S3A:6 MICROPARTICLES WITH MITOCHONDRIAL MOLECULES AND IMMUNOGLOBULINS ASSOCIATE WITH ACTIVE DISEASE IN SYSTEMIC LUPUS ERYTHEMATOSUS

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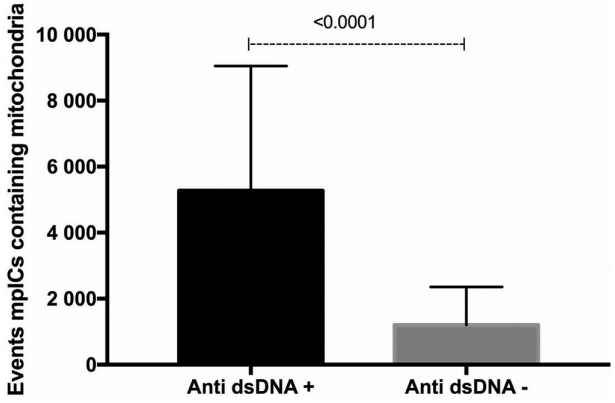
Background/purpose Systemic lupus erythematosus (SLE) is a prototypic autoimmune disease characterised by immune complexes, especially those with nuclear molecules bound by antinuclear antibodies. Although the source of these antigens is not fully known, increased apoptosis and defective clearance of dead cells have been proposed. During apoptosis and cell activation, microparticles (MPs) are released extracellularly. MPs are small membrane-bound particles that can contain molecules arising from both the nucleus and cytoplasm. Moreover, these MPs are often covered with immunoglobulins, thus forming MP-immune complexes (mpICs).

Methods Plasma samples from 47 patients with SLE and 24 healthy controls were investigated. MPs and mpICs were analysed by flow cytometry and defined by size; MPs (<0.7 µm) or mpICs (>0.7 µm). Samples were labelled with MitoTracker deep red FM to investigate mitochondrial content. Flow cytometry was also used to assess outer mitochondria markers Tom-20 and hexokinase I, as well as the presence of IgG.

Results Levels of both MPs and mpICs in SLE patients were significantly elevated compared to controls (figure 1A). Although MP concentrations were higher than those of mpICs, mpICs contained more mitochondria compared to MPs (figure 1B). mpICs also displayed IgG and exposed the outer mitochondria markers. The number of mpICs containing mitochondria correlated strongly to the presence of anti-dsDNA antibodies (figure 2) as well as to levels of TNFα (r^2 0.2, $p<0.05$), IL-6 (r^2 0.23, $p<0.01$) and IL-7 (r^2 0.24, $p<0.01$). Moreover, patients with active renal disease had significantly higher levels of IgG-coated mpICs containing mitochondria. Patients with SLAM above 6, had significantly higher numbers of mpICs containing mitochondria and exposing outermitochondria markers Tom-20 and hexokinase I.

Conclusion MPs and mpICs are significantly more abundant in the blood of SLE patients compared to controls. Importantly, the majority of the mitochondria were present in the larger mpIC sup-population. Moreover, mpICs that contain mitochondria also display outer mitochondria markers, with levels correlating with levels of anti-dsDNA antibodies, disease activity and pro-inflammatory cytokines. mpICs may therefore contribute to SLE pathogenesis, with mitochondria representing a source of cell antigens that can trigger innate and adaptive immune responses as well as deposit in the tissue.



Abstract S3A:6 Figure 2 SLE patients with anti-dsDNA antibodies have higher number of mpICs contacting mitochondria

