Insights Into the Pathogenesis of Thyroid-Associated Orbitopathy

Evolving Rationale for Therapy

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Attempts to understand the pathogenesis of thyroid-associated orbitopathy (TAO) have failed, in part because of confounding features associated with its variable clinical presentation. In the absence of a more complete insight into disease mechanisms, no specific and effective therapy can be developed. It is our view that much of the information necessary to unravel the complexities of TAO and therefore formulate rational therapy has already been gathered.

CLINICAL FEATURES OF TAO

Thyroid-associated orbitopathy varies widely in its pattern of presentation. Generalizations about this disease are not particularly useful when treatment plans are developed for an individual patient, but the following description will serve as a point of reference for the subsequent discussion. Thyroid-associated orbitopathy is identified in approximately 20% of those seen with Graves disease on initial examination. A far larger group manifests subclinical, self-limited forms of TAO. The prevalence of these milder forms of the disease is estimated to be as high as 80%. It commonly affects women in the fifth decade of life and is usually diagnosed soon after the glandular aspects of Graves disease appear. Components of the orbital process include symmetric soft tissue swelling, proptosis, lid retraction (with characteristic temporal flare), and strabismus, due in large part to fibrosis of the extraocular muscles. The self-limited disease requires only supportive measures except in cases where severe corneal exposure keratitis or compressive optic neuropathy threatens vision and requires immediate medical attention. The active phase of TAO typically lasts 1 year, after which most patients improve. Residual stigmas of the disease often persist after the active phase resolves, but few patients require surgical rehabilitation.

SOME UNANSWERED QUESTIONS

It is a widely held view that TAO is an autoimmune disease and is not believed to result directly from the metabolic perturbations caused by thyroid hormone overproduction. If this assertion were correct, then a frequent absence of improvement after successful treatment of the dysthyroid state would be expected. The apparent dissociation between glandular and orbital disease would also explain why patients with euthyroid Graves disease or Hashimoto thyroiditis can manifest TAO. Whether the levels of antibodies associated with thy-
roid enlargement and overactivity, termed thyroid-stimulating immunoglobulins, correlate well with the development, severity, or activity of orbital disease has remained controversial.\textsuperscript{18-22} Despite substantial efforts, an autoantigen, restricted in its expression to the orbit and thyroid gland, has not been identified.\textsuperscript{23,24} An antigen found exclusively in the areas affected by Graves disease could link these tissues and thus might provide an explanation for the anatomic site restriction of connective tissue manifestations in Graves disease. Moreover, immunoglobulin complexes have not been found in affected orbital tissue.

An intriguing feature of TAO is the age-related variation in disease expression. Patients younger than 40 years are more likely to exhibit orbital fat expansion and proptosis in the absence of infiltration of the extraocular muscles and eyelid retractors. It is our impression that the clinical behavior of orbital inflammation in even younger patients is particularly sensitive to changes in serum thyroxine and thyrotropin levels.\textsuperscript{25} In contrast, older patients are considerably more likely to develop multiple fusiform enlargement of the extraocular muscles.\textsuperscript{25-29} We cannot explain the predilection of the disease for the inferior and medial recti. Patients older than 70 years are more likely to develop severe extraocular muscle involvement resulting in diplopia and compressive optic neuropathy. This often occurs in the absence of proptosis or cutaneous inflammation.

The temporal relationship between the thyroid and orbital diseases is variable. Whereas in 80\% of patients the onset of the glandular and orbital diseases occurs within 18 months of each other, the clinical appearance of the two can be separated by as much as 20 years in some cases.\textsuperscript{5,7} Unlike other autoimmune diseases that are typically chronic with unpredictable episodes of acute relapse, most patients with TAO undergo spontaneous remission within 18 months of disease onset. This resolution does not appear to vary according to the type of therapy used.

Only 5\% of patients will develop recurrent orbital inflammatory disease. The pattern and clinical features of recurrent, acute disease may differ from those of the initial episode. In contrast to the first presentation, we have found that recurrent orbital disease is more often associated with the onset of dysthyroidemia. In many cases, these subsequent exacerbations resolve rapidly after normalization of thyroid function.

