**Background** Juvenile-onset systemic lupus erythematosus (JSLE) is an autoimmune disorder characterised by immune dysregulation, chronic inflammation and increased cardiovascular risk. Our findings in adult-onset SLE link immune cell dysregulation with defects in plasma membrane signalling platforms (lipid rafts). In JSLE little is known about the immune profile or whether abnormal lipid metabolism contributes to pathogenesis.
**Methods** Flow cytometry was used to measure metabolic marker expression on immune cell subsets from 39 healthy donors (HCs) and 35 JSLE patients. Metabolic biomarker analysis including lipoprotein composition was performed on matching serum.
**Results** JSLE patients had significantly elevated membrane lipid rafts in T-cells, B-cells and plasmacytoid dendritic cells compared to HCs suggesting dysregulated membrane receptor signalling. Furthermore, lipid raft expression correlated positively with cell activation markers, disease activity, erythrocyte sedimentation rate and dsDNA titre and negatively with complement protein C3 supporting the hypothesis that altered metabolism is associated with JSLE pathogenesis. Importantly, ROC curve analysis showed that lipid raft expression on these cell types is an excellent diagnostic of high disease activity in JSLE. Metabolomic analysis of matching serum revealed that high disease activity patients had significantly decreased atheroprotective high density lipoproteins (HDL) and increased atherogenic low density lipoproteins (LDL) suggesting altered transport of lipids. In addition, lipids associated with membrane rafts such as sphingomyelin, phosphatidylcholine, phosphoglycerides and cholesterol correlated negatively with HDL in high disease activity patients but positively in low disease activity patients. Immune cell lipid rafts correlated positively with LDL and negatively with HDL together suggesting altered lipid uptake/efflux from these cells; this may alter immune cell signalling in JSLE patients. Stratification of patients based on their lipid profile by hierarchical clustering revealed 3 groups that were unique in both immnophenotype and clinical presentation.
**Conclusions** Differences in the metabolic profiles of immune cell subsets and lipoprotein lipid transport in JSLE contribute to disease pathogenesis and severity. Regulation of lipid metabolism may therefore have therapeutic benefit for JSLE patients providing a dual effect of reducing inflammation and atherosclerotic risk. These therapeutics may perform better in patients that present specific clinical and phenotypic features.

## PS5:88 ALTERED CELL SURFACE N-GLYCOSYLATION OF AUTOIMMUNE T-CELLS RESULTS IN DECREASED BINDING OF IMMUNOREGULATORY GALECTIN-1

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Glycosylation (sugar code) is frequently altered on the surface of various cells in patients with immune-mediated diseases resulting in changes in signal transduction and metabolic control. However, alteration of glycosylation patterns of T cells has not yet been characterised in autoimmune disorders. We have previously demonstrated that T-cells of patients with systemic lupus erythematosus (SLE) are resistant to the apoptotic effects of galectin-1 (Gal-1), an immunoregulatory lectin.

T-cells from patients with active SLE (n=18), rheumatoid arthritis (RA) (n=14) or Sjögren's syndrome (SS) (n=14) and from healthy controls (n=19) were examined. Cell surface glycosylation was analysed with lectin-binding assay, and the expression of glycosyltransferase and glycosidase enzymes participating in the construction of the glycan chains was measured with reverse transcriptase polymerase chain reaction (RT-PCR).

Resting SLE T-cells bound significantly higher amounts of several lectins, while RA and SS resting T-cells were similar to controls in their glycosylation pattern. Activated T-cells from all autoimmune groups bound significantly less Gal-1 than controls, while other lectins bound similarly. Gene expression including alpha mannosidases (MAN1A1, MAN1A2, MAN2A1 and MAN2A2) and beta-N-acetylglucosaminyltransferases (MGAT1–5) in autoimmune activated T-cells did not differ from controls with the only exception of MAN1A2 in SS. However, we found a significant increase in the mRNA ratios of certain sialyltransferases and neuraminidases, specifically in ST6GAL1/NEU1 in SLE and SS, and in ST3GAL6/NEU1 in SLE and RA patients compared to controls. Treatment of cells with neuraminidase resulted in a remarkable increase in Gal-1 binding