S3A:7 NEUTROPHIL EXTRACELLULAR TRAPS MARKERS ARE ELEVATED IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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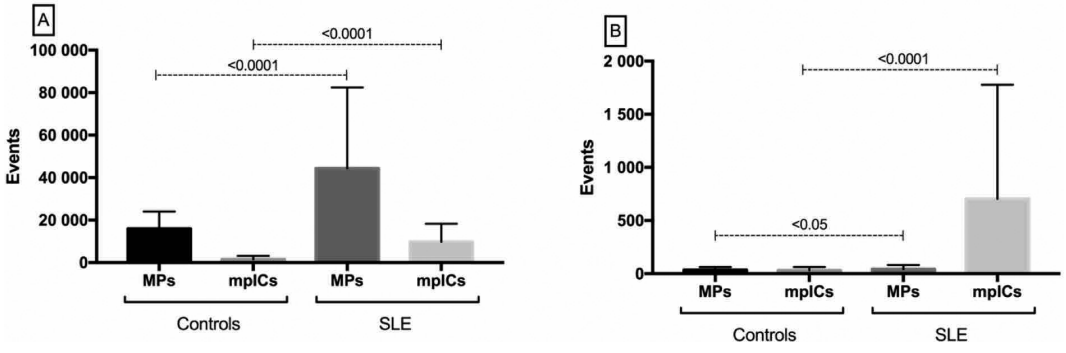
Introduction Impaired removal of apoptotic waste in patients with systemic lupus erythematosus-SLE has been long known as important factor that trigger autoimmune response. Neutrophil extracellular traps could be another source of autoantigens in patients with SLE.

Methods We analysed sera from 84 SEL patients (60 patients had one sample and 24 patients were followed 2 or 3 times) and 50 healthy blood donors. Serum levels of myeloperoxidase, B-cell activating factor-BAFF, cell free DNA, complement components C3 and C3, antibody to dsDNA by CLIFT end ELISA assays, netolitic activity and DNAse I were measured.



Abstract S3A:6 Figure 1 Microparticles (MPS) and MPS in immune complexes (mpICs) in patients with systemic lupus erythematosus and healthy controls. (A) Number of total MPs and mpICs defined by size and complexity by flow cytometry, in healthy controls and SLE. (B) Number of total MPs and mpICs containing mitochondna (labelled with MitoTracker) n healthy controls and SLE

Results Patients with SLE had higher cfDNA (1.69±0.23 vs 1.42±031 ng/mL, p=0.0003), MPO (1607±2353 vs 1503 ±1106, p<0.05) and BAFF levels (160735±2353.23 vs 891.16±184.31, p<0.05). DNAse concentration was also lower in healthy controls (5.84±5.72 vs 9.38±6.97, p<0.05). BAFF showed strong correlation with anti-dsDNA antibodies determined by ELISA method (ρ=0.564, p=0.000), MPO activity (ρ=0.256, p=0.021), DNAse I concentration (ρ=0.27, p=0.012) and cfDNA concentration (ρ=0.262, p=0.014). DNA determined by ELISA test showed correlations with DNAse concentration (ρ=0.249, p=0.022), DNA determined by CLIFT (ρ=0.341, p=0.001) and C3 complement component (ρ=−0.4, p=0.023). MPO activity showed correlations with cfDNA levels (ρ=0.386, p=0.001), DNAse concentration (ρ=0.501, p=0.000), and anti-MPO antibodies (ρ=0.293, p=0.006). Cell free DNA levels additionally correlated with DNAse activity (ρ=0.288, p=0.007) as well with netolytic activity (ρ=0.244, p=0.026). Netolytic activity also correlated with anti-dsDNK antibodies determined by ELISA (ρ=−0.299, p=0.039).

Conclusions Increased NETs` footprints (myeloperoxidase and cfDNA) are present in lupus sera. As probably compensatory mechanism increased DNAse I concentrations also were found in lupus sera. NET burden is followed by production of various antibodies recognising different NET structures.

S3d – APS

S3D:4 REAL LIFE SINGLE CENTRE RESULTS ON RITUXIMAB TREATMENT OF PATIENTS WITH PRIMARY AND LUPUS ASSOCIATED ANTIPHOSPHOLIPID SYNDROME

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Recurrent thrombotic events occur in 20% of patients with APS despite of adequate antithrombotic therapy. As phospholipid-cofactor antibodies are key elements of pathophysiology, B cell depleting rituximab is a rational therapeutic approach.

