Prediction of connective tissue disease in at-risk cohort using a novel two-factor interferon stimulated gene expression score

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Background: A period of ANA positivity and other immune dysregulation precedes connective tissue disease (CTD), providing a potential opportunity for disease prevention. Type I interferons (IFN-I) play a role in pathogenesis but their role in disease initiation is unclear.

Objective: To evaluate clinical, immunological and imaging biomarkers of progression to CTD, with a view to enabling early intervention for disease prevention.

Methods: A prospective observational study was conducted in 150 at-risk of CTD individuals as defined by ANA positive; ≤1 clinical systemic lupus erythematosus (SLE) criteria; symptom duration <12 months and treatment-naïve. Peripheral blood mononuclear cells were analysed for a novel two-factor IFN stimulated genes (ISG) scores; Score A and B as previously described. 49 healthy and 114 SLE patients were used as negative and positive controls. The joints were assessed using musculoskeletal ultrasound. Progression was defined by meeting classification criteria for SLE, primary Sjogren's syndrome (pSS) or other CTDs.

Results: 118 individuals with 12-month follow-up data were studied (104 female, median age 48 years, 43 had a family history of autoimmune rheumatic disease (AIRD); 17% had no SLE clinical criteria). At 12 months, 20 (17%) progressed to CTD (SLE=14, pSS=5). At baseline, only IFN Score A was increased in at-risk of CTD vs healthy controls; p=0.009. Score B was only increased in established SLE. At baseline, Score B was low in at-risk of CTD individuals who did not progress and increased in those who progressed; p<0.001. ROC indicated that a Score B delta CT of <5.20 yielded Area Under the Curve of 0.81 with 63% sensitivity, 84% specificity, 46% positive predictive value and 91% negative predictive value in predicting progression. However, there was no difference in Score A between these two groups; p=0.445. In multivariable analysis, only a family history of AIRD; OR 4.99 95% CI (1.27-19.63) and Score B; 2.06 (1.29-3.28) increased the odds of CTD progression at 12 months.

Conclusion: A novel two-factor ISG score and a family history of AIRD predict progression from ANA positivity to clinical CTD. These may allow stratification of individuals with imminent CTD for early intervention. Analyses of other immunological biomarkers and longitudinal tests are in progress as well as a validation cohort.