Researchers identify an immune cell linked to inflammation and scarring in Graves' eye disease

January 8 2010

A cell type that causes significant scarring in lung disease appears to have a similar effect in Graves' disease, University of Michigan Health System researchers have found. The cells, called fibrocytes, are present at a higher than normal frequency in patients with Graves' disease, according to a new study, the first to associate fibrocytes with this autoimmune disease.

The discovery is a major step forward in explaining how and why the orbit of the eye is subject to scarring and inflammation in Graves' disease.

The findings may also lead to new treatment strategies to target scarring or fibrosis, say authors Raymond Douglas, M.D., Ph.D., and Terry Smith, M.D., specialists in Graves' disease at the University of Michigan Kellogg Eye Center. The study appears in the January issue of the *Journal of Clinical Endocrinology & Metabolism*.

Graves' disease is an autoimmune disorder which results in an overactive thyroid. Up to half of those affected by the disease will develop inflammation or fibrosis around their eyes, creating the bulging appearance associated with Graves' eye disease, also called thyroid-associated ophthalmopathy. Excessive scarring can cause such manifestations as double vision or even loss of vision.

"Today we have medications to reduce inflammation, but these drugs typically do not treat the fibrotic effects of thyroid eye disease," says Douglas, oculoplastics surgeon. "Our study is the first to implicate fibrocytes in the disease process, a finding that should open up new possibilities for treatment."

Fibrocytes are immune cells derived from bone marrow that circulate through the bloodstream. They can infiltrate tissue, like the lungs, kidney, and liver, generating excess connective tissue and areas of fibrosis, for example, following pulmonary or kidney injury.

To determine whether fibrocytes play a similar role in Graves' disease, these investigators and their colleagues examined tissue samples from 70 patients with the disease and compared them to 25 healthy subjects. The samples were gathered while Douglas and Smith were on the faculty of the University of California at Los Angeles.

They found that fibrocytes were present at substantially higher frequencies—as much as five times greater—in patients with Graves' disease. These levels were observed in both the bloodstream and in the orbital tissues of patients who had developed thyroid eye disease.

In earlier studies, Douglas and Smith identified the antigens that trigger the overactive immune response in Graves' disease. Now they report that fibrocytes express the same antigens: thyroid-stimulating hormone receptor (TSHR) and insulin-like growth factor-1 receptor (IGF-1R). In addition, the Kellogg researchers say, when these receptors are activated, they produce a large quantity of cytokines which could stimulate immune cells to the orbit, causing inflammation in thyroid eye disease.

"We now have a much clearer picture of the disease process, including the pathway by which fibrocytes reach the orbit," says Douglas. "Drugs currently under development for other fibrotic diseases are designed to

disrupt this pathway and prevent fibrocytes from reaching their target." According to Douglas, "These therapies may be just as effective for our patients with thyroid eye disease."

As follow-up to the study, the Kellogg researchers plan to more fully identify the role of fibrocytes in the disease process and test whether several new agents, such as rituximab, can reduce these cells as they circulate through the bloodstream. The authors also recently demonstrated that rituximab was highly effective in treating patients with severe Graves' disease.

Provided by University of Michigan