Most cases of TAO are initially seen with symmetric-appearing orbital involvement. However, a few patients exhibit marked asymmetry of the orbital disease.\textsuperscript{1-3,8} Still fewer have unilateral disease that resolves before acute disease affects the second orbit, sometimes more than 1 year later.

How and whether orbital radiotherapy alters the natural course of TAO, especially the acute phase of the disease, remain unclear. The elimination of activated orbital lymphocytes inadequately explains the phenomena. If radiotherapy merely destroyed resident lymphocytes, new populations of these cells would most likely repopulate the orbit and reinitiate the inflammatory response.\textsuperscript{30}

We do not understand how smoking promotes and prolongs acute-phase TAO.\textsuperscript{31-33} This effect has been demonstrated almost exclusively in women. Why men appear to be spared the disease-promoting effect of cigarette smoke is uncertain. It would be enlightening to determine the impact of continued smoke exposure on the persistence of orbitopathy and whether the course of the disease is altered after its cessation.

RECENT INSIGHTS INTO THE PATHOGENESIS OF TAO

An appreciation of the embryologic derivation of orbital fibroblasts is essential to understanding the pathogenesis of TAO. Unlike most other regions of the body, connective tissue investing the orbit contains fibroblasts derived from the neural crest. Although the significance of this embryologic derivation is not fully understood, cells from the neural crest possess a particularly high degree of phenotypic plasticity.\textsuperscript{34} In addition to the orbital fibroblast, other periorbital cell types, including osteoblasts and parasympathetic and postganglionic sympathetic neurons, also derive from neural ectoderm.\textsuperscript{35} We hypothesize that orbital fibroblasts exhibit a set of unique phenotypic attributes rendering them particularly susceptible to the actions of proinflammatory cytokines and other disease mediators, and that their embryologic derivation may underlie, at least in part, their inflammatory phenotype.
The statement, “Few tissues are less interesting than adipose,” attributed to Jakobiec, reflects the pervasive attitude toward orbital fat. Inspection of this tissue shows a complex array of fibrovascular septae, highly permeable blood vessels, and smooth muscle cells. This network, elegantly described by Koornneef, may represent the end-organ target of TAO. Structures analogous to the fibrous septae in fat may exist in extraocular muscles in the form of the endomysium, perimysium, and epimysium. These sites are involved with intense scarring during the process of acute TAO, resulting in restrictive strabismus. Muscle fibers are relatively spared in TAO, suggesting that connective tissue and not extraocular muscle fiber represents the primary disease target.

DIFFERENCES BETWEEN ORBITAL FIBROBLASTS AND THOSE IN OTHER ANATOMIC REGIONS

The behavior of orbital fibroblasts in vitro has been examined in detail. They express characteristic profiles of surface receptors, gangliosides, and inflammatory genes. A number of phenotypic attributes exhibited by orbital fibroblasts suggest that they may play an active role in tissue remodeling and modulation of local inflammatory responses. Unlike some fibroblasts, those from the orbit display cell-surface CD40, a receptor initially found on B lymphocytes and important to the activation of those cells. The receptor CD40 is activated by CD154, also known as CD40 ligand, which is displayed on the surface of T lymphocytes. When CD40 on orbital fibroblasts is engaged by CD154, several inflammatory fibroblast genes are activated. Interleukin 6 and interleukin 8 expression is dramatically up-regulated, which, in turn, can result in enhanced chemotaxis of bone marrow–derived inflammatory cells to the orbit. Prostaglandin endoperoxide H synthase 2, the inflammatory cyclooxygenase, is induced by CD40 ligation on orbital fibroblasts. This induction results in substantial increases in the production of prostaglandin E2. Synthesis of hyaluronan, an important glycosaminoglycan polymer thought to accumulate in the orbital connective tissue in TAO, is also increased by CD40 ligation. Many of the consequences of CD40 ligation in human fibroblasts are mediated through the activation of nuclear factor κB and can be attenuated with physiologic concentrations of glucocorticoids. This finding is entirely consistent with the therapeutic benefit associated with these corticosteroids in acute TAO. The actions of other proinflammatory cytokines, such as interleukin 1, and the T-lymphocyte–derived molecule leukoregulin, also result in exaggerated orbital fibroblast gene inductions that may have important roles in the orbital inflammatory response.

