OUTSTANDING ORAL ABSTRACT PRESENTATIONS

O001 / #144

Topic: ***AS03 - Antiphospholipid Syndrome***

SCIENTIFIC HYBRID SESSION: BASIC TRACK PRESENTATIONS - OUTSTANDING ABSTRACT PRESENTATIONS
23-05-2025 9:00 AM - 10:00 AM

ANTI-B2GLYCOPROTEIN I-INDUCED NEUTROPHIL EXTRACELLULAR TRAPS CAUSE ENDOTHELIAL ACTIVATION

Silvia Mancuso[1,2], Mattia Caliste[2], Andrea Petretto[3], Elisa Corsiero[4], Nicole Grinovero[3], Antonella Capozzi[1], Gloria Riitano[1], Cristiana Barbati[1], Simona Truglia[2], Cristiano Alessandri[2], Maurizio Sorice[1], Michele Bombardieri[4], Fabrizio Conti[2]
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Background/Purpose: Neutrophil extracellular traps (NETs) formation – NETosis – involvement in antiphospholipid syndrome (APS) pathogenesis is known, but the role of anti-β2glycoprotein I antibodies (aβ2GPI)-induced NETs in triggering a procoagulant and proinflammatory phenotype in endothelial cells (EC) remains to be evaluated. This study investigated whether aβ2GPI-induced NET can activate ECs and whether aβ2GPI-induced NET and phorbol myristate acetate (PMA)-induced NET have different proteomic profiles.

Methods: Healthy donors (HD) neutrophils were stimulated with aβ2GPI isolated from a pool of primary APS patient sera by affinity chromatography, normal human IgG or PMA. NETs were stained with anti-neutrophil elastase and DAPI, and the ability of aβ2GPI to bind NETs and inhibit DNA degradation was investigated. Following aβ2GPI, aβ2GPI-induced NET and PMA-induced NET stimuli, we evaluated EC activation investigating ICAM-1 (Intra-Cellular Adhesion Molecule 1), VCAM-1 (Vascular Cell Adhesion Molecule 1) and tissue factor (TF) expression using flow cytometry; and EC dysfunction analyzing extracellular microvesicles (EMVs) release via flow cytometry and NanoSight analysis. Mass spectrometry-based proteomics was performed on aβ2GPI-induced NET and PMA-induced NET.

Results: Unlike normal IgG, aβ2GPI induced NETosis and bound to NETs by colocalizing with the neutrophil elastase signal at 93.6 % without preventing NET degradation. Compared with unstimulated EC, aβ2GPI-induced NET triggered a robust expression of TF, VCAM and ICAM in EC with a change-fold MFI of 6 (SE 0.1), 4.2 (SE 0.09), 2.3 (SE 0.09). VCAM-1 and ICAM-1 were higher expressed in EA.hy926 treated with aβ2GPI-induced NET than those treated with aβ2GPI ($p < 0.0001$ in all instances) (Figure 1).

aβ2GPI induced a significant increase in EMVs compared to untreated samples and those treated with NETs. Fifty-six proteins were identified, 7 resulted upregulated in aβ2GPI-induced NET and downregulated in PMA-induced ones. GO enrichment analysis revealed that proteins upregulated in aβ2GPI-induced NET were enriched for ubiquitin protein ligase binding and SLC2A4 translocation to the plasma membrane. Notably, triosphosphate isomerase 1 (TPI1), 14-3-3 epsilon protein (YWHAE) and tubulin alpha-1B (TUBA1B) proteins, upregulated in aβ2GPI-induced NET, showed functional relationships among themselves at network analysis that were distinct from other proteins, indicating unique interconnections within some aβ2GPI-induced NET proteins that differentiate them from PMA-induced NET proteins (Figure 2).

Figure 1. Endothelial cells activation by aβ2GPI IgG-induced NETs.
***p<0.001.

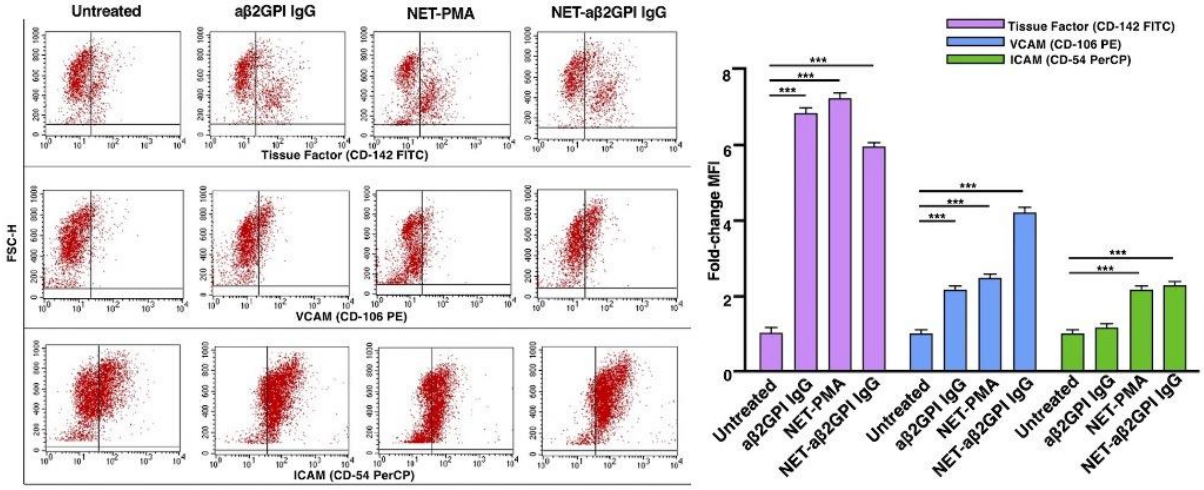
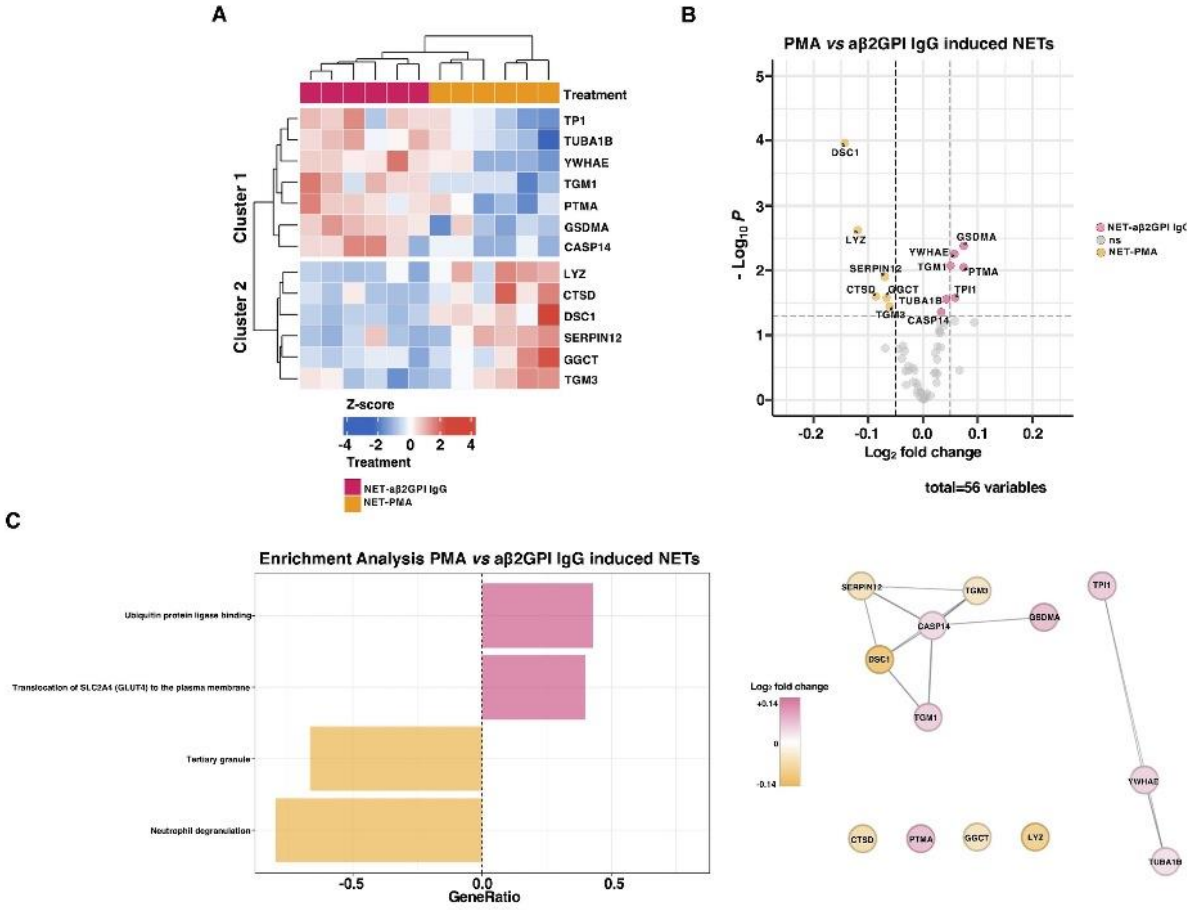


