expression revealed suppression in the relative fold change of IL-6 by 23%, IL-8 by 30%, TNF-α by 11%, and IFN-γ by 21% with Tai Chi.
Conclusions: These data suggest that moderate exercise and stress management can have potent immunoregulatory effects on the chronic, systemic inflammation associated with SLE and identify daily Tai Chi exercise as a viable adjunct therapy to compliment current pharmacological interventions.
References:
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AB0152 DISEASE ACTIVITY AND DAMAGE SCORES CORRELATED DIFFERENTLY WITH THE PATIENT REPORTED OUTCOMES IN PATIENTS WITH PRIMARY SJÖGREN'S SYNDROME COMPARED TO LUPUS ASSOCIATED WITH SECONDARY SJÖGREN'S SYNDROME

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Background: Previous studies showed a poor correlation between EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) and EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) in patients with Sjögren's syndrome (SS) (1). There are no previous studies correlating these scores with the SS Disease Damage Index (SSDDI) or assessing comparatively patients with primary (pSS) and secondary SS associated with lupus (SLE/SS).
Objectives: We aimed to assess how well scores assessing disease activity, damage and patient reported outcomes correlate with each other in patients with pSS compared to SLE/SS.
Methods: We conducted a cross-sectional study of 55 patients with pSS and 15 SLE/SS. Detailed clinical and laboratory data, along with patient reported outcomes (ESSPRI) and disease activity and damage scores (ESSDAI, BILAG and SSDDI) were collected. We compared the clinical and laboratory parameters of the two patient groups (pSS and SLE/SS) and assessed the correlations between maximum ESSDAI score since diagnosis and ESSDAI, ESSPRI, SSDDI and BILAG scores at the time of assessment.
Results: The table below shows comparatively the differences between the pSS and SLE/SS patient groups.

Table 1

Demographic	pSS (n=55)	SLE/SS (n=15)	Significance
Sex n (female/male %)	55 (100/0)	15 (100/0)	
Ethnicity n (C/A/MN/O)	43/6/3/3	9/1/5/0	P=0.4571
Age mean (range)	58 (28–84)	56 (25–78)	P=0.5923
Disease duration mean (range)	12 (2–34)	23 (3–40)	P=**0.005
Anti-Ro+ % (n)	76 (42)	73 (11)	P=0.7273
Anti-La+ % (n)	49 (27)	27 (4)	P=0.0565
ESSPRI median [IQR]	5 [3–7]	4 [2– 6]	P=0.3382
ESSDAI median [IQR]	2 [0– 4]	2 [1–4]	P=0.8884
Maximum ESSDAI [IQR]	4 [2–6]	3 [2–6]	P=0.9519
SSDDI median [IQR]	1 [1–2]	1 [0–2]	P=0.1992
Global BILAG median [IQR]		0 [0–2]	
Treatment			
Hydroxychloroquine (%)	65	40	P=0.0775
Methotrexate (%)	5	33	P=**0.0092

Unpaired T test performed; **p<0.01, n = total number, % percentage, IQR = interquartile range, ethnicity: C = Caucasian, A = Asian, MN = African Caribbean, O = Chinese, anti-Ro = anti-Sjögren's-syndrome-related antigen A, anti-La = anti-Sjögren's-syndrome-related antigen B.

We found significant correlations of SSDDI score with disease duration and maximum ESSDAI score in patients with pSS (r=0.27, p=0.05 and r=0.67, p=0.0001, respectively). In SLE/SS patients, ESSPRI scores correlated with both BILAG and maximum ESSDAI score (r=0.55, p=0.03 and r=0.7, p=0.02, respectively). The SSDDI score correlated with the disease duration only in pSS patients (r=0.27, p=0.05).
Conclusions: Our study showed that there was no similar correlation between various disease scores in patients with pSS compared to SLE/SS patients. If the patient reported outcomes correlated with the disease activity (ESSDAI and BILAG) in SLE/SS patients, this correlation was not seen in pSS patients, in which the significant correlations were found only between damage scores, highest disease activity score and disease duration.
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AB0153 DELETION OF RECEPTOR FOR ADVANCED GLYCATION END PRODUCTS (RAGE) DOES NEITHER AFFECT AUTO-ANTIBODY PRODUCTION NOR DEVELOPMENT OF RENAL DISEASE IN PRISTANE-INDUCED LUPUS

