

Streszczenie w języku angielskim.

Graves' orbitopathy (GO) is a complication of Graves' disease, characterized by inflammation of the periorbital tissue, adipose tissue expansion, and fibrosis. Infiltration of immune cells into the periorbital tissue and their subsequent dynamic interaction with orbital fibroblasts are considered crucial factors in triggering the inflammatory-remodeling cascade. Although orbital fibroblasts are supposed to represent key cellular elements in the pathogenesis of GO, their interaction with immune cells is hardly explored. That study aimed to study *in vitro* the effects of autologous peripheral blood mononuclear cells (PBMC) on orbital fibroblasts derived from GO patients with active and inactive stages of disease, with experimental assessment of the immunomodulatory effect of methylprednisolone and vitamin D3, on regulating changes in the mutual interactions between orbital fibroblasts and immune cells. Moreover, evaluation of changes in the phenotype of immune cells after co-culturing with orbital fibroblasts, especially in the context of regulatory T cells and Th17.

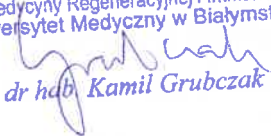
Orbital fibroblasts and PBMC collected from active and inactive Graves' orbitopathy patients were co-cultured for 48 hours in the presence of vitamin D3 and/or steroids. Flow cytometric, qPCR, immunoenzymatic, and OLINK assessment allowed for evaluation of changes during cell-to-cell interactions.

Orbital fibroblasts from inactive GO displayed higher expression of genes related to tissue remodeling. Co-culture of fibroblasts with PBMC enhanced fibroblast proliferation, especially during the active stage. Moreover, cytokine secretion patterns and extracellular matrix compound deposition by orbital fibroblasts were also found to differ between disease stages. Methylprednisolone (MP) attenuates fibroblast proliferation, particularly in inactive GO. Further combination of MP with vitamin D3 suppresses the secretion of IL-6 and CCL-20. Co-culturing PBMC with orbital fibroblasts from the active stage markedly expands the CD4⁺Foxp3⁺ and CD8⁺Foxp3⁺ subsets, an effect that diminishes in an MP-dose-dependent manner. Proteomic profiling revealed that orbital fibroblasts can also produce the chemokines CXCL1/CXCL6, promoting the recruitment of immune cells. Whereas, PBMCs, especially those from active GO, release increased levels of MCP-4. Furthermore, enhanced CD44 secretion by active fibroblasts underscores their increased proliferative potential.

The pathogenesis of GO involves mutual interactions between orbital fibroblasts and immune cells, which may be disease stage-specific and can be modulated by MP and vitamin D3. These data determined that chronic signaling between orbital fibroblasts

and immune cells determines the transition from severe inflammation to irreversible tissue remodeling, offering potential targets for immunosuppressive and antifibrotic therapies.

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