Clinical THYROIDOLOGY
AMERICAN THYROID ASSOCIATION FOUNDED 1923

TSH Expression by Fibrocytes Provides New Insights into the Pathophysiology of Thyroid-Associated ophthalmopathy

Gillespie EF, Papageorgiou KI, Fernando R, Raychaudhuri N, Cockerham KP, Charara LK, Goncalves ACP, Zhao S-X, Ginter A, Lu Y, Smith TJ, Douglas RS. Increased expression of TSH receptor by fibrocytes in thyroid-associated ophthalmopathy leads to chemokine production. J Clin Endocrinol Metab 2012;97:E740-E746. Epub March 7, 2012.

SUMMARY

Background

A fundamental insight into the pathophysiology of thyroid-associated ophthalmopathy (TAO) is still lacking, although it is widely accepted that an autoimmune process involving fibroblasts plays a crucial role. There is considerable evidence that TSH receptor antibodies, or a subset of them, are crucial factors in the pathogenic process (1). Indeed, orbital–fibroblast-TSH receptors have unequivocally been identified and are likely to be a dominant autoimmune target. These cells may modulate immune responses by producing cytokines in response to TSHR activation.

Fibrocytes are bone marrow–derived pluripotent cells that can migrate to sites of tissue inflammation and remodeling (2). In healthy subjects, they represent a subset of only 0.5% of the circulating monocytes, but in patients with Graves' disease, their abundance is increased (3). Here, the authors identified and quantified TSHR-positive fibrocytes in peripheral blood in patients with TAO and controls.

Methods and Results

The authors recruited 31 patients with TAO and 19 healthy subjects. Patients with Graves' disease without TAO were excluded. The fibrocytes of interest were identified by flow cytometry. Monocytes expressing CD45 and CD34 were selected. Furthermore, these fibrocytes were stimulated with TSH or with the monoclonal TSHR antibody M22, and their response was compared with Interleukin-1b (IL-1β) stimulation. One known responding marker, IL-8 mRNA was measured by quantitative real-time PCR.

The results showed that, in TSHR, levels of positive fibrocytes were at least 5 to 6 times higher in peripheral blood than in orbital fibroblasts. As expected, the expression of TSH receptors in normal fibrocytes was very low—approximately 2%. The receptor could be clearly identified in approximately 18% of circulating fibrocytes from patients with TAO. Stimulation of the cells by TSH or M22 induced production of several proinflammatory cytokines that could also be induced with IL-1β.

Conclusions

The authors elegantly demonstrate that peripheral fibrocytes, known to migrate to inflammatory sites, are increased in number in patients with TAO and that they express TSH receptors more frequently than fibrocytes from normal subjects. The density of these TSH receptors on circulating fibrocytes exceeded the density in orbital fibroblasts, which are thought to be critical for the autoimmune process in TAO. When standardized to the number of circulating monocytes, TSHR-positive cells were more frequent in patients with TAO than in controls, even though a small number of control cells also expressed some TSH receptors. In order to test the functional relevance of these receptors, the fibrocytes were stimulated with TSH or M22 to study the production of many different cytokines. The panel of responses varied slightly between TSH and M22, with the responses to M22 being stronger. These findings strongly support an important role of fibrocytes in the pathogenesis of TAO.

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ANALYSIS AND COMMENTARY

Treatment of TAO is still frustrating for many patients and often patience is the most important advice the physician can give. Indeed, in the majority of cases, eye symptoms will ameliorate within years ,and eventually the outcome is satisfactory, even though it is rare for all symptoms to resolve completely. There is hope for some therapeutic innovations, since basic research is steadily progressing. The presence of TSH receptors or a truncated form of them was discovered in the orbital cavity at least 20 years ago. We know that these receptors are expressed in fibroblasts in the process of being transformed into fat cells. Closely related fibrocytes can be identified in a subset of monocytes in the peripheral blood. They are more frequent in cases of Graves' disease and a high percentage of these cells express the TSH receptor. The most recent data from this group indicate that the very same cells also contain thyroglobulin, another crucial antigen in the orbital cavity (4). Normal circulating fibrocytes migrate to sites of injury and provoke an antigen-specific T-cell stimulation. It is therefore highly likely that the family of fibroblasts and fibrocytes expressing TSH receptors are implicated in the inflammatory process in the orbit that, because of its rigid structure, has little possibility for expansion. The authors mention that recently Neumann et al. suggested that a small molecule antagonist binding to TSH receptor could offer a new possibility of treating TAO, allowing interruption of the autoimmune process (5). Such molecules might help to treat hyperthyroidism and TAO at the same time and would certainly represent a major breakthrough.

— Albert G. Burger, MD

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