For instance, uridine diphosphate glucose dehydrogenase and members of the hyaluronan synthase gene family are induced substantially in orbital fibroblasts treated with proinflammatory cytokines. We believe that these inductions underlie the exaggerated increases in hyaluronan synthesis observed in cytokine-activated cultures. The increases in orbital fibroblast synthesis of hyaluronan, in turn, result in the accumulation of the glycosaminoglycan that occurs in TAO.

Many of these cellular responses differ quantitatively or qualitatively in orbital and nonorbital fibroblasts. We postulate that the peculiar phenotype of orbital fibroblasts renders the human orbit susceptible to inflammation, such as that occurring in TAO. Moreover, fibroblasts from other anatomic regions of the body that are affected by autoimmune diseases, such as rheumatoid arthritis, exhibit several cellular characteristics that are not unlike those of their orbital counterparts. A number of interesting parallels have been shown to exist between TAO orbital fibroblasts and synovial fibroblasts from patients with arthritis.

A subpopulation of orbital fibroblasts appears capable of undergoing adipocytic differentiation in vitro. It is as yet unclear whether the fat compartment of the orbit expands on the basis of an increased number and/or size of adipocytes or whether hyaluronan infiltration accounts entirely for the increases in fatty connective tissue volume. Another open question relates to whether orbital fibroblasts present the immune system with altered antigenic targets after differentiation into adipocytes. Does the density of thyrotropin receptors displayed by the preadipocyte change after differentiation? Are there differences in the expression or the coupling of CD40 to its downstream signaling pathways and gene targets in the mature adipocyte?

Our ignorance concerning the pathogenesis of TAO includes the obscure mechanism by which immunocompetent cells are trafficked to the orbit. Are the same factors involved in the initiation of the orbital and thyroidal components of Graves disease? Much of our inability to define the very early pathogenic events in TAO results from limited access to relevant tissue during the acute disease phase. As a result, we have not identified the earliest cells that infiltrate the soft tissues of the orbit. We have relied largely on histologic examination of the stable phase occurring late in the process, when reactive events rather than those involved in the initiation of the disease are likely to predominate.

Recent interest in the thyrotropin receptor as the critical autoantigen in TAO derives largely from the contention that it is expressed exclusively on thyroid epithelial cells and in tissues manifesting Graves disease, including orbital connective tissue and pretibial skin. Indeed, reports have appeared demonstrating the thyrotropin receptor messenger RNA (mRNA) in orbital tissues from patients with TAO and from individuals without the disease. Early studies relied on nonquantitative polymerase chain reaction but have been substantiated subsequently by reports using in situ hybridization. They have clearly demonstrated target transcripts in orbital tissues. Several studies have shown that orbital fibroblasts can also express both thyrotropin receptor mRNA and protein. One recent study failed to detect thyrotropin receptor mRNA in abdominal adipose–connective tissue by means of an RNase protection assay. However, another study indicated that thyrotropin receptor mRNA is expressed in fat deposits distant from the orbit and by fibroblasts and preadipocytes derived from several tissues including those not ordinarily manifesting Graves disease. These receptors appear to be functional by virtue of their com-
petence to activate the p70S6K pathway, a newly identified downstream target of the thyrotropin receptor expressed by the thyrocyte. Thus, the concept that the thyrotropin receptor represents an anatomically restricted antigen and that this limited expression underlies the localization of disease manifestations is probably incorrect. This is not to say that the thyrotropin receptor does not play an important role in the pathogenesis of TAO. We believe a more likely disease model involves the thyrotropin receptor functioning as a conduit for the exchange of molecular information between the immune system and connective tissue, such as that investing the orbit.

Our current overview of orbital fibroblast involvement in the pathogenesis of TAO is summarized in Figure 3. From that schematic diagram, it becomes clear how multiple interactions are possible between immunocompetent cells and fibroblasts. However, there is certainly no reason to believe that fibroblasts, once activated, would not modify the behavior of the immune cells trafficked to the orbit. Thus, the model should be seen as a dynamic interplay between cells that leads to a variety of tissue changes and could culminate in terminal events such as fibrosis.

