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The recent research presented at the European Workshop on Rheumatology Research (EWRR) sheds light on significant aspects of the pathogenesis and clinical implications of systemic sclerosis (SSc). Out of 225 accepted, 25 had Systemic sclerosis as main topic.
The studies focused on various immunological factors, including monocytes/macrophages, B cell phenotypes, immune complexes, receptor-mediated endothelial cell activation, and novel biomarkers, providing novel insights into disease mechanisms and potential therapeutic targets.

Gotelli et al. and Smith et al. explored the role of hybrid (TLR4+M2) monocytes/macrophages in SSc-ILD patients, finding that these cells are expanded in both lung tissue and peripheral blood. The presence of a higher percentage of circulating M2 monocytes and mixed monocyte subsets was particularly notable in diffuse cutaneous SSc and SSc-ILD patients. Additionally, a third study highlighted that M2 phenotype macrophages in progressive SSc-ILD patients exhibit higher gene expression and release of TGFβ1 and increased expression of the MerTK receptor, suggesting their potential role in disease progression. Di Donato et al. further demonstrated that dermal fibroblasts from SSc patients activate type I interferon in THP1 monocytes via the cGAS/STING pathway, and inhibiting this pathway suppressed interferon-inducible genes in SSc PBMCs, pointing to new therapeutic possibilities.

Alzahrani et al. conducted detailed B cell phenotyping in ATA+ and ACA+ SSc patients, revealing enhanced activation and migratory potential of memory B cell subsets and double-negative B cells in ATA+ patients compared to ACA+ patients. ATA+ patients showed a significant increase in IgG+ B cells within switched memory and double-negative compartments, with these cells exhibiting an activated phenotype marked by increased expression of HLA-DR and CD80. Moreover, these B cells displayed distinct homing markers associated with skin and lung tissue, unlike ACA+ patients, suggesting differential regulation of B cell responses that correlate with clinical manifestations in SSc.

Contrary to previous assumptions, another study found no evidence that SSc patient-derived IgG activates angiotensin II type1 receptor (AT1R) or endothelin-1 type A receptor (ETAR) in endothelial cells. Using a variety of assays, including xCELLigence real-time cell analysis, rt-qPCR, and ELISA, they demonstrated that SSc IgG did not induce receptor-mediated endothelial cell activation or cytokine production, challenging the role of these autoantibodies in vascular injury in SSc.

Chighizola et al. used an innovative dynamic 3D multicellular in vitro model to evaluate the pathogenic effects of immune complexes containing scleroderma-specific antibodies. Their findings showed that immune complexes from SSc patients disrupt vascular architecture and induce a fibrotic phenotype in skin fibroblasts, emphasizing the role of these immune complexes in mediating pro-fibrotic and pro-inflammatory effects in SSc.

Neppelenbroek et al. investigated the activation of topoisomerase1 (TOP1)-reactive B cells in SSc. Their study revealed that DNA binding enhances the recognition of TOP1 by autoantibodies, which may significantly influence B cell activation. This enhanced recognition was linked to increased

levels of TOP1-DNA cleavage complexes (TOP1cc), which correlated with lung and skin fibrosis in SSc patients. These findings suggest that differential recognition of TOP1 and TOP1cc by autoantibodies is clinically relevant and may drive disease progression in SSc.

Finally, Pellico et al. identified the overexpression of BAG3 (BCL2-associated athanogene 3) in serum and skin of SSc patients. Elevated BAG3 levels were particularly significant in patients with the diffuse cutaneous subset of SSc (dcSSc) and were associated with a late nailfold video-capillaroscopic pattern and interstitial lung disease. The study highlighted that BAG3 is strongly expressed in skin biopsies of dcSSc patients, suggesting its role in the fibrotic process. These findings propose BAG3 as a potential biomarker for fibrosis in SSc, opening avenues for further research on its role as a therapeutic target.

Together, these studies provide a deeper understanding of the immunopathological mechanisms in SSc, highlighting the diverse roles of immune cells and autoantibodies in disease progression and offering new avenues for targeted therapies and biomarker identification.

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