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%; $p(\text{MWU})=0.018$). Furthermore, SLE-patients showed an increase in CD19 +IgD CD27 +CD38 high plasmablasts (SLE 2.1%±3.4% vs HC 0.4%±0.4%, $p(\text{MWU})<0.001$). Moreover, SLE-plasmablasts showed decreased CD73 expression as compared to HC (SLE 2.1%±1.9% vs HC 3.5%±2.2%; $p(\text{MWU})=0.034$). 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 antagonists.

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(γ c)-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 potentially activating T-cells. Systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS) are characterised by an IFN signature, caused by elevated levels of IFN α . Plasmacytoid DC (pDC) are held responsible for the increased levels of IFN α 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 IFN α 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*, IFN α upregulated TLR7 in pDC and augmented TLR7-mediated IFN α production. In contrast to pDC, IFN α primed mDC for enhanced T-cell proliferation via the upregulation of co-stimulatory molecules. Furthermore, in SLE/

APS, pDC and mDC produced BAFF and expressed chemokine receptors.

Conclusion pDC and mDC are differentially affected by IFN α in SLE and APS. IFN α primes pDC for enhanced IFN α production which potentiates T-cell activation by mDC, thereby sustaining the IFN signature in SLE and APS.

PS5:92

CLARIFICATION OF THE ROLE OF DNASE 1 ON THE ONSET OF SYSTEMIC LUPUS ERYTHEMATOSUS IN A MURINE MODEL

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Systemic lupus erythematosus (SLE) is a prototypical autoimmune disease resulting in multi-organ damage and a high rate of morbidity. Onset of SLE is characterised by dysregulated activation of T and B lymphocytes and the production of autoantibodies directed against nuclear components. The autoantibodies generated during the onset of SLE often recognise components released by neutrophils during NETosis, a type of cell death defined by the generation of neutrophil extracellular traps (NETs). The endonuclease DNase1 has been shown to be involved in the clearance of NET components. The sera of SLE patients contain inhibitors of DNase 1 and/or anti-NET antibodies that block the ability of DNase 1 to degrade NETs. Thus, whilst NETs are important for clearing infection they must be tightly regulated and degraded to prevent the onset of autoimmunity.

In this study we monitored the production of auto-antibodies in the serum of wild type and DNase 1-deficient mice from the age of 2 to 12 months, along with proteinuria levels and the development of glomerulonephritis. We show that DNase 1-deficient mice develop a SLE-like phenotype with elevated auto-antibody production and kidney damage by 12 months. This model also demonstrates the female bias in SLE as the female DNase 1-deficient mice had the highest level of kidney damage. As DNase I activity, B cells and aberrant NETosis are central to progression of SLE understanding their mechanisms of action are of great therapeutic interest.

PS5:93

MARGINAL-ZONE-LIKE B CELLS DEFICIENCY REPEATEDLY DETECTED IN PERIPHERAL BLOOD AS A POSSIBLE BIOMARKER OF HYPOSPLENISM/ASPLENIA IN SLE

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Objective SLE is a disease associated with a risk of serious infections, in case of hyposplenism/asplenia especially by encapsulated bacteria. For opsonization and phagocytosis of these agents are essential IgM natural Abs, produced only by B cells of the splenic marginal zone. Significant deficiency of marginal-zone-like B cell CD19 +CD27+IgM+ subpopulation absolute values $\times 10^{-6}/L$ in peripheral blood (PB) was demonstrated in a prospective, comparative, cross-over SLE study¹;

goal of the present study is follow up persistence of this phenomenon.

Design and method Sixty adult SLE (ACR/1982, update 1997) pts and 10 age- and sex-matched healthy controls (HC) were enrolled in month 0', and 56 SLE pts also repeatedly after twelve-month-period, i. e. month 12'; overlap syndromes, infection, monoclonal gammopathy and renal failure in SLE under study were excluded. The DuraClone IM panel (Beckman Coulter) was used to identify CD19 +CD27+IgM+B cell subpopulation in PB samples by flow cytometry Navios (Beckman Coulter) with software analysis using Kaluza version 1.2: data obtained were expressed in relative% of PB lymphocytes and absolute values $\times 10^{-6}/L$. Parallel analysis of serological SLE biomarkers included C3, C4, ANA/IF (maximal titre), ANA/ELISA, anti-dsDNA/IFCL (maximal titre), anti-dsDNA/ELISA and antinucleosome Abs. Data obtained were statistically processed using Medcalc-Statistical Software programme.

Results Significant differences ($p < 0.001$) were obtained between absolute values of CD19 +CD27+IgM+B cells in HC (median 31.36, 95% CI: 24.49 to 63.35) and SLE month 0' (median 9.82, 95% CI: 6.01 to 14.26), and also SLE month 12' (median 10.09 95% CI: 7.12 to 14.42), but not between values obtained in SLE month 0' and month 12' ($p > 0.05$); not significant differences were found in analysis using relative% of PB lymphocytes ($p > 0.05$). In SLE month 0' was found a slight significant correlation between absolute values of CD19 +CD27+IgM+B cells and anti-dsDNA/ELISA Abs ($r_s = -0.28$, $p = 0.034$) without a confirmation in month 12' control ($r_s = -0.09$, $p = 0.491$).

Conclusions The data obtained demonstrated persistent character of marginal-zone-like B cells deficiency in peripheral blood, and are suggesting as possible biomarker of functional hyposplenism/asplenia in SLE.

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PS5:94

CHARACTERISATION OF SLE B CELLS FROM PATIENTS IN REMISSION – PERSISTENT IL-10 SECRETORY DEFECT

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Background SLE is an autoimmune disorder characterised by polyclonal B cell activation, the production of anti-double stranded (ds) DNA autoantibodies and cytokines. Molecular and clinical studies regarding SLE often address clinically active patients and not patients in remission. This study reports on immunoglobulin, anti-dsDNA-aab and IL-10 secretory capacity of cultures of CD19 +lymphocytes from SLE patients in remission in comparison to normal donors. The aim was to evaluate whether endogenous factors (BAFF, CD40, IL4), exogenous factors (CpG-ODN-motifs, SAC) or their combinations differentially influence immunoglobulin, cytokine and anti-dsDNA-aab production in not active SLE patients vs healthy controls.

Methods Blood samples were obtained from a group of 13 SLE patients attending clinics at the rheumatology unit at the Heinrich-