S5a – Biomarker & indices

S5A:4 CIRCULATING TYPE I, II AND III INTERFERONS (IFNs) ASSOCIATE WITH IFN-SCORES, BUT DEFINE DISTINCT SUBSETS OF ACTIVE SLE

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Background Serum induced IFN gene expression (IFN-score) is considered a golden standard to assess IFN activity in SLE. So far, IFN-scores have not been compared to serum levels of type I, II and III IFNs.

Aim To investigate how IFN-scores and SLE manifestations relate to serum levels of IFNs type I (alphas), II (gamma) and III (lambda 1).

Methods 461 SLE patients and 322 controls were included. IFN-score was measured by WISH cell assay. INF-alphas and IFN-lambda1 were measured by ELISA. IFN-gamma was measured by MSD 30-plex assay.

Results SLE patients had higher IFN-scores and higher levels of IFN-alphas, IFN-gamma and IFN-lambda1 ($p<0.001$). IFN-scores correlated with levels of IFN-gamma and IFN-alpha ($\rho=0.39$, and $\rho=0.25$, $p<0.0001$). Further, patients were grouped according to high levels (>3 rd quartile) of each IFN/IFN-score. The group with high IFN-scores had higher disease activity (SLAM, SLEDAI): weight loss (41%), fatigue (33%), fever (39%), rash (44%), lymphadenopathy (45%), arthritis (40%), nephritis (55%) ($p<0.01$). Interestingly, incidence of neuropsychiatric SLE, antiphospholipid (aPL) antibodies (abs), and also damage score was lower ($p<0.05$).

The characteristics of IFN-gamma high group included higher disease activity (SLAM, SLEDAI), and specifically: active nephritis (52%), lymphadenopathy (40%), arthritis (42%), lymphopenia (37%), anaemia (35%) and positivity for Sm (41%), SmRNP (36%) and RNP68 (45%), Ro52 (35%) and Ro60 (33%) ($p<0.03$).

The common features of IFN-alpha high group included younger age, shorter disease duration, active rash (34%), lymphadenopathy (43%), Ro52 (38%) and La (43%) ($p=0.01$). Presence of aPL abs and previous vascular events were lower and renal affection was uncommon ($p<0.01$).

In general, high IFN-scores reflected SLE manifestations that could be further stratified by high IFN-gamma levels and to a lesser extent by high IFN-alpha. High IFN-lambda1 did not define any phenotype of active SLE, except presence of anti-nucleosome abs.

Conclusion We demonstrate that high IFN-score associate more strongly with type II rather than type I IFNs. Importantly, major manifestations of SLE: active nephritis and arthritis, and also anti-Sm/SmRNP antibodies associate with IFN-gamma; while rash associate with IFN-alpha.

Our findings are of major importance while tailoring clinical trials with anti-IFN therapies and demonstrate that importance of IFN-gamma has so far been underscored.

S5A:5 GALECTIN-9 IS PRODUCED BY DENDRITIC CELLS AND SERUM LEVELS OUTPERFORM CXCL10 AS A BIOMARKER TO DETECT THE IFN SIGNATURE IN SLE AND APS

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Objective The most prominent alteration in the immune system of patients with systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS) is the increased expression of type I interferon (IFN) inducible genes, known as the IFN signature. This signature is related to disease activity, vascular disease and predicts future flares and the response to anifrolumab. There is an urgent need for easily measurable biomarkers to detect an IFN signature. Galectin-9 may steer T-cell responses and is a potential biomarker for autoimmune diseases. In the present study we investigated the performance of galectin-9 as a biomarker to detect the IFN signature in SLE and APS and its production by dendritic cell (DC) subsets.

Methods Serum levels of galectin-9 and CXCL10 were measured by Luminex in an identification cohort ($n=43$) and replication cohort ($n=148$) of patients with SLE, SLE +APS and primary APS (PAPS) and healthy controls (HC). Isolated monocytes were used to quantify IFN scores by measuring the expression of 4 type I IFN inducible genes. The performance of potential biomarkers for the IFN signature were assessed by Receiver Operating Characteristics curves. RNA sequencing on plasmacytoid and myeloid DC isolated from patients with SLE, SLE +APS and PAPS ($n=54$) were analysed to identify potential sources of galectin-9 in SLE and APS.

Results In both identification and replication cohort, serum levels of galectin-9 and CXCL10 were elevated in SLE, SLE +APS and PAPS patients as compared with HC (all $p<0.05$) and both galectin-9 and CXCL10 correlated with the

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