND INCREASED DISEASE ACTIVITY IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Background: Systemic lupus erythematosus (SLE) is a clinically heterogeneous disease oftentimes characterised by a waxing and waning disease course. However, mechanisms of disease flare remain elusive.

Objectives: This study examined relationships between SLE disease activity, immune pathways, and serologic evidence of viral exposures and reactivation within molecular subsets of SLE patients.

Methods: Serial or single samples of plasma, serum and RNA (n=290) were collected from 184 adult SLE patients who met ACR classification and cohort-matched controls (n=49). Disease activity was assessed by modified SELENA-SLEDAI. Immune pathways were evaluated by modular transcriptional analysis of Illumina Beadchip Microarray gene expression data, as well as by plasma soluble mediators (n=32) by multiplex, bead-based assay and ELISAs. This information was used to subset patients into seven molecular-defined categories by random forest modelling. Viral seropositivity and antibody concentrations were detected by ELISA for antibodies against EBV-Viral Capsid Antigen (VCA) (IgG and IgA), EBV-Early Antigen (EA) (IgG), Cytomegalovirus (CMV) (IgG), and Herpes Simplex Virus (HSV-1) (IgG).

Results: Serologic evidence of EBV reactivation was more common in SLE patients compared to controls, as measured by antibodies against EBV-EA [IgG] (40% vs 13%; OR=4.57, p=0.0006) or EBV-VCA [IgA] (36% vs 17%; OR=2.70, p=0.019). No differences were noted in CMV or HSV1 seropositivity rates between patients and controls. IgG responses against EBV-VCA were nearly universal among these adult patients and controls; however, concentrations of EBV-VCA IgG were higher in SLE patients compared to controls (ISR=4.44 vs 3.52; p=0.0021), as were EBV-VCA IgA and EBV-EA IgG antibody responses. In cross sectional analysis, SLE patients with higher disease activity (SLEDAI ≥ 6 ; n=126) had higher concentrations of EBV-EA IgG than patients with lower (n=166) disease activity (ISR=0.822 vs 0.540; p=0.033). SLE patients with serologic evidence of EBV reactivation by EA IgG responses had higher levels of interferon associated molecules, IP10 (p=3.4 $\times 10^{-14}$), BLYS (5.5 $\times 10^{-5}$), and IL-10 (p=0.00013). HSV1 IgG positive SLE patients also showed higher levels of IP10 (2.2 $\times 10^{-7}$). Antibody responses toward EBV-EA were enriched in molecularly defined patient clusters with higher expression levels of interferon and inflammatory modules, as well as with interferon and inflammatory soluble mediators. Patients within these clusters were also more likely to have major organ involvement, such as renal or neurologic disease.

Conclusions: Serologic evidence of EBV reactivation is more common in SLE patients compared to healthy controls. EBV-EA IgG responses are elevated in SLE patients with active disease and correspond with increases in interferon-associated mediators. This study provides serologic evidence suggesting a possible role for viral reactivation in SLE disease activity.

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FRI0288 THYMIC STROMAL LYMPHOPOIETIN (TSLP) BIOLOGICAL EFFECTS ON HUMAN PERIPHERAL BLOOD B LYMPHOCYTES IN PRIMARY SJÖGREN'S SYNDROME

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Background: Thymic stromal lymphopoietin (TSLP) is an epithelial lymphopoietic cytokine belonging to interleukin (IL)-7 family, acting as a B-cell growth factor. A pathogenetic role of TSLP in primary Sjögren's syndrome (pSS) and pSS-related B-cell lymphoproliferation has been recently indicated.¹

Objectives: to investigate the biological effects of TSLP on human peripheral blood B lymphocytes in pSS.

Methods: Peripheral blood B lymphocytes from 15 pSS patients, stratified according to their lymphoproliferative status (fully benign, fbSS: n=5; myoepithelial sialadenitis, MESA: n=5; B-cell non-Hodgkin lymphoma, NHL: n=5) and from 5 healthy blood donors (HBDs) were isolated by immunomagnetic negative selection and cultured with three different stimuli: i) TSLP; ii) combination of TSLP and IL-4; iii) combination of CD40 functional grade monoclonal antibody and IL-4. B-cell activation status was evaluated by flow cytometry, by analysing the expression of surface IgM after stimulation. An ELISA assay was also performed to assess the immunoglobulins (Ig) production in the B-cell culture supernatants after the exposure to the three different stimuli.

Results: peripheral blood B lymphocytes isolated from fbSS patients were significantly activated by the combination of TSLP and IL4 (p=0.0218), as well as by the classic co-stimulation of antiCD40 plus IL4 (p=0.044), but not when TSLP was used alone. This pattern of responsiveness was observed also in HBDs. By contrast, the peripheral B-cells of NHL pSS patients were significantly activated by the TSLP alone (p=0.0157), without the necessity of other additional stimuli. A similar response to TSLP alone was observed also in MESA B-cell cultures but with no significance. As concerns Ig production in culture supernatants of peripheral B-cells, in fbSS patients we observed a significant increase of Ig production both after the exposure to TSLP plus IL4 (p=0.0417) and after the stimulation with antiCD40 plus IL4 (p=0.0293), but not with TSLP alone. By contrast, TSLP alone induced Ig production both in MESA (p=0.0368) and in NHL peripheral B-cells (p=0.0268). Unexpectedly, the combined stimulus of TSLP plus IL4 did not produce any significant effect in both these subgroups, and was less effective than TSLP alone also in stimulating B-cell surface IgM expression.

Conclusions: human peripheral blood B-cells from pSS patients showed an increased responsiveness to TSLP, however with significant differences. In HBDs and in fbSS, TSLP induced a significantly higher B-cell activation and immunoglobulin production only with the addition of IL4, whereas in NHL TSLP alone was sufficient. In addition, IL-4 co-stimulus induced a lower activation than TSLP alone in NHL. Overall, also functional tests support a role of TSLP as an important driver of B-cell stimulation and lymphoma progression in pSS. Interactions of TSLP with other B-cell stimulating factors also deserve particular attention.

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FRI0289 ROLE OF CXCL13 AND CXCL12 IN SJÖGREN'S SYNDROME: ASSOCIATION WITH HISTOLOGICAL, CLINICAL AND LABORATORY FEATURES

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Background: Ectopic production of the lymphoid chemokines CXCL13 and CXCL12 has been described in tertiary lymphoid structures (TLS) that harbour in the salivary glands of patients with Sjögren's Syndrome (pSS). Whilst CXCL13 expression correlates with clinical features, its potential role as a biomarker to