Figure 2. Proteomic analysis of aβ2GPI and PMA-induced NETs.



Conclusions: Taken together, these results emphasize that NETs from aβ2GPI and PMA are different in both composition and biological function. In conclusion, our findings describe how aβ2GPI-induced NET amplify endothelial cell activation and TF induction, unveiling a novel mechanism connecting the process of NETosis to thrombotic pathogenesis in APS.

O002 / #224

Topic: *AS06 - Comorbidities*

SCIENTIFIC HYBRID SESSION: BASIC TRACK PRESENTATIONS - OUTSTANDING ABSTRACT PRESENTATIONS
23-05-2025 9:00 AM - 10:00 AM

B-CELL ACTIVATING FACTOR INDUCES SYSTEMIC LUPUS ERYTHEMATOSUS-ASSOCIATED PULMONARY ARTERIAL HYPERTENSION VIA GZMK+ CD8+ T CELL MEDIATED ENDOTHELIAL CELL APOPTOSIS

Xuehan Jiang[1], Leyao Ma[2], Yutong Li[2], Mengtao Li[2], Peiran Yang[1]
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Background/Purpose: Background: Pulmonary arterial hypertension (PAH) is a severe complication of systemic lupus erythematosus (SLE) and a leading cause of mortality among SLE patients. PAH is marked by early-stage endothelial cell dysfunction. SLE pathology involves excessive autoantibody production by B cells, driving inflammatory cascades and systemic inflammation. B cell activating factor (BAFF) supports autoimmune B cell survival, proliferation, and differentiation, and the BAFF-targeted therapeutic, Belimumab, is in clinical use for SLE. However, the role of BAFF, and B cells more broadly, in the development and progression of PAH in SLE remains unclear.

Methods: Methods: We conducted transcriptomic analysis on peripheral blood samples from SLE and SLE-PAH patients. Mice overexpressing human BAFF (hBAFF-Tg mice) were used to establish a model of SLE-PAH. Serum assays, flow cytometry, hemodynamic measurements, right ventricular hypertrophy evaluation, and histological analysis were conducted. Additionally, single-cell transcriptome sequencing was performed on lung tissue from hBAFF-Tg mice to elucidate downstream mechanisms, and female MRL/lpr mice, a widely accepted model of SLE-PAH, were treated with Belimumab to assess therapeutic efficacy.

Results: Results: BAFF expression was significantly elevated in the peripheral blood of SLE-PAH patients, with upregulation of inflammation-associated pathways compared to SLE patients without PAH (Figure 1A). hBAFF-Tg mice showed spontaneous SLE phenotypes by 20 weeks, including increased dsDNA and IgG levels, reduced plasma C3, B cell activation and aggregation, and splenomegaly (Figure 1B). These mice also displayed increased right ventricular systolic pressure, right ventricular hypertrophy, and pulmonary arteriole thickenin (Figure 1C-E). Single-cell transcriptome analysis revealed that BAFF overexpression led to increases in B and T cell populations in lung tissue, identifying two novel immune cell subtypes: (1) IL9R+ mature B cells showing

features of upregulated T cell activation, and (2) GZMK+ CD8+ T cells, an effector population capable of recruiting additional T cells. Mechanistically, IL9R+ B cells activated GZMK+ T cells, which induced apoptosis in endothelial cells (Figure 1F-I). Intravenous administration of Belimumab at 5mg/kg and 50mg/kg alleviated established SLE-PAH in MRL/lpr mice (Figure 2).