Aims were to identify and characterise APS patients receiving rituximab. All together 179 (60 primary, 119 lupus-associated) APS patients were found in our database of whom 15 (8.4%) were treated with RTX. As younger and male patients dominated in RTX +group, 15 from RTX naive patients were matched regarding age and gender for a case control study. First symptoms appeared at the age of 30 in both groups. Patients were followed for 4 and 7 years, the diagnosis delayed 4 and 1 year in RTX +and RTX- groups, respectively. This 3 year difference might contribute to higher disease severity. Primary APS (47% vs 32%), cerebrovascular events (13 vs 2), valvular heart disease (5 vs 2), and high risk triple aPL positivity (13 vs 5) were more prevalent in RTX +group. All 4 deep venous thrombosis cases in the RTX +group were complicated with pulmonary embolism in comparison with 1 PE within 6 RTX- DVT patients. Raynaud syndrome resulted in digital ulcer more frequently in RTX +than in RTX- group (4/4 vs 1/6). Antimalarials were given to 3 and 10, cumarin or NOAC were iniciated in 15 and 5 patients in the RTX +and RTX- groups, respectively. Rituximab was started 2 (0.5–6) years after diagnosis. Within 10 (3–60) moths follow-up on RTX there were no incident thrombotic events. Two thirds of patients could stop steroid. RTX was stopped in 6 cases: 3 due to remission (of whom 2 relapsed), 1 LFU, and 2 adverse events (1 longstanding B cell depletion, 1 peroneus paresis). Other AEs were 1 mild infusion reaction, 1 leukopenia, 1 UTI. As summarised, delay in APS diagnosis and male gender were associated with more severe disease and the need for rituximab. Antimalarials and associating lupus were identified as markers of more favourable disease outcome. In patients with recurrent thrombotic events despite of adequate anticoagulant therapy, RTX can be a rational and effective choice with favourable safety profile.

S3D:5 PLASMA SOLUBLE TRIGGERING RECEPTOR EXPRESSED ON MYELOID CELLS-1 IS ELEVATED IN PATIENTS WITH THROMBOTIC PRIMARY ANTIPHOSPHOLIPID SYNDROME

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10.1136/lupus-2018-abstract.16

Background Antiphospholipid antibodies (APLA) are necessary, but not sufficient for the development of thrombosis in APS. Soluble triggering receptor expressed on myeloid cells-1 (sTREM-1) is an innate-immune receptor found in the blood and reflects innate immune cells activation.

Aim To determine if plasma sTREM-1 can be served as a biomarker for thrombosis in patients with PAPS.

Methods A cross-sectional, case-control study. Plasma level of sTREM-1 was analysed by ELISA in a group of consecutive patients diagnosed with either PAPS (Sapporo criteria) or asymptomatic persistently positive APLA, and healthy controls (HC).

Results The study group comprised of 33 patients with PAPS (age 52.0±17.4 years.), 10 asymptomatic APLA-positive patients (50.6±17.9 years.) and 73 HC (42.6±13.3 years.). The mean plasma sTREM-1 level was significantly higher in the PAPS group compared to HC (316.3±119.3 pg/ml, vs 230.2±85.5 pg/ml, p=0.0002), as well as past obstetric APS (195.12±58.52 pg/ml, p=0.014), and asymptomatic APLA (215.8±pg/ml vs HC, p=0.019). Plasma sTREM-1 in PAPS patients with an acute event of thrombosis was significantly higher than in patients with past thrombotic event (p=0.012), past obstetric APS (p=0.0001) and HC (p<0.0001). Plasma sTREM-1 level was significantly higher in PAPS patients who ever had stroke (p=0.007) or venous thromboembolic event (p=0.018). On receiver operator curve (ROC) analysis, plasma sTREM-1 showed an area under the curve (AUC) 0.7292 in differentiating between thrombotic APS (ever) and non-thrombotic APS or asymptomatic APLA-positivity. A multivariate regression model to predict sTREM-1 level by thrombotic PAPS ever, age and sex found that sTREM-1 level is independently associated with thrombotic PAPS (p<0.004) as well as with female gender (p=0.017) and older age (p=0.0006). Plasma sTREM-1 level was neither associated with anti-cardiolipin, anti-β2 glycoprotein I (IgG/IgM/IgA) Abs' titers and/or