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Background: Systemic lupus erythematosus (SLE) is characterized by autoantibodies to diverse autoantigens, especially to nuclear components such as double-stranded DNA (dsDNA) or nucleosomes. Still, it remains unclear why poorly immunogenic molecules such as dsDNA and nucleosomes become targets of humoral autoimmunity in SLE. Increased signaling via pattern-recognition receptors (PRRs) through pathogen-associated molecular patterns (PAMPs) or endogenous damage-associated molecular patterns (DAMPs) released from damaged or stressed host cells and tissues, may be critically involved in the break of tolerance against such nuclear antigens. One important PRR in this context may be RAGE. Among many others, RAGE recognizes High mobility group box 1 (HMGB1). HMGB1 is a DNA-binding nuclear protein that has been found at elevated levels in patients with SLE and other autoimmune diseases; likewise perpetuation of RAGE signaling sustains inflammation and leads to the establishment of chronic inflammatory disorders.
Objectives: We therefore examined, using the Pristane-induced SLE model, if increased RAGE signaling may be involved in the break of tolerance against nuclear antigens and contributes to chronic inflammation.
Methods: To that end, WT and RAGE-/- animals were injected intra-peritoneally with a single dose of pristane. Disease manifestations were determined after 7 months and included the determination of proteinuria and renal pathology by evaluating the glomerular cellularity and matrix on H&E stained paraffin-embedded kidney sections and glomerular depositions of IgG and C3c. In addition to that we checked for auto-antibody production at several time points during disease development and immune cell distribution, differentiation and phenotype in inflamed kidneys and spleen.
Results: Apart from a slight decrease in $GL7^{hi}Fas^{hi}$ germinal center B cells and $B220^{+}CD21^{low}CD23^{hi}$ follicular B cells in RAGE-/- animals, we did not detect differences in auto-antibody secretion or disease manifestations between RAGE-/- and WT mice.
Conclusions: Our data contrast with recently published data showing that a deletion of RAGE exacerbated lupus nephritis and lymphoproliferation in a different SLE model (B6-MRL Fas lpr/j). Therefore, we are currently looking into the effects of RAGE deletion in additional models of auto-antibody-mediated immune disease.
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AB0154 CIRCULATING CPG DNA PROMOTER FRAGMENTS IN SLE ACTIVATE INTRARENAL TLR9 SIGNALING AND ACCELERATE RENAL INFLAMMATION AND FIBROGENESIS

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Background: In systemic lupus erythematosus (SLE), lupus nephritis (LN) is associated with chronic inflammation and perpetuated fibroblast activation, both determined by epigenetic mechanisms involving aberrant CpG DNA promoter methylation. During SLE progression, global methylation patterns are commonly lost. These CpG DNA promoter methylation patterns are not limited to the kidney, circulating CpG-rich DNA is also detectable in the blood allowing for biomonitoring ("liquid biopsy"). However, little is known about its specific contribution to determining disease progression. In the kidney, CpG-rich DNA activates TLR9 signaling mechanisms involved in inflammation and fibrogenesis. Based on these observations, we hypothesized that CpG-rich DNA promoter fragments potentially accelerate renal inflammation and fibrogenesis in SLE-associated LN.
Objectives: To analyze the role of circulating CpG-rich DNA on endothelial TLR9 signalling and the effect of experimental modification of oligodinucleotides on kidney inflammation in the Pristane-induced murine model of SLE.
Methods: We isolated circulating CpG-rich DNA from blood samples in a cohort of SLE patients. Then, we tested how these DNA promoter fragments influenced the LN phenotype in a TMPD ("pristane")-induced mouse model. Further, we investigated how this renal response could be influenced by the administration of either human or synthetic methylated/unmethylated CpG-rich DNA oligodinucleotides. Additionally, the effects of the administration of cicruclating CpG-rich DNA fragments on TLR9-signalling was analyzed in endothelial cell cultures.
Results: We show that circulating CpG-rich DNA promoter fragments are detectable in SLE patients' blood. Furthermore, SLE-associated LN is associated with accumulation of unmethylated CpG-rich DNA promoter fragments, implicating a mechanistic connection. These observations were further corroborated in a rodent model of TMPD-induced SLE where administration of CpG-rich DNA (isolated from LN patients or synthetic unmethylated CpG-rich DNA oligonucleotides) worsened the renal phenotype in terms of inflammation and fibrogenesis.
Causal contribution of TLR9 was further confirmed in *Tlr9*$^{+/-}$-knockout mice with protection from renal inflammation and kidney fibrosis after administration of unmethylated CpG-rich DNA promoter oligonucleotides. TLR9-mediated intrarenal