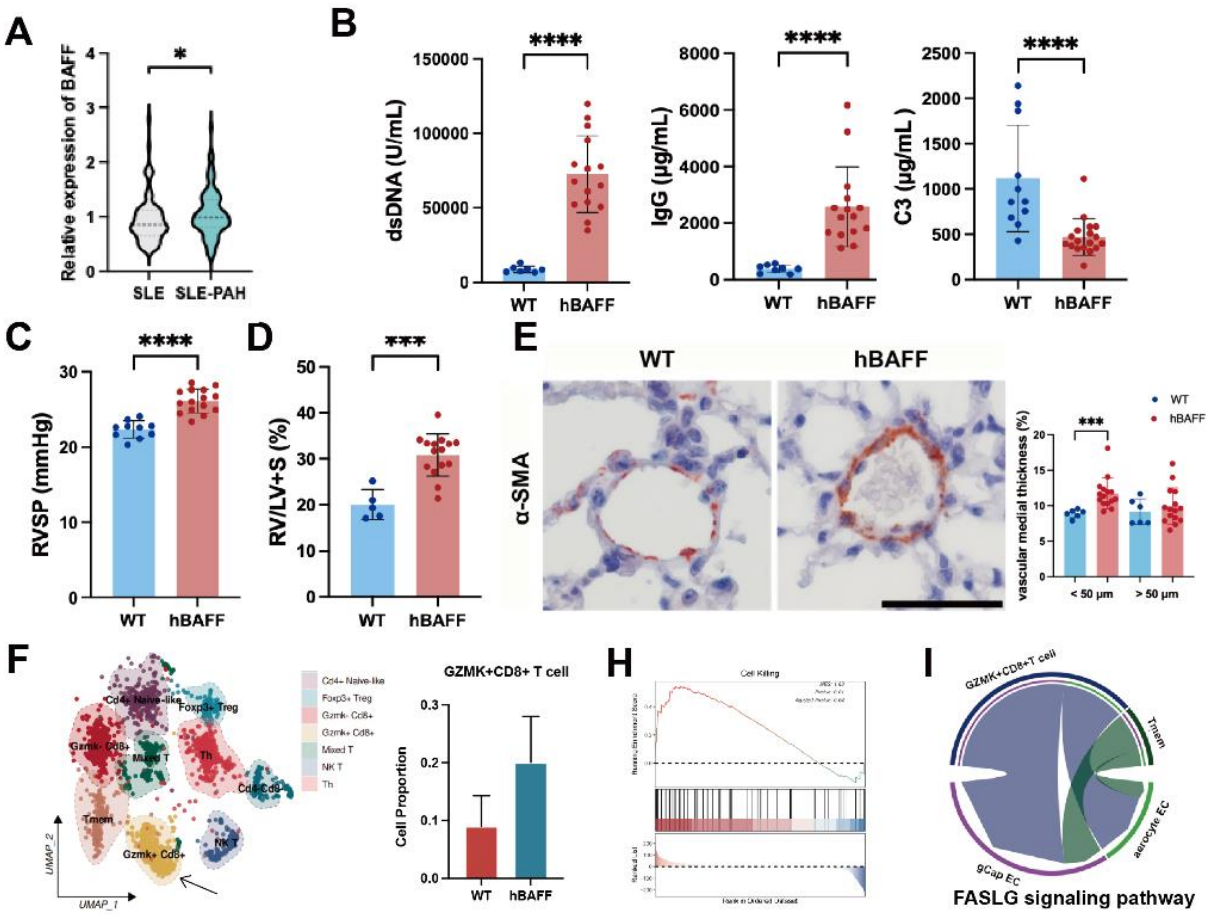

Figure1: hBAFF-Tg exhibits spontaneous SLE and PAH

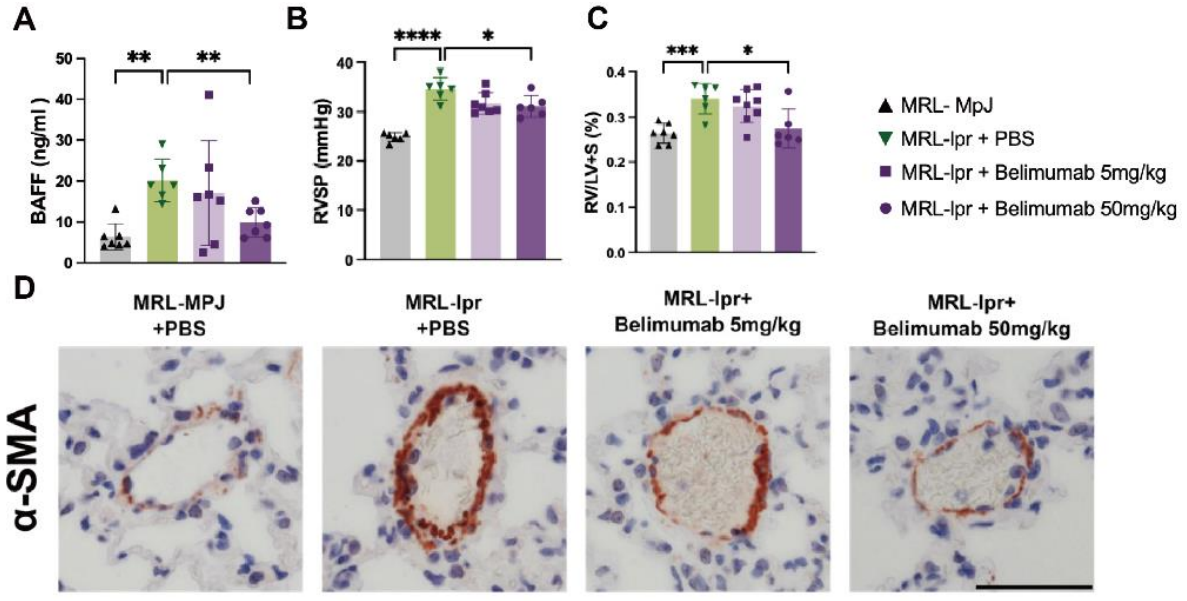

Figure2: Belimumab alleviates murine SLE-PAH

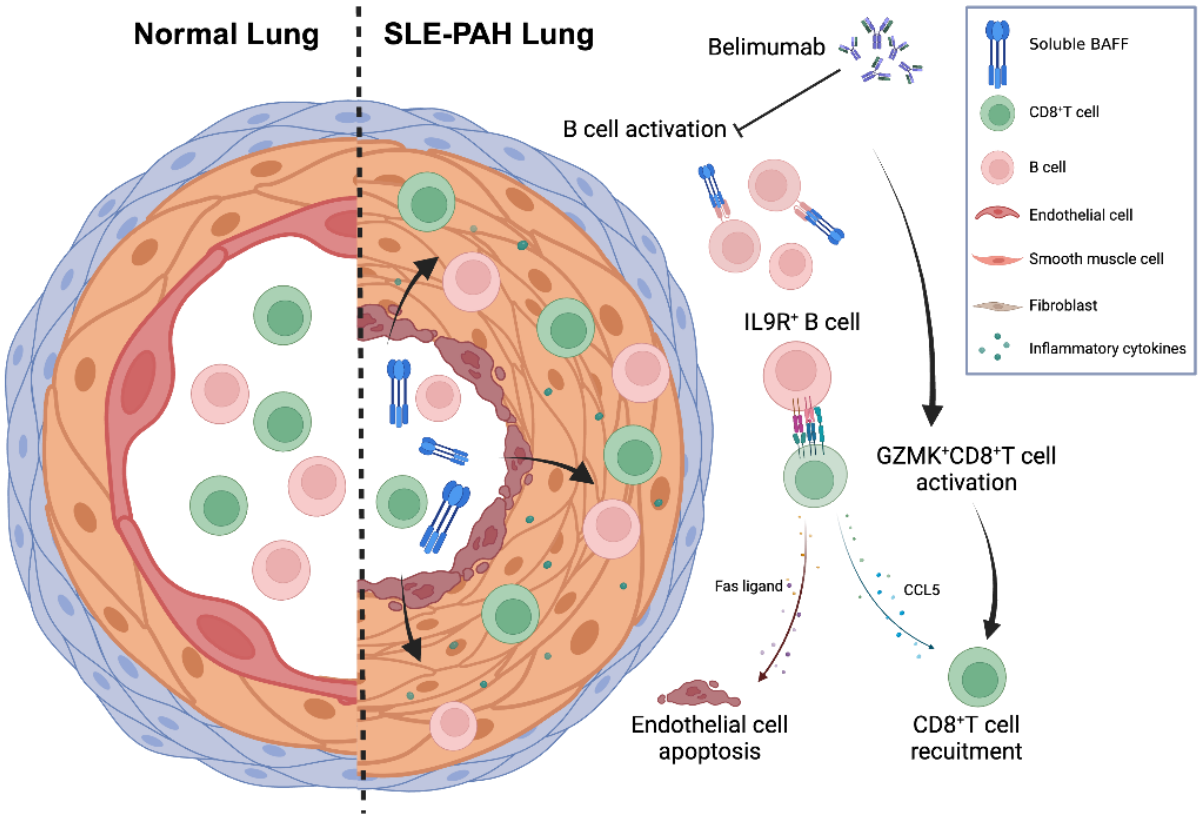

Figure3: Graphic abstract

Conclusions: Conclusions: BAFF contributes to SLE-PAH development by activating IL9R+ B cells and aggregating GZMK+ CD8+ T cells, leading to endothelial cell apoptosis and pulmonary vascular remodeling. These findings suggest a unique therapeutic potential of Belimumab in targeting BAFF and the critical process of B cell activation in SLE-PAH treatment.

O003 / #470

Topic: ***AS01 - Adaptive Immunity***

SCIENTIFIC HYBRID SESSION: BASIC TRACK PRESENTATIONS - OUTSTANDING ABSTRACT PRESENTATIONS
23-05-2025 9:00 AM - 10:00 AM

CHARACTERIZATION OF MEMORY T CELL SUBSETS DURING FLARES AND DISEASE QUIESCENCE IN LUPUS

Carol Nassar[1], Rene Quevedo[2], Maria Teresa Ciudad[2], Zoha Faheem[1], Kieran Manion[2], Carolina Munoz-Grajales[2], Michael Kim[2], Dafna D Gladman[2], Murray Urowitz[3], Zahi Touma[4], Tracy Mcgaha[2], Joan Wither[5]
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Background/Purpose: Around 70% of Systemic Lupus Erythematosus (SLE) patients follow a relapsing-remitting pattern of disease, with unpredictable flares of disease activity followed by variable periods of disease quiescence. $CD4^+$ T cell subsets have been shown to play an important role in driving the autoantibody production which causes flares in SLE, however the precise T cell changes that accompany flares are unknown. Here, we characterized the antigen-experienced memory T cell compartment at various phases of disease to gain insight into this question.

