Systemic Sclerosis – Agonistic Auto-Antibodies Directed Against the Angiotensin Receptor Type 1 and the Endothelin Receptor Type A and Their Effects on Immune Cells

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Background Systemic sclerosis (SSc) is characterised by autoimmunity, vasculopathy and fibrosis. The functional link between these three pathophysiological components is still missing. Recent research suggests an involvement of the vasoconstrictive soluble peptides endothelin-1 and angiotensin II, and of the activation of their receptors by the natural ligands and agonistic autoantibodies against these receptors in SSc-associated vasculopathy.

Objectives We could identify auto-antibodies against the angiotensin receptor type 1 (AT1R) and the endothelin receptor type A (ETAR) in SSc patients. The pathophysiological effects of these antibodies on immune cells and their association with clinical data have not been studied so far.

Materials and methods Peripheral blood mononuclear cells (PBMC) from healthy donors were isolated by gradient centrifugation and stimulated in vitro by affinity-purified IgG from SSc patients containing anti-AT1R and anti-ETAR antibodies as well as by IgG from healthy donors. After stimulation the expression of several markers and cytokines were measured by flow cytometry or ELISA.

Results Stimulation of PBMC from healthy donors by SSc patient IgG resulted in a significantly increased expression of IL-8 compared to the stimulation by IgG of healthy donors. This effect can be blocked by commercial AT1R and ETAR blockers. In contrast, expression of soluble CD14 as well as of the surface marker CD14 was significantly decreased. Correlation analysis of the IL-8 expression with clinical data of the SSc patients whose IgGs were used revealed an association of the high IL-8 expression with the early stage of disease, in fact in vitro stimulation of PBMC with IgG of patients who were within the first 8 years after onset of the disease caused a significantly higher IL-8 secretion in comparison to the stimulation with IgG of patients at a later stage.

Conclusion SSc patient IgGs containing anti-AT1R and anti-ETAR antibodies seem to have effects on inflammation and immune regulation. Especially the release of IL-8, which is a strong inflammatory cytokine mainly secreted by monocytes among the immune cells, may play an important role in the early stage of disease contributing to vascular inflammation and injury, which are regarded to be the first events leading to tissue damage and fibrosis.