Exploration of mechanisms involved in systemic sclerosis physiopathology

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Résumé

Objective: Exploration of signaling pathways and pathophysiological mechanisms involved in the maintenance of inflammatory and fibrotic phenomena in systemic sclerosis.
Materials: Analysis of transcriptomic, cytometric, cytokine, and autoantibody data from the European cohort of the PRECISESADS project.

Results: A comparative analysis of 289 systemic sclerosis patients with 289 age- and sex-matched controls reveals increased expression of interferon genes and activation of innate immunity, particularly neutrophils, in our patients. Unsupervised clustering of patients distinguishes three groups with varying degrees of similarity to the control group. Cluster 1 (164 patients) is similar to controls, Cluster 2 (92 patients) is intermediate, and Cluster 3 (28 patients) is highly distinct from controls. A common interferon signature is found within all three clusters. Cluster 3 is characterized by a strong neutrophilic signature and decreased expression of B and T cell genes. Cluster 2 (92 patients) is characterized by an interferon signature and decreased expression of T, B, and NK cell genes. Cytometry data confirm this signature, showing increased neutrophils in Cluster 3, decreased CD4 T cells in Clusters 2 and 3 compared to controls, and decreased NK cells in Cluster 2 compared to controls. Inflammatory cytokines such as IL6 and TNF-alpha are increased in clusters 1 and 2 compared to controls (data lacking for cluster 3). However, IL1 RA is increased in cluster 3. Antibody profile is balanced between anti-centromere and anti-Scl70 antibodies in clusters 1 and 2, cluster 3 is characterized by a predominance of anti-Scl70 antibodies. The clinical manifestations in cluster 3 are also more severe, with more pulmonary arterial hypertension and pulmonary fibrosis.

Discussion: This study confirms the interferon signature associated with systemic sclerosis already described in the literature. It also highlights the biological heterogeneity of systemic sclerosis patients, with different groups of patients presenting distinct clinical, transcriptomic, cytometric, and cytokine characteristics.
Conclusion: Systemic sclerosis is a clinically described disease encompassing partially different biological mechanisms, which should be taken into account in therapeutic approaches.

Mots-Clés: Systemic sclerosis, cluster, interferon, neutrophils, heterogeneity

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