Methods: CITE-seq was used to assess the transcriptomic profiles of $CD4^+$ memory T cells in flaring (change in the clinical SLEDAI-2K > 0 in the last month prompting a change in therapy) and quiescent (clinical SLEDAI = 0 for at least a year, prednisone dose < 10) SLE patients. $CD4^+$ memory T cells were isolated from previously archived PBMCs, stained with oligo-conjugated antibodies against surface proteins, and then partitioned, barcoded, and sequenced. Samples from 15 distinct patients at two separate clinical visits spaced at least one year apart were examined. TCR sequencing was performed to assess clonotype expansion/contraction. The longitudinal nature of our data permitted examination of transcriptional changes both between and within patients.

Results: Integration of the gene and surface protein expression data led to identification of 23 unique immune populations [Fig.1.A]. Samples from flaring patients were more enriched for T follicular helper (Tfh), T peripheral helper (Tph), and Th1 cells. Conversely, quiescent patients were more enriched for central memory T cells (TCMs), specifically TCM1/2/6, compared to flaring patients ($p < 0.05$) [Fig.1.B&C]. There was no difference

in the proportion of exhausted Treg cells between flaring and quiescent patients at baseline suggesting that exhaustion of this subset is a consistent feature of SLE, potentially contributing to an inherent level of immune dysregulation regardless of clinical flare status. Differential gene expression analyses at baseline showed a high prevalence of IFN-induced genes in most identified cell subsets within the genes that were upregulated in flaring compared to quiescent patients, with a few exceptions (e.g., Th1). TCR repertoire analyses of samples at baseline revealed a higher proportion of expanded clonotypes in various clusters, such as Th17, in flaring patients [Fig.2.A], which was not seen in quiescent patients [Fig.2.B]. Similarly, clonal overlap among subsets was more pronounced in the flaring patient samples [Fig.2.C] than in the quiescent samples [Fig.2.D]. This overlap indicates that these T cells have shared antigen specificity, suggesting cell plasticity or differentiation from a common precursor – which will be investigated by trajectory pathway analyses.

