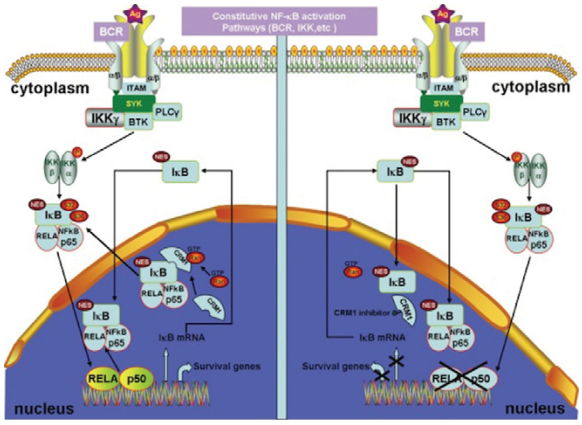

cells. It is likely that inhibition of the canonical NFκB pathway underlies KPT-350's inhibitory effect. Together, our findings suggest the potential of SINE compounds to have a significant impact on disease progression in SLE.

References:

[1] Figure - Zhang KJ and Wang M. Chin J Cancer Res 24(4): 380–393:2012.

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OP0305 TYPE I IFN SYSTEM ACTIVATION IN NEWBORNS EXPOSED TO ANTI-RO/SSA AUTOANTIBODIES IN UTERO

M. Wahren[1], M. Hedlund[1], G.E. Thorlacius[1], M. Ivanchenko[1], N. Kyriakidis[1], L. Rönnblom[2], M.-L. Eloranta[2], A. Espinosa[1], S.-E. Sonesson[1]. *[1]Karolinska Institutet, Stockholm; [2]Uppsala university, Uppsala, Sweden*

Background: Overexpression of type I IFN-stimulated genes has been demonstrated in both SLE and SS, and induction of IFNα production in plasmacytoid dendritic cells by immune complexes containing RNA and autoantibodies, including Ro/SSA and La/SSB autoantibodies, has also been shown. During pregnancy, these autoantibodies pass over the placenta to the fetus, but it is not know if an IFN-activation takes place also in the fetus.

Objectives: In the present study, we investigated if the type I IFN system is activated in newborns exposed to anti-Ro/SSA autoantibodies *in utero*.

Methods: Anti-Ro/SSA positive mothers and their babies as well as healthy controls were included in the study. Maternal and cord blood drawn at birth was immediately separated into plasma and PBMC. mRNA expression was analyzed by microarrays, cell surface markers were assessed by flow cytometry and circulating IFNα levels by DELFIA.

Results: We observed increased expression of IFN-regulated genes and elevated plasma IFNα levels not only in anti-Ro/SSA positive women but also in their newborns, with maternal and fetal IFN scores showing a significant positive correlation (r=0.74, p=0.005). Increased expression of MHC class II was observed on $CD14^+$ monocytes of anti-Ro/SSA antibody-exposed babies, suggesting cellular activation. Notably, the IFN score of babies born to mothers receiving immunomodulatory treatment was similar to that of controls.

Conclusions: We demonstrate for the first time that anti-Ro/SSA antibody-exposed babies at risk for neonatal lupus have a pre-activated immune system with an IFN signature, elevated plasma IFNα, and increased MHC class II expression on circulating monocytes. Our data also suggest that maternal immunomodulatory treatment may modulate the IFN activity in the baby.

Disclosure of Interest: None declared

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OP0306 DOWNREGULATION OF MICRORNAS IN PLASMACYTOID DENDRITIC CELLS IS ASSOCIATED WITH A TYPE I INTERFERON SIGNATURE IN SYSTEMIC LUPUS ERYTHEMATOSUS AND ANTIPHOSPHOLIPID SYNDROME

L.L. Van Den Hoogen[1,2], J.A. van Roon[1,2], R.D. Fritsch-Stork[2], C.P. Bekker[1,2], A. Pandit[1,2], M. Rossato[1,2], T.R. Radstake[1,2]. *[1]Laboratory of Translational Immunology; [2]Rheumatology and Clinical Immunology, UMC Utrecht, Utrecht, Netherlands*

Background: The most prominent alteration in the immune system of patients with SLE is a type I interferon (IFN) signature, which we recently also reported in patients with primary APS (PAPS). In SLE and APS, this signature is related to disease activity and vascular disease. Plasmacytoid dendritic cells (pDC) are considered key players in the pathogenesis of SLE and APS as they are major producers of type I IFNs. MicroRNAs (miRNAs) are short non-coding RNAs that modulate gene expression through RNA interference mechanisms and have been implicated in the dysregulation of immune cells in patients with autoimmune diseases. Here we investigated miRNA expression in pDC of patients with SLE and APS in relation to the type I IFN signature.

Objectives: To identify if pDC dysregulation in patients with SLE and APS is associated with alterations of their miRNA expression profile.