inflammation can be therapeutically targeted by administration of synthetic methylated CpG-rich DNA oligonucleotides, ultimately associated with suppression of TLR9-mediated signaling responses and renal injury in experimental SLE/LN.
Conclusions: Collectively, our results implicate accumulation of unmethylated CpG-rich promoter DNA fragments in SLE-associated LN. Furthermore. these unmethylated CpG-rich promoter DNA fragments causally contribute to TLR9-mediated inflammation and renal fibrogenesis. Administration of methylated CpG-rich oligonucleotides antagonized intrarenal TLR9-mediated inflammatory signaling responses and fibrogenesis. Therefore, biomonitoring of CpG-rich promoter DNA fragments and modulation of intrarenal TLR9 signaling is a promising therapeutical target in SLE-associated LN.
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AB0155 LEARNING SLE PATHOLOGICAL MECHANISMS FROM MULTI 'OMICS PROFILES

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Background: Precision medicine aims at providing intervention based on clinical and molecular stratification of patients, and is an important approach for targeting heterogeneous diseases. A diverse autoimmune disease is systemic lupus erythematosus (SLE), where dysregulation of several immune processes affects multiple organs. Fundamental for targeted treatment of such a heterogeneous disease is the identification of biomarkers predictive for the biological basis of clinical phenotypes.
Objectives: Despite recent progress, few markers for SLE are currently used in the clinic. In order to learn SLE pathological mechanisms and associated biomarkers, we obtained a diverse dataset from a cohort of active SLE patients (SLEDAI >6), including blood transcriptomics, serum proteomics, cytokines, and auto-antibody profiles. Integration of multi-omics data provides a rich dataset to explore associations between molecular and clinical readouts.
Methods: From a machine-learning perspective, biomarker discovery is defined as the process of selecting an optimal subset of variables for the prediction of parameters of interest. However, variable selection approaches are often underpowered for datasets that contain fewer samples than the number of variables. To overcome this problem we present a method based on L1 regularized regression and recursive variable elimination to generate networks of predictive markers across multiple data types.
Results: The proposed method allows us to graphically visualize the relationships among SLE phenotypes, and their molecular fingerprints. Identified networks of markers are validated by mapping to known biological pathways, and when available by comparison to independent patient cohorts. Despite the small number of patients (n=20), we identify known pathological mechanisms, including a type I IFN gene signature, several cell type specific signatures, and potential novel markers of clinically defined SLE subtypes.
Conclusions: Systemic lupus erythematosus is a complex autoimmune disease characterized by a variety of clinical manifestations. While multi-omics profiles from SLE patients pose challenges because of their intrinsic high dimensionality, they also provide a unique insight into the molecular processes of disease. Our integrated analysis gives a novel perspective on the pathological mechanisms of clinical SLE phenotypes.
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AB0156 THYMIC STROMAL LYMPHOPOIETIN (TSLP) IN PRIMARY SJÖGREN'S SYNDROME AND RELATED LYMPHOMA: THE POSSIBLE CONTRIBUTION OF A NOVEL GROWTH FACTOR