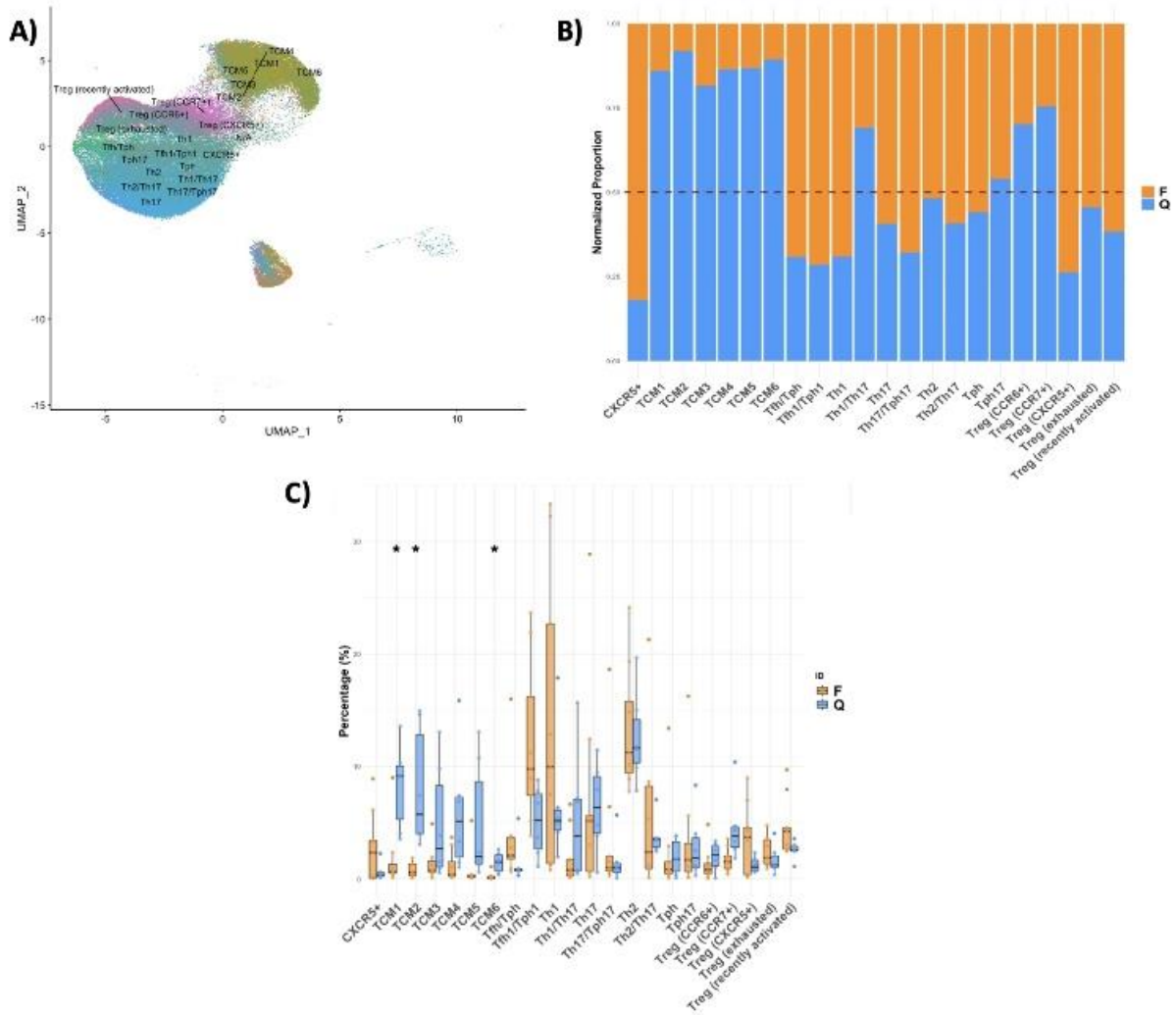

Figure 1: **A)** UMAP depicting 23 annotated clusters. **B)** Bar chart of normalized weighted proportions of cells across clusters at baseline based on disease status: Flaring (F, orange) and Quiescent (Q, blue). **C)** Boxplots showing distribution of proportional percentages of subsets for each patient at baseline based on disease status. Each dot represents an individual patient's data point. To assess for statistical difference, Mann-Whitney U test was used, with p-values adjusted for multiple comparisons using the Benjamini-Hochberg method (*, adjusted $p < 0.05$).

