THU0229   **DNA HYPOMETHYLATION AND DECREASED HYDROXYMETHYLATION IS ASSOCIATED WITH DECREASED ANTIOXIDANT RESPONSE IN SYSTEMIC LUPUS ERYTHEMATOUS PATIENTS**

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Background: Systemic lupus erythematous (SLE) shows increased DNA demethylation. An intermediate step to DNA demethylation is the DNA hydroxymethylation, where 5-mC is oxidized into 5-hmC. Hydroxymethylation is not completely understood and it may be related to oxidative stress in SLE patient.
Objectives: To analyze the association between the hydroxymethylation and demethylation, with the antioxidant response and SLE pathophysiology.
Methods: We analyzed in 142 SLE patients and 34 healthy controls the serum concentration of glutathione (GSH) and glutathione disulphide (GSSG) by UPLC-MS/MS, superoxide dismutase (SOD) and total antioxidant capacity (TAC) by colorimetric methods. 5-mC and 5-hmC levels were measured by colorimetric methods. Complete blood-test was made and clinical data by personal interview was collected. Biostatistical analysis with R (3.3.2.) was performed.
Results: There is a correlation between the methylation and hydroxymethylation rate (P<0.001), and both were lower in patients than in controls (P=0.024; P<0.001). GSH and GSSG values were lower in patients (P=0.033 y P=0.003), but GSH/GSSG ratio was not statistically different in both groups. SOD levels were higher in patients (P=0.001), but TAC did not show significant differences. Higher demethylation is associated to lower TAC values in patients and healthy controls (P=0.005; P=0.01). In patients, decreased SOD values are associated with higher demethylation and lower hydroxymethylation rates (P<0.001; P=0.007). SOD and TAC levels are increased in SLE patients with higher demethylation and lower hydroxymethylation (P=0.001; P<0.001). We did not observe any association between 5-mC or 5-hmC levels and GSH, GSSG or GSH/GSSG ratio. Higher demethylation is associated to vascular symptoms (defined by RELESSER study) and lupus anticoagulant (AL) positivity (P=0.041; P=0.015), and lower hydroxymethylation to mucocutaneous damage (defined by RELESSER study) and AL positivity (P=0.015; P=0.009). Lower levels of GSH and GSSG were associated to increased accumulated damage assessed by SLICC (P=0.01; P=0.005), and lower SOD values with longer disease duration (P=0.001).
Conclusions: We observed higher demethylation and lower hydroxymethylation in SLE patients than in controls, related to increased SOD activity. Moreover higher demethylation leads to lower TAC levels. These epigenetic disorders are related to antioxidant response disruptions in SLE patients, probably because of the chronic inflammatory condition. Our results suggest that epigenetic processes are involved in SLE physiopathology.

THU0230   **HIF1A (RS11549465) AND AKNA (RS10817595) GENE POLYMORPHISMS ARE ASSOCIATED WITH PRIMARY SJÖGREN'S SYNDROME**

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Background: HIF-1α is the main transcriptional regulator of cellular and developmental response to hypoxia, and also participates in the integration of the T cell receptor and cytokine receptor-mediated signals of CD4+ helper cells. Another transcription factor also involved in the immune responses is the AT-hook transcription factor (AKNA).
Objectives: To evaluate the allele and genotype frequencies of polymorphic sites of *HIF1A* and *ANKA* genes in primary Sjögren's syndrome (pSS).
Methods: We included 110 patients with pSS and 141 ethnically matched healthy controls. Three *HIF1A* gene polymorphisms *(Pro582Ser, Ala588Thr, and C191T)* and two *AKNA* genes polymorphism *(-1372C>A, and Pro624Leu)* were genotyped using TaqMan probes in a Real-Time PCR instrument. Associations between pSS and genotypes, alleles and inheritance models of the SNPs of interest were evaluated by logistic regression adjusted by age and gender.
Results: Most of the patients were females (95.4%), median age 55 years and median disease duration of 7.8 years. The *C/T* genotype and the *T* allele of the *HIF1A Pro582Ser* polymorphism protected against pSS (OR=0.22; 95% CI=0.09–0.52; P<0.01; and OR=0.26; 95% CI=0.12–0.58; P<0.01; respectively). Whereas under a recessive model adjusted by age and gender, the *AKNA*