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Background: Primary Sjögren's syndrome (pSS) is an autoimmune lymphoproliferative systemic disease with a higher risk of non-Hodgkin B cell lymphoma (NHL) evolution. In SS, salivary gland (SG) epithelium plays a crucial role in initiating and perpetuating the autoimmune response. Thymic stromal lymphopoietin (TSLP) is both an epithelial and lymphopoietic cytokine involved in the maintenance of immune tolerance at interfaces between body and environment and in the regulation of lymphocytes homeostasis.
Objectives: To study TSLP in serum and SG biopsies of pSS patients stratified by the lymphoproliferative histopathologic status, from fully benign lesions (fbSS) to myoepithelial sialoadenitis (MESA) and to NHL, in order to evaluate a possible role of TSLP in SS pathogenesis and in lymphoma evolution.
Methods: Serum TSLP levels were determined by ELISA in pSS patients (n=30: 12 fbSS, 10 MESA, 8 NHL) and in controls (healthy blood donors - HD n=20; non-autoimmune sicca without SS - nSS n=10). TSLP was also studied by immunohistochemistry in SG biopsies of the same patients and nSS controls. Correlations with clinical and histopathologic parameters were performed. Of note, sequential samples were also included from three patients evolving from fbSS to NHL.
Results: TSLP serum levels were significantly higher in pSS compared to nSS (p=0.03) and HD (p=0.0002), with a progressive significant increase from fbSS to MESA (p=0.004) and finally to NHL (NHL vs fbSS p<0.0001; NHL vs MESA p=0.003), where the increase was dramatic. This was observed also in metachronous samples from the three pSS patients evolving to NHL. A positive significant correlation between TSLP serum levels and disease activity assessed by ESSDAI was found (p<0.0001).
Of note, in the affected tissue, TSLP showed an opposite pattern of expression than in the serum. Concerning the salivary epithelium, a declining expression of TSLP was shown from fbSS (expression was similar to nSS) to MESA and finally to NHL. Strikingly, however, the three pSS patients evolving to lymphoma were the only ones showing a low TSLP epithelial expression also at baseline. Concerning the glandular lymphoid infiltrate, the TSLP expression again decreased with progression to NHL. Again, the three pSS patients evolving to lymphoma were the only ones showing a low TSLP inflammatory expression also at baseline.
Conclusions: Serum TSLP increases in pSS and correlates with lymphoma progression. Discrepancies are however observed between serum levels and tissue TSLP expression: while the baseline TSLP tissue expression is evident and similar to controls, tissue TSLP decreases with lymphoma progression. TSLP likely represents an additional growth factor and biomarker for pSS pathogenesis and lymphoproliferation.
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AB0157 TREX 1 MUTATION IN THE MEMBERS OF A FAMILY WITH SYSTEMIC LUPUS ERYTHEMATOSUS AND ANTIPHOSPHOLIPID SYNDROME

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Background: There are reports showing Three Prime Repair Exonuclease 1 (*TREX1*) mutations in atypical Systemic Lupus Erythematosus (SLE) patients.
Objectives: Here we report a family with SLE and Antiphospholipid Syndrome (aPL) who are positive for *TREX1* mutation and complicated with AA amyloidosis
Methods: DNA samples were extracted from peripheral blood samples of two affected (mother and daughter) and two unaffected individuals of the same family. Exome sequencing was performed for the daughter and data was processed according to GATK Best Practices recommendations. Exome variants were used to search for a rare candidate variant causing the disease. Identified variant was screened in four family members using Sanger sequencing.
Results: The index case (mother) was a 63 year-old woman who had developed polyarthritis and recurrent cerebrovascular accident (CVA) at the age of 44. She was positive for ANA, anti-ds-DNA and IgG anti-cardiolipin antibodies. On anticoagulant therapy she still experiences frequent CVAs. The daughter who is 43 years old had experienced depression, non-erosive arthritis and alopecia at the age of 13. She was positive for ANA, dsDNA and ACA and was treated with hydroxychloroquine, prednisolone, and rituximab. She had attacks of deep vein thrombosis despite anticoagulant therapy. A renal biopsy was performed because of an increase in her creatinine level, with no proteinuria and normal urinary sediment, which revealed AA amyloidosis. She was heterozygous for p.R202Q variant in *MEFV* gene. Further genetic testing was performed for the mother and the daughter as well as two other non-affected members of the family.
Candidate variant search in exome data resulted a novel c.2T>A (p.M1?) variant in *TREX1* gene. The variant was in heterozygous state for both affected members. Since the variant disrupts translation initiation codon (ATG/AAG), it is predicted to cause loss of complete protein production.
Conclusions: There is evidence that *TREX1* is involved in the pathogenesis of SLE, especially with neuropsychiatric disease. Here we report a familial SLE and aPL syndrome complicated with AA amyloidosis, with a novel *TREX1* variant. Such cases will increase our ability to understand the genetic spectrum of SLE and may allow the development of more effective therapies.
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