Molecular mechanisms in Connective Tissue Disease

Objectives: To identify shared and differential changes in the splicing machinery of immune cells from APS, SLE and APS plus SLE patients, and their involvement in the activity and clinical profile of these autoimmune disorders.

Methods: Monocytes, lymphocytes and neutrophils from 80 patients (22 APS, 35 SLE and 23 APS plus SLE) and 50 healthy donors (HD) were purified by mononuclear enrichment. Principal component analysis (PCA) visualized the gene expression patterns of immune cells from APS, SLE and APS plus SLE patients, and their involvement in the activity and clinical profile of these autoimmune disorders.

Results: Patients with primary APS, SLE and APS plus SLE displayed significant and specific alterations in the splicing machinery components in comparison with HD, that were further specific for each leukocyte subset. Besides, these alterations were associated with distinctive clinical features. Hence, in APS, clustering analysis allowed to identify two sets of patients representing different molecular profile groups with respect to the expression levels of splicing machinery components. Principal component analyses confirmed a clear separation between patients. Clinically, cluster 1 characterized patients with higher thrombotic episodes and recurrences than cluster 2 and displayed a higher adjusted global APS score (aGAPSS). Accordingly, these patients showed higher levels of inflammatory mediators than cluster 2. Similarly, in patients with APS plus SLE, clustering analysis allowed to identify two sets of patients showing differential expression of splicing machinery components. Clinical and laboratory profiles showed that cluster 2 characterized patients that had suffered more thrombotic recurrences, most of them displaying an aGAPSS over 12 points and expressing higher levels of inflammatory mediators than cluster 1. The incidence of lupus nephropathy was similarly represented in both clusters. Lastly, in SLE patients, molecular clustering analysis identified two sets of patients showing distinctive clinical features. One cluster characterized most of the patients positive for anti-dsDNA antibodies, further suffering lupus nephropathy, and a high proportion of them also presenting atheroma plaques and high levels of inflammatory mediators.

Conclusion: We provide evidence that the effects of five DMARDs on RA synovium culminate in the same pathways (namely, cell and myeloid leukocyte activation). This confirms previous studies suggesting the existence of common mediators downstream of DMARDs, independent of their primary targets, and suggests attractive new therapeutic targets.

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