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Graves' disease immunoglobulins induce expression of T-cell chemoattractants in fibroblasts

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Keywords

Chemoattractants, fibroblast activation, Graves' disease, IgG, IL-16, RANTES

Context

Graves' disease (GD) is an autoimmune disease of the thyroid gland. Extrathyroidal manifestations of GD include ophthalmopathy and dermopathy, which are characterised by infiltration of inflammatory cells such as T lymphocytes and accumulation of hyaluronan. Infiltration and activation of T cells are most likely mediated by chemokines and T-cell activators, however, the mechanisms by which immunocompetent cells traffic to affected tissues in GD and by which fibroblasts are activated are still unknown. Similar to the situation in rheumatoid arthritis, it is hypothesised that inflammatory mediators play an important role in fibroblast activation at the sites of disease manifestation. A self-antigen expressed only at the sites of GD manifestations could account for the distribution of GD leading directly to the activation of fibroblasts followed by production of chemoattractants and activators of inflammatory cells. Moreover, some reports have suggested direct effects of IgG isolated from patients with GD (GD-IgG) on human fibroblasts. Therefore, the authors investigated whether IgG from patients with GD activate the expression and release of T-cell chemoattractants such as IL-16 and RANTES from fibroblasts.

Significant findings

GD-IgG upregulated T-cell chemoattractant activity in fibroblasts from the thyroid gland and from areas with extrathyroidal GD manifestations, but not in fibroblasts from donors without thyroid disease. The protein levels of IL-16 and RANTES were increased by GD-IgG in GD fibroblasts from the affected regions. T-cell migration could be partially reduced by neutralisation with anti-IL-16 and anti-RANTES antibodies. The authors excluded GD-IgG induced T-cell chemoattractant activity by ligation

of the key autoantigen, thyroid-stimulating hormone receptor (TSHR). It is concluded that autoantibodies present in the IgG fraction from patients with GD induce T-cell chemoattractant activity in fibroblasts from patients with GD through a yet unknown antigen.

Comments

The authors present novel evidence to support their hypothesis that certain manifestations of autoimmune diseases are driven by specific pathogenic autoantibodies. Similar mechanisms have been recently proposed for rheumatoid arthritis in the K/B?N T-cell receptor transgenic mouse model (see Additional information [1]). Moreover, the authors show that fibroblasts are able to initiate the accumulation of inflammatory infiltrates in autoimmune diseases after stimulation, thereby further supporting the concept of fibroblasts acting as sentinel cells rather then passive bystanders in inflammatory disorders (see Additional information [2]). It would be of interest for future studies to examine whether similar mechanisms contribute to other autoimmune diseases, to identify additional chemoattractants induced by (GD)-IgG and to further characterise the IgG fraction as well as the surface receptor involved in fibroblast activation.

Methods

Chemotaxis assay, IgG preparation, immunoprecipitation, western blot analysis

Additional information

1. Matsumoto I, Staub A, Benoist C, Mathis D: **Arthritis provoked by linked T and B cell recognition of a glycolytic enzyme.** *Science* 1999, **286**: 1732-1735.
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