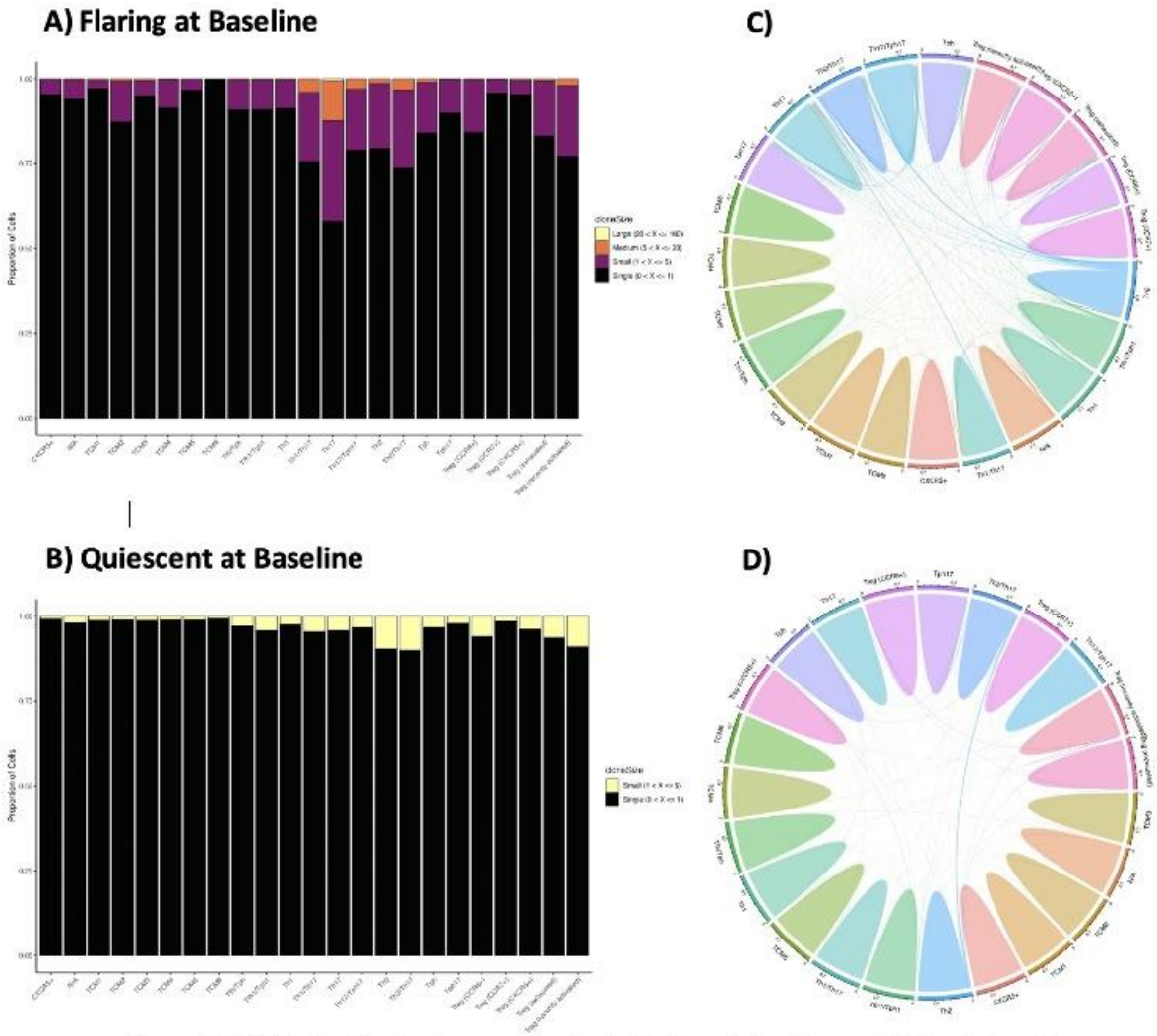

Figure 2: *Left:* Stacked barchart representing the distribution of clonally expanded T cells in each of the identified clusters at baseline (visit 1) in (**A**) flaring and (**B**) quiescent patients. *Right:* Chord diagrams representing clonal overlap between the clusters at baseline in (**C**) flaring and (**D**) quiescent patients. The width of each chord indicates the normalized proportion of unique or shared clones between groups which highlights the extent of clonal overlap.

Conclusions: Although flaring patients demonstrate expansion of relatively few T cell subsets (Tfh, Tph, Th1 cells), analysis of TCR clonotypes suggests that T cells involved in the autoimmune response are found in several additional T cell subsets (Th17, Th2), indicating that there is substantial functional diversification/plasticity in the response. These findings are absent in quiescent patients, which instead show enrichment of TCMs expressing diverse TCRs. Our findings suggest that expanded populations of antigen-specific T cells can be seen in flaring patients, and that further characterization of these cells may provide insight into the specificity of the T cells that support auto-antibody production in lupus flares.

O004 / #223

Topic: *AS05 - CNS Lupus*

SCIENTIFIC HYBRID SESSION: CLINICAL TRACK PRESENTATIONS - OUTSTANDING ABSTRACT PRESENTATIONS
23-05-2025 9:00 AM - 10:00 AM

LONGITUDINAL NEUROCHEMICAL CHANGES IN THE HIPPOCAMPUS ASSOCIATED WITH MOOD AND COGNITIVE IMPAIRMENT IN SYSTEMIC LUPUS ERYTHEMATOSUS

Danilo Pereira[1], Renan Frittoli[2], Paulo Julio[2], Lilian Costallat[2], Leticia Rittner[2], Simone Appenzeller[2]
[1]Revista Brasileira de Reumatologia, Campinas, Brazil, [2]University of Campinas, Campinas, Brazil

Background/Purpose: Systemic lupus erythematosus (SLE) is an autoimmune disease with multiorgan involvement. The hippocampus is one of the most thoroughly investigated structures in the brain and hippocampal atrophy was found in SLE patients. Proton magnetic resonance spectroscopy (^{1}H-MRS) has proved to be a noninvasive tool for detecting neuronal metabolic dysfunction in neurological diseases. The purpose of this study was to investigate the presence of neurochemical changes in the hippocampus in SLE patients using proton magnetic resonance spectroscopic imaging (^{1}H-MRSI) technique and to determine if clinical, laboratory and treatment features are associated with its occurrences.

Methods: We included 58 SLE patients (mean age of 39.21±11.49 years, range 20-68) and 58 healthy controls (mean age of 40.91±12.02 years, range 23-66). ^{1}H-MRSI over the bilateral hippocampus was done with a Philips 3T MRI scanner and signals from N-acetyl-containing compounds (NAA), choline-based compounds (Cho), glutamate (Glu), glutamine (Gln), Glx (the sum of Glu and Gln) and creatine (Cr) to determine NAA/Cr, Cho/Cr and Glx/Cr ratios. After a minimum of 12 months ^{1}H-MRSI acquisitions were repeated in 58 SLE patients and 51 controls. Neurological manifestations were analyzed according to the ACR classification criteria and SLE disease activity index (SLEDAI). Cognitive impairment was screened using the Montreal Cognitive Assessment (MoCA), symptoms of anxiety (Beck's Anxiety Inventory - BAI) and depression (Beck's Depression Inventory - BDI)[4]. BAI scores may range from 0 to 63: minimal anxiety levels (0-7), mild anxiety (8-15), moderate anxiety (16-25), and severe anxiety (26-63) and BDI scores are classified as minimal depression (0-13), mild depression (14-19), moderate depression (20-28), and severe depression (29-63).

Results: The median score for MoCA was 21.07±4.66. Using a MoCA cutoff score of < 26, total of the 49 patients (87.93%) were identified to have mild cognitive impairment. The median score for BAI was 25.67±14.60 and 46 patients (79.31%) had

moderate/severe anxiety symptoms. The median BDI score was 22.88±9.16 and 37 patients (63.79%) had moderate/severe depressive symptoms. We found a significant reduction in NAA/Cr ratios in SLE patients when compared to healthy controls (p = 0.049) correlated positively with MoCA scores (r=0.432, p=0.001), and negative correlation with BDI scores (r=-0.334, p = 0.010) and associated with use of prednisone during the treatment (p=0.039). Follow-up study showed a reduction in NAA/Cr ratios (p=0.042) correlated negatively with BDI scores (r=-0.313, p=0.017), when compared to SLE patient's baseline values (Table 1).

Table 1 – Results of comparison of of metabolites levels of the bilateral hippocampi in SLE patients and healthy controls

	Mean value (SD)		**Kruskal-Wallis test**
Metabolite (mmol/L)	**58 SLE**	**58 HC**	***p* value**
NAA/Cr	1.623 (0.22)	1.781 (0.19)	**0.049***
Cho/Cr	0.363 (0.10)	0.382 (0.14)	0.281
Glx/Cr	0.478 (0.16)	0.511 (0.26)	0.268
			Paired t-test
	58 SLE (initial)	**58 SLE (follow-up)**	***p* value**
NAA/Cr	1.623 (0.22)	1.507 (0.36)	**0.042***
Cho/Cr	0.363 (0.10)	0.360 (0.13)	0.916
Glx/Cr	0.478 (0.16)	0.517 (0.24)	0.272
	58 HC (initial)	**51 HC (follow-up)**	***p* value**
NAA/Cr	1.781 (0.19)	1.688 (0.25)	0.151
Cho/Cr	0.382 (0.14)	0.376 (0.11)	0.794
Glx/Cr	0.511 (0.26)	0.513 (0.33)	0.822

Conclusions: This is the first longitudinal study to assess levels of metabolic changes in hippocampus in SLE patients using ^{1}H-MRSI. Metabolic abnormalities in the hippocampus were associated with cognitive impairment, symptoms of anxiety and depression during the treatment. Therefore, NAA/Cr ratios may be used as a surrogate marker in follow-up studies of SLE.