Methods: The frequency of circulating pDC was determined by flow cytometry in patients with SLE (n=49), SLE+APS (n=34) and PAPS (n=27) and healthy controls (HC, n=22). RNA was extracted from pDCs isolated from the peripheral blood of patients with SLE (n=20), SLE+APS (n=10), PAPS (n=10) and HC (n=12). pDC miRNA and transcriptome profiles were assessed by RT-qPCR by OpenArray and RNA-sequencing (RNAseq) respectively. Patients were stratified by the presence (IFN-high) or absence (IFN-low) of an IFN signature on the basis of RNAseq. pDC stimulated with TLR7 agonists were analyzed for changes in miRNA expression.

Results: The numbers of circulating pDC were reduced in peripheral blood of patients with SLE, SLE+APS and PAPS (all $p<0.001$) and did not differ among the patient groups. Among 131 expressed miRNAs, 36, 17 and 21 miRNAs were differentially expressed ($p<0.05$) in patients with SLE, SLE+APS and PAPS, respectively, as compared with HC. All but one of these miRNAs were downregulated in the patients versus HC. Only 1 miRNA was differentially expressed when comparing between SLE and SLE+APS patients and between SLE+APS and PAPS patients. No changes in expression of genes related to the biogenesis of miRNAs were observed in the pDC of the patient groups. RNAseq data revealed an IFN signature in pDC, which was strongest in SLE and SLE+APS patients. IFN-high (n=23) patients showed a stronger downregulation of miRNAs as compared with IFN-low (n=17) patients. A total of 9 miRNAs were differentially expressed between IFN-high and IFN-low patients. Pathway enrichment on targets of the top three miRNA ($p<0.001$) distinguishing between IFN-high and –low patients indicated that these miRNAs are potentially regulating pathways relevant for pDC function such as TLR signaling and endocytosis. Activation of pDCs by TLR7 agonists induced a downregulation of miRNAs in pDC, resembling the miRNA expression pattern seen in patients, in particular those with a high type I IFN signature.

Conclusions: Reduced numbers of circulating pDC and downregulation of miRNAs in pDC is shared between SLE, SLE+APS and PAPS patients. Altered miRNA expression in pDC is associated with the presence of a type I IFN signature in SLE and APS. Our data suggest that the reduced expression of a subset of miRNA underlies pDC dysregulation in SLE, SLE+APS and PAPS patients.

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Comorbidities in rheumatoid arthritis

OP0307 TREATMENT OF BAFF TRANSGENIC MICE WITH ANTI-TNF: MONOCLONAL ANTI-TNF ARE ASSOCIATED WITH A HIGHER RISK OF LYMPHOMA THAN ETANERCEPT

G. Nocturne[1], L. Bineta[2], S. Boudaoud[2], J. Pascaud[2], R. Seror[1], C. Nicco[3], C. Chereau[3], F. Mackay[4], F. Vincent[4], T. Lazure[5], S. Ferlicot[5], L. Stimmer[6], S. Roulland[7], R. Krzysiek[8], S. Hacein-Bey[8], F. Batteux[3], X. Mariette[1]. *[1]Rheumatology; [2]INSERM U1184, le Kremlin Bicêtre; [3]U1016, Paris, France; [4]Melbourne University, Melbourne, Australia; [5]Pathology, le Kremlin Bicêtre; [6]CEA, Fontenay aux roses; [7]Marseille Luminy, Marseille; [8]Immunology, le Kremlin Bicêtre, France*

Background: Risk of lymhoma in patients with rheumatoid arthritis (RA) and disease activity is the main risk factor. The impact of treatment, notably of anti-TNF, is unclear: decreasing the risk of lymphoma by controlling activity or alterring anti-tumor immunosurveillance. Anti-TNF are not associated with an increased risk of lymphoma in large epidemiologic studies. However, the risk might vary according to the type or to the dose of anti-TNF.

Objectives: To assess if the risk of lymphoma might differ according to the type of anti-TNF, comparing monoclonal anti-TNF to the soluble receptor. For that, we used BAFF transgenic (Tg) mice as a model of autoimmunity-associated lymphomas. They develop lupus and Sjögren and 3% of them spontaneously developed lymphoma at 12–18 months

Methods: Six months aged BAFF-Tg mice were treated with anti-TNF for 12 months: etanercept (ETA) (n=15, 8 mg/kgx3/week), monoclonal anti-mouse TNF: TN3 19.12 (n=15, 20 mg/kg/week), adalimumab (ADA) (n=12, 20 mg/kg/week) or controls (n=22). Sera were assessed monthly. Crude mortality was compared among the different groups. Histological examination of the spleen was performed. The Fisher's exact test was used to compare the incidence of lymphoma among the groups.

Results: Adjunction of low dose of methotrexate during the 3 first days of treatment prevented immunization in the 3 groups for life. Using L929 cells, a cell line sensitive to TNF induced death, we confirmed that ADA was 8 to 12 times less efficient than ETA to inhibit soluble murine TNF. As expected, the mean level of ETA, TN3 and ADA were 7 μg/ml, 69 μ g/ml and 105 μg/ml, respectively. The