-1372C>A polymorphism A/A genotype was associated with an increased risk of pSS (OR=2.60; 95% CI=1.11–6.12; P=0.03). Parotid enlargement was associated with the *HIF1A* gene polymorphism (rs11549465), conferring protection for the C/T genotype vs. C/C (OR=0.22; 95% CI 0.05–0.90, P=0.03). The allele T of the same polymorphism was also associated with parotid enlargement (OR=0.24; 95% CI=0.65–0.95; P=0.04). We did not find any association with any other clinical or serological feature.
Conclusions: We identified *HIF1A Pro582Ser T* allele and *C/T* genotype as well as *AKNA -1372C>A* polymorphism A/A genotype as genetic factors associated with pSS. Further studies in other populations are needed to validate our findings and to shed some light on their functional implications.
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THU0231   **IL-17 POLARIZATION OF MAIT CELLS DERIVE FROM THE ACTIVATION OF TWO DIFFERENT PATHWAYS**

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Background: Primary Sjogren Syndrome (pSS) is a chronic inflammatory disorder affecting exocrine glands. Both IL-23 and the downstream cytokines IL-17 and IL-22 are recognised as key players in the disease. Therefore, the identification of the cellular sources and inducers of IL-17 is crucial in the understanding of the drivers of inflammation in pSS. Mucosal-associated invariant T (MAIT) cells recognize riboflavin derivatives presented by the MHC class I-like molecule MR1.
Objectives: Recently, MAIT cells have been implicated in the pathogenesis of autoimmune disorders and found expanded in salivary glands of pSS patients. Their expression of IL7R and IL23R, makes them potential contributors to the pathogenesis of pSS.
Methods: Mononuclear cells from 16 patients with pSS and 14 subjects with non Sjogren Syndrome secca syndrome (nSS) were isolated from blood and salivary glands. We assessed the phenotype and cytokine expression of MAIT cells by surface and intracellular flow cytometry analysis. The function of MAIT cells was assessed upon *in vitro* stimulation with recombinant IL-7, IL-23 or their specific ligand lumazine (a Vitamin B2 precursor previously reported to be recognized by and specifically activate MAIT cells).
Results: MAIT cells were reduced in frequency in peripheral blood but not in minor salivary glands of patients with pSS, compared with nSS. *In vitro* stimulation of MAIT cells from pSS patients induced cytokine production which was dependent on priming with IL-7, IL-23 or specific antigen (lumazine) stimulation. Particularly, IL-7 and IL-23 guarantee IL-17 polarization of MAIT cells by two different pathways via the activation of STAT3 or RORc respectively.
Conclusions: This study confirms a potential role for MAIT cells in pSS and, for the first time, links IL-7 and IL-23 to the IL-17 polarization of MAIT cells in these patients.

THU0232   **INHIBITING THE ACTIVATION OF COMPLEMENT C5 BY MESENCHYMAL STEM CELLS IN THE TREATMENT OF LUPUS NEPHRITIS**

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Background: Excess activation of the complement system is involved in the development and progression of systemic lupus erythematosus (SLE). Allogeneic umbilical cord mesenchymal stem cells (UC-MSC) transplantation has achieved good clinical efficacy for refractory SLE, however, the exact mechanism is unclear. Our previous work found that deposits of C5a and C5b-9 were significantly enhanced in severe lupus nephritis (LN), which suggested that antagonists of C5 might contribute to the treatment of LN, in other words, effective therapy for LN may be involved in inhibiting the activation of C5.
Objectives: To observe the clinical effect of UC-MSC on SLE model mice (B6.lpr), and explore the mechanism of MSC inhibiting the activation of complement C5 in lupus mice.
Methods: 26-week-old female B6.lpr mice were randomly allocated in four groups, which were given the following treatments, CTX (200mg/kg), UC-MSC (1x10^{6}), C5aRa (W-54011, 1mg/kg), and an equal volume of 0.5%DMSO. 24 hours urine and peripheral blood were collected periodically. All mice were sacrificed at 40 weeks of age. Urine protein to creatinine ratio was used to estimate daily urine protein excretion. Plasma creatinine was measured by a biochemical analyzer. Plasma levels of C3, C5a, soluble C5b-9, and anti-dsDNA