O005 / #41

Topic: ***AS18 - Paediatric SLE***

SCIENTIFIC HYBRID SESSION: CLINICAL TRACK PRESENTATIONS - OUTSTANDING ABSTRACT PRESENTATIONS
23-05-2025 9:00 AM - 10:00 AM

DECREASED FUNCTIONAL FRONTO-CEREBELLAR CONNECTIONS ARE ASSOCIATED WITH GREATER DISEASE ACTIVITY AND GLUCOCORTICOID USE IN ADOLESCENTS WITH CHILDHOOD-ONSET LUPUS

Diana Valdés Cabrera[1], Oscar Mwizerwa[2], Asha Jeyanathan[2], Lawrence Ng[2], Tala El Tal[3], Birgit Ertl-Wagner[4], Ann Yeh[5], Helen Branson[4], Adrienne Davis[6], Linda Hiraki[7], Deborah Levy[2], Andrea Knight[2]
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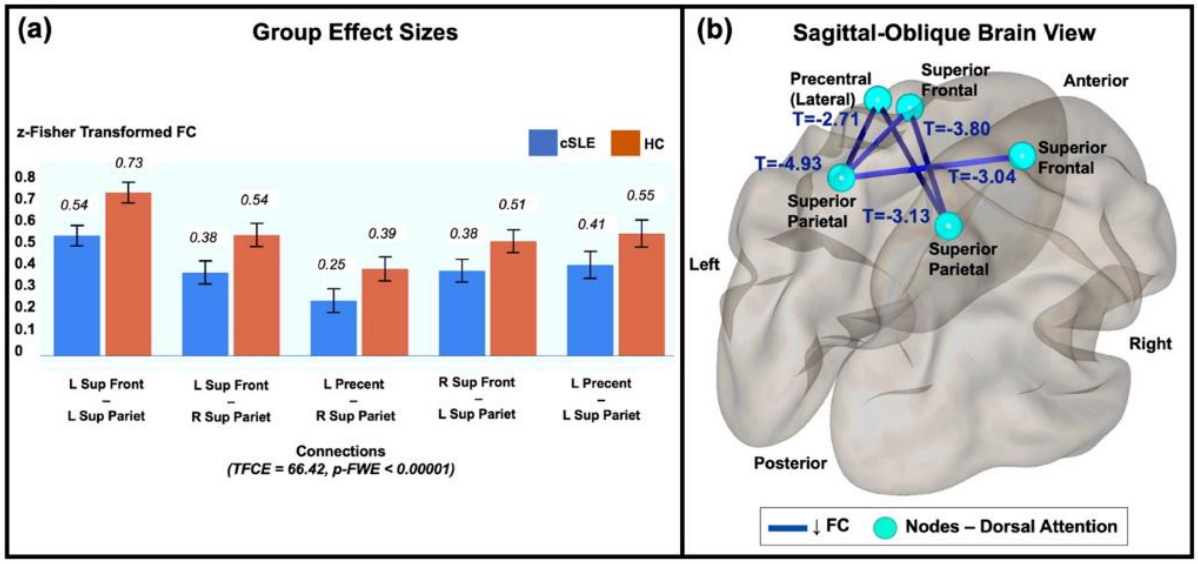
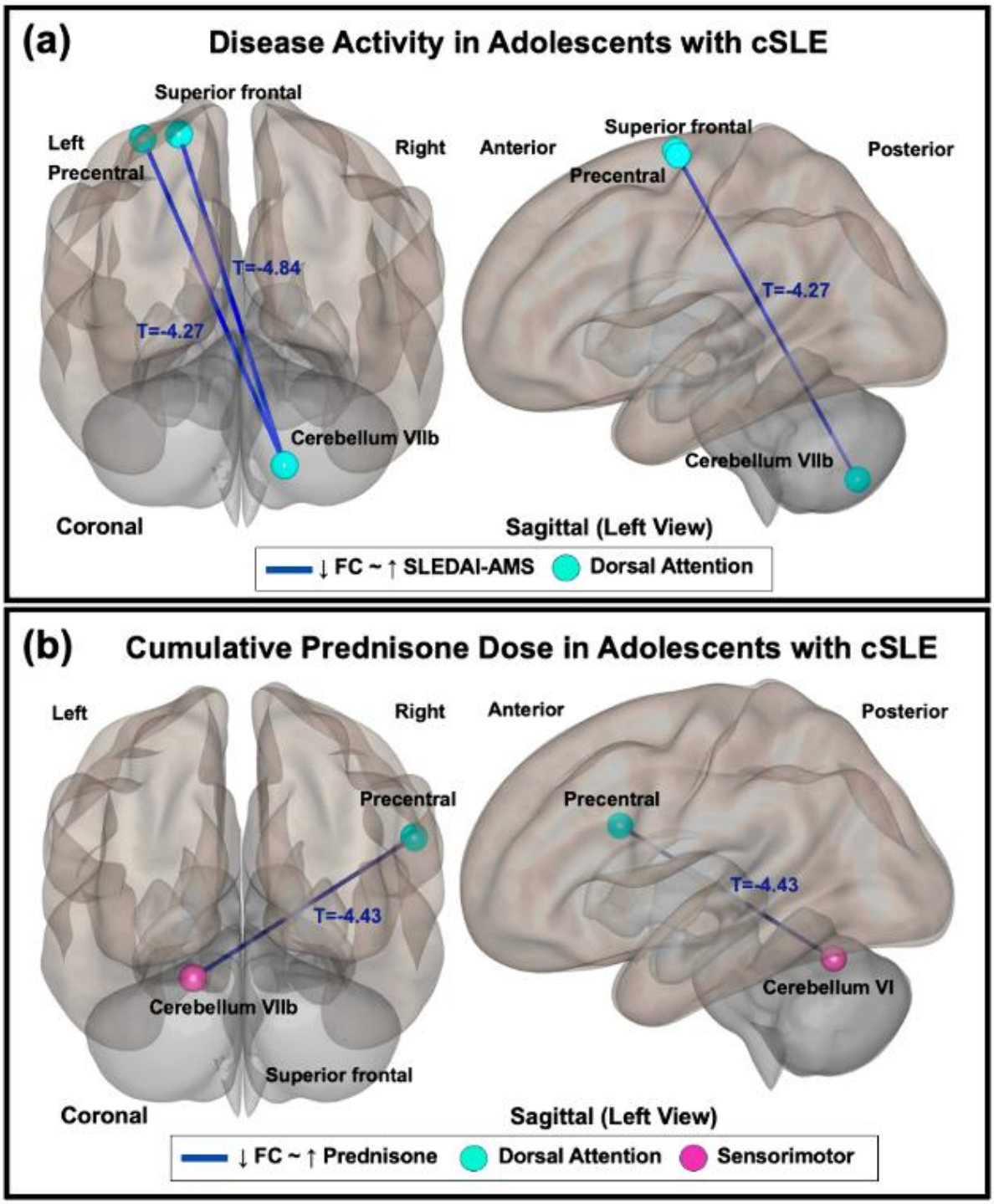
Background/Purpose: Adolescents with childhood-onset systemic lupus erythematosus (cSLE) typically experience higher prevalence of brain involvement when compared to adult-onset patients. They are vulnerable to neuropsychiatric syndromes (NPSLE) that may strike during neurodevelopment and could alter the functioning of brain networks that are crucial for cognition and behavior. Brain alterations in functional connectivity (FC) can be examined with resting-state functional magnetic resonance imaging (rs-fMRI) and have been observed in adults with lupus. However, FC abnormalities in relation to disease characteristics have been understudied in cSLE. We aimed to examine differences in brain FC between adolescents with cSLE and healthy controls (HC) utilizing rs-fMRI, and to evaluate if FC is associated with disease duration, activity and glucocorticoid use in cSLE.