The glycosylation pattern of resting SLE T-cells was consistent with a pre-activated phenotype. Decreased Gal-1 binding found in all three diseases can be explained with an increased terminal sialylation, which may be a consequence of an altered expression of sialyltransferase and neuraminidase genes, whose concerted action is responsible for the degree of sialylation of glycan structures. Accordingly, neuraminidase treatment resulted in remarkably increased Gal-1 binding. We propose that increased sialylation may at least partially explain the previously found resistance to the immunoregulatory effects of Gal-1 in SLE, hence contributing to the pathomechanism of the examined diseases.

## PS5:89 LOOKING FOR A SLE SIGNATURE ON PERIPHERAL B CELL SUBSETS: DOES A PREPONDERANT CD38 POSITIVE PLASMABLAST-SUBPOPULATION LACK CD73 AS A SIGN OF A DIMINISHED B REGULATORY POOL?

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**Background** Systemic Lupus Erythematosus (SLE) is an autoimmune disorder characterised by polyclonal Bcell activation, production of dsDNA-autoantibodies and cytokines. Subsets of Bcells play a central role in SLE-pathogenesis. The inflammatory milieu is characterised by the accumulation of adenosine, which confers immunosuppressive effects. In SLE, the role of CD73, an enzyme involved in the extracellular generation of adenosine from ATP, is not well characterised. This study aimed to characterise expression of CD73 B cell subsets of SLE-patients as compared to healthy controls (HC).
**Methods** B cell subsets were characterised from peripheral blood of 23 SLE patients attending the outpatient clinic at the Rheumatology Unit of University Hospital Düsseldorf and of 15 HC by FACS. All patients fulfilled the revised SLE-criteria

of ACR and were randomly collected in clinical remission state (SLEDAI 1.1±1.9).

**Results** By comparison of B cell subsets between SLE and HC, CD38 was dominantly expressed by SLE patients (SLE 74.2% ±12.9% vs HC 64.2%±12.2%; p(MWU)=0.018). Furthermore, SLE-patients showed an increase in CD19 +IgD CD27 +CD38 high plasmablasts (SLE 2.1%±3.4% vs HC 0,4% ±0.4%, p(MWU)<0.001). Moreover, SLE-plasmablasts showed decreased CD73 expression as compared to HC (SLE 2.1% ±1.9% vs HC 3.5%±2.2%; p(MWU)=0.034). SLE-B cells revealed a trend towards an augmented CD38highCD138 +plasmacell fraction (SLE 0.40%±0.5% vs HC 0.08% ±0.07%; p=0.07), without any difference in CD73 expression. On the other hand, exhausted-memory B cell fraction (CD19 +IgD CD27-CD21-CD138-), showed an increased CD73 expression in SLE (SLE 13.7%±9.2% vs HC 6.2% ±5.4%; p=0.004).

**Conclusion** Our study confirms CD38 +plasmablasts as being increased in peripheral blood from SLE patients as compared to HC. Furthermore, the data reveal a deficiency for CD73 on SLE plasmablasts, which suggests a decreased regulatory capacity of SLE plasmablasts as compared to HC, supporting the notion of a reduced regulatory B cell pool in SLE. On the other hand, the enlarged CD73 +exhausted memory pool in SLE could point to an accelerated flow of CD73 +regulatory B cells into an exhausted B cell fraction. These findings support the hypothesis of a persistent regulatory B cell defect even in a state of SLE remission.

## PS5:90 ENHANCED IL-7 RECEPTOR SIGNALLING IN SLE PROMOTES T-HELPER CELL PROLIFERATION THROUGH UPREGULATION OF MICRORNA-182 AND DOWNREGULATION OF FOXO1

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**Background** Recent reports have shown dysregulated microRNAs (miRNAs) in murine models of lupus, among them increased expression of microRNA-182 (miRNA-182), which has been demonstrated to target the transcription factor FOXO1 in activated murine CD4 +T cells, leading to spontaneous T cell activation and clonal expansion. Here we aimed to investigate the expression of miR-182 and FOXO1 in T cells from human SLE patients.

