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IMMUNOPHENOTYPE OF SJÖGREN'S SYNDROME AND SYSTEMIC LUPUS ERYTHEMATOSUS PATIENTS IDENTIFIED TWO ENDOTYPES WITH POTENTIAL THERAPEUTIC IMPLICATIONS

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Background: Primary Sjögren's syndrome (pSS) and systemic lupus erythematosus (SLE) are chronic autoimmune rheumatic diseases (ARDs) that share a strong female gender bias, as well as genetic, clinical and serological characteristics. Although significant progress has been made in improving treatment and patient related outcomes in pSS and SLE, there is a need for improved early diagnosis, adequate therapy monitoring, treatment of refractory manifestations and strategies to address co-morbidities. However, the results of many clinical trials are disappointing, and nobiologic treatments are licensed in pSS, while few are available for SLE patients with refractory disease.

Objectives: Identifying shared immunological features between patients with pSS and SLE that could lead to better treatment selection using a stratification approach.

Methods: Immune-phenotyping of 29 immune-cell subsets in peripheral blood from patients with pSS (n=45), SLE (n=29) and secondary SS associated with SLE (SLE/SS) (n=14) with low disease activity or in clinical remission, and sex-matched healthy controls (n=31), was performed using flow cytometry. Data were analysed using logistic regression and multiple t-tests and supervised machine learning (balanced random forest-BRF, sparse partial least squares discriminant analysis-sPLS-DA). Patients were stratified by k-means clustering. Clinical trajectories were analysed over 5 year follow-up.

Results: Comparing the immune profile of pSS and SLE patients using a variety of statistical and machine learning (ML) approaches, identified very few statistically significant differences between the two cohorts despite patients having a different clinical presentation and diagnosis. Thus, we hypothesised that immune-based subtypes could be shared between pSS, SLE and SLE/SS patients. Unsupervised k-means clustering was applied to the immunological features of the combined patient cohorts and two distinct patient endotypes, were identified: Group-1 (n=49; pSS=24, SLE=19, SLE/SS=6) and Group-2 (n=39; pSS=21, SLE=10, SLE/SS=8). Significant differences in immune-cell phenotypes across B-cell and T-cell subsets were identified by logistic regression, BRF (AUC=0.9942, assessed by 10-fold cross-validation) and sPLS-DA analysis. Comparison of the multiple analysis approaches identified eight common immune-cell subsets, including total and memory CD4+ and CD8+ T-cell subsets but no B-cell subsets. Using this common immune-signature the stratification between the groups was maintained and slightly improved (AUC=0.9979 and accuracy 96.16%). Interestingly, patients in Group-2 had elevated disease activity measures at baseline and over a 5-year trajectory compared to Group-1. Finally, correlation analysis identified correlations between disease activity markers and the top ranked immune features from the ML models.

Conclusion: The identified immune-cell signatures could reflect the underlying disease pathogenesis that spans diagnostic criteria and could be used to select patients for targeted therapeutic approaches.

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