Methods: Patients with cSLE aged 11-17 years and age and sex-matched HC underwent T1-weighted MRI and rs-fMRI at 3 T. Disease activity was evaluated with the time-adjusted mean Systemic Lupus Erythematosus Disease Activity Index 2K (SLEDAI-AMS), calculated as the area under the curve over one year before the MRI scan. Cumulative glucocorticoid use was calculated as prednisone equivalent dose in grams. Brain networks were parcellated with independent component analysis, thresholded, and transformed into regions of interest (ROIs). Group FC differences between all ROIs and regional volumes from structures with abnormal FC were evaluated with age-adjusted general linear models. In the cSLE group, regression analyses evaluated associations

between FC and disease duration, activity and cumulative prednisone dose. All connections were family wise error (FWE) corrected with Threshold Free Cluster Enhancement (TFCE, p-FWE < 0.05).

Results: Results: Participants included 60 patients with cSLE (52 females; age – median, IQR: 16, 3 years; 3 with NPSLE diagnosis) and 59 HC (49 females; age – median, IQR: 15, 2 years). For patients, median disease duration was 0.9 (IQR = 1.2) years, 45% had active disease (SLEDAI-AMS ≥ 4) in the year prior to study visit (median, IQR: 2.7, 5.4), and 73% were exposed to prednisone (cumulative prednisone dose – median, IQR: 1.9, 6.0 grams). Patients with cSLE had lower FC compared to HC in a cluster of frontoparietal connections (TFCE = 66.42, p-FWE = 0.00001; Figure 1). Lower right superior frontal cortex volumes were observed in patients with cSLE compared to HC (T = -2.34, p = 0.021). In the cSLE group (Figure 2), lower FC in superior frontal and cerebellar regions was associated with higher disease activity (TFCE = 55.10, p-FWE = 0.004) and higher cumulative prednisone dose (TFCE = 49.53, p-FWE = 0.013).





Conclusions: Patients with cSLE, compared to HC, exhibited decreased FC and, to a lesser extent, atrophy in frontoparietal regions known to associate with somatosensory and visuospatial functions. Moreover, higher cSLE disease activity and prednisone exposure may dysregulate the functioning of fronto-cerebellar networks involved in sensory information processing. Further longitudinal studies are needed to investigate the effect of cSLE and its treatment on brain function and development over time.

O006 / #412

Topic: ***AS12 - Genetics, Epigenetics, Transcriptomics***

SCIENTIFIC HYBRID SESSION: CLINICAL TRACK PRESENTATIONS - OUTSTANDING ABSTRACT PRESENTATIONS
23-05-2025 9:00 AM - 10:00 AM

DISTINCT MOLECULAR PROFILES OF REMISSION POST-CD19 CAR-T CELL THERAPY VERSUS STANDARD IMMUNOSUPPRESSION IN SYSTEMIC LUPUS ERYTHEMATOSUS

Panagiotis Garantziotis[1,2], Lorenzo Beretta[3], Julius Lindblom[4], Dionysis Nikolopoulos[4], George Bertsias[5], Melanie Hagen[1,2], Jule Taubmann[1,2], Andreas Wirsching[1,2], Aline Bozec[1,2], Ricardo Grieshaber-Bouyer[2], Precisesads Clinical Consortium[6], Matthias Schneider[7], Guillermo Barturen[6,8], Dimitrios Boumpas[9,10], Marta Alarcón-Riquelme[11], Georg Schett[2], Ioannis Parodis[4,12]
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Background/Purpose: Remission, as defined by the Definition of Remission in SLE (DORIS) criteria, is the primary therapeutic target in systemic lupus erythematosus (SLE). While DORIS remission correlates with the reversal of key pathogenic processes (Parodis I, et al. Ann Rheum Dis. 2024), novel approaches like CD19-targeted chimeric antigen receptor (CAR)-T cell therapy have shown potential to induce durable, drug-free

remission. Yet, the molecular characteristics of CAR-T cell-induced remission compared to standard immunosuppression-induced remission remain unclear.

Methods: To delineate unique molecular profiles of CD19 CAR-T cell therapy-induced remission, we performed a comparative analysis of Reactome pathways. Pseudo-bulk expression profiles were generated from single-cell RNA sequencing of peripheral blood mononuclear cells (PBMCs) in seven SLE patients post-lymphodepletion and CAR-T cell infusion. As a comparator, transcriptional profiles from 34 SLE patients in DORIS remission on standard immunosuppression from the PRECISESADS project (1) were analysed. Functional pathway annotations were derived using the Functional Analysis of Individual Microarray Expression (FAIME) algorithm.

Results: Of 314 pathways, 22 pathways related to the immune system were significantly differentially regulated, with CAR-T cell-induced remission being associated with a greater suppression of type I interferon, complement activation, and interleukin signalling pathways. Notably, Fc gamma receptor IIIa-mediated IL-10 synthesis and lipid metabolism pathways were selectively upregulated, suggesting enhanced anti-inflammatory responses and metabolic rewiring. CD19 CAR-T cell-induced remission was also marked by decreased DNA damage response activation compared to remission on standard immunosuppression.

Conclusions: Our findings reveal a distinct immune and metabolic landscape associated with CD19 CAR-T cell-induced remission in SLE, supporting the notion of CD19 CAR-T cell-mediated immunological reset.