**Methods** Expression levels of miR-182 were analysed with RT-PCR in purified peripheral blood CD4 +T cells from 9 patients with SLE and age/sex-matched healthy controls (HC). Multicolor flow cytometry was performed to analyse CD4 +T cell expression for FOXO1, Ki-67, Foxp3, the interleukin-7 receptor-α (CD127) and phosphorylated STAT-5a (pSTAT5). Analysis of serum IL-7 levels was performed with ELISA in 27 SLE patients and HC. Induction of miR-182 was assessed *in vitro* after polyclonal T cell stimulation in the presence of IL-7, and inhibition of T cell proliferation investigated using mir-182 antagomirs.

**Results** MiRNA-182 was significantly upregulated in CD4 +T cells from SLE patients compared to HC, while the FOXO1 expression was significantly decreased. The percentage of proliferating Ki-67 +conventional Foxp3- CD4 +T cells (Tcons) was significantly higher in SLE compared to HC (3.85% vs 1.58%, p<0.001) and their basal pSTAT5 levels significantly enhanced, suggesting a recent stimulation with common gamma chain(γc)-signalling cytokines. SLE Tcons displayed decreased expression levels for the FOXO1 target gene CD127 (MFI 2021 vs 2553, p=0.049) and serum IL-7 levels were significantly higher in SLE compared to HC (17.0 pg/ml vs 10.2 pg/ml, p=0.001). *In vitro*, miR-182 could be induced by IL-7, and specific inhibition of miR-182 inhibited T cell proliferation and survival.

**Conclusion** Our data suggest that enhanced IL 7R/STAT5 signalling mediates the induction of miR 182 expression, which promotes the proliferation of conventional Foxp3- T cells SLE. Collectively, our data provide new insights in the pathophysiology of T cell hyperactivity in SLE and identifies miR-182 as a candidate target for future therapeutic approaches.

## PS5:91 INCREASED EXPRESSION OF TLR7 IN PLASMACYTOID DENDRITIC CELLS DRIVES TYPE I IFN MEDIATED IMMUNOPATHOLOGY IN SLE AND APS

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**Background/purpose** Dendritic cells (DC) are key cells in the pathogenesis of autoimmune diseases by potently activating T-cells. Systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS) are characterised by an IFN signature, caused by elevated levels of IFNα. Plasmacytoid DC (pDC) are held responsible for the increased levels of IFNα in SLE and APS. The molecular mechanisms underlying the increased activation of pDC in SLE and APS are unknown. Using RNA sequencing (RNAseq) and further *in vitro* validation experiments on plasmacytoid and myeloid DC (mDC) obtained from patients with SLE and APS we assessed the causes and consequences of increased type I IFN signalling on the dysregulation of both pDC and mDC in patients with SLE and APS.

**Methods** RNAseq was performed on pDC and mDC isolated from peripheral blood of patients with SLE, SLE +APS and primary APS (PAPS) and healthy controls (n=54). Weighted gene correlation network analysis (WGCNA) was used to identify pDC- and mDC-specific gene modules and to stratify patients into those with (IFN-high) or without (IFN-low) an IFN signature. The response of pDC and mDC (in co-culture with T-cells) to IFNα and TLR agonists were analysed by RT-qPCR and flow cytometry to functionally validate RNAseq data.

**Results** WGCNA identified IFN modules in pDC and mDC that perfectly stratified patients from HC. Comparing the IFN modules of pDC and mDC revealed cell specific alterations related to the IFN signature in pDC/mDC. Increased expression of TLR7 and its downstream intermediates was confined to IFN-high patients in pDC. In contrast, genes involved in the activation of T-cells were related to the IFN module in mDC. Both pDC and mDC showed increased expression of BAFF. *In vitro*, IFNα upregulated TLR7 in pDC and augmented TLR7-mediated IFNα production. In contrast to pDC, IFNα primed mDC for enhanced T-cell proliferation via the upregulation of co-stimulatory molecules. Furthermore, in SLE/