**CLINICAL AND THERAPEUTIC CONSEQUENCES OF THE ORBITAL FIBROBLAST PHENOTYPE**

It appears likely to us that the orbital fibroblast possesses a central role in the pathogenesis of TAO. How does this new insight help clarify the questions remaining?

The expansion of the orbital fat compartment in TAO could result from the differentiation of orbital fibroblasts with adipogenic potential after exposure to an altered cytokine milieu occurring in the disease. Loss of this adipogenic potential with aging could account for the more pronounced expansion of fat found in younger patients as compared with older adults with TAO. In older individuals, nonadipogenic fibroblasts might predominate and thus preferentially exhibit biosynthetic activities that lead to fibrosis. Of interest is the small subset of patients who demonstrate evidence on computed tomography and magnetic resonance imaging of fatty density within the substance of extraocular muscles (Figure 4). This process could represent adipocyte expansion in the endomysium and perimysium.

The supraorbital fat pads enlarge in advanced TAO. This, we believe, is a consequence of both enhanced adipocyte differentiation and proinflammatory cytokine-driven hyaluronan accumulation. We suspect that a similar process is occurring in the premalar fat pads, accounting perhaps for the subtle changes in facial morphologic characteristics that have been attributed to effects of long-term corticosteroid use.

![Figure 3. Schematic diagram of our current model of the proposed immune cascade in thyroid-associated orbitopathy. The orbital fibroblast is involved in a dynamic interplay with immunocompetent cells such as T and B lymphocytes and mast cells. CD40 and its ligand CD154 are prominent features of this interaction.](image)

![Figure 4. Magnetic resonance image of a patient with Graves disease demonstrating fat-density infiltrates within the extraocular muscles.](image)
Preliminary studies conducted in culture have demonstrated that the synthesis of glycosaminoglycans and collagen is enhanced when fibroblasts are subjected to low oxygen tension. Moreover, dermal fibroblasts subjected to similar atmospheric conditions expressed high levels of transforming growth factor β and collagen mRNA and exhibited increased rates of proliferation. Thus, conditions that lower oxygen levels in orbital tissue could influence the inflammatory responses occurring there. Orbital ischemia might result from obstruction of venous and, perhaps, lymphatic outflow. Outflow through the superior and inferior ophthalmic veins may become obstructed as a consequence of diffuse expansion of the extraocular muscles or connective tissue. Alternatively, it may be caused by obstruction of the superior ophthalmic vein. The inferior ophthalmic vein may be compressed within the infraorbital canal by Mueller orbital muscle. Feldon and colleagues demonstrated that the ligation of the superior ophthalmic vein in the cat results in an orbital syndrome resembling TAO. If the cycle of ischemia-induced inflammation were interrupted, improvement might occur. This mechanism has been proposed as underlying the rapid improvement in inflammation and edema seen after orbital decompression. We would argue that the benefit associated with those surgical maneuvers might result directly from the decompression of the orbital circulation. Were it not for greater attendant risk, surgery might be routinely indicated in cases of acutely congested orbits.

Multiple factors could contribute to decreased oxygen tension in orbital tissues and therefore might affect the course and severity of TAO. The association between smoking and the increased incidence of TAO in women with Graves disease may be related to a decrease in orbital tissue oxygen tension. Although no direct and reliable evidence currently supports this concept, it is our impression that smoking in both men and women causes more persistent and severe TAO.

The mechanism by which orbital radiotherapy resolves acute-phase TAO is not understood. External beam photon radiation in the range of 2000 rad (20 Gy) sterilizes the orbital field of resident lymphocytes. If the entire effect of radiotherapy were explained by its lymphocidal actions, a population of newly trafficked T cells could repopulate the orbit and inflammation would recur rapidly. What if the lymphocytes in the orbit were somehow independently driving the disease? Would their demise reset the process? It is unclear whether there is, in addition, a long-lasting effect of radiotherapy on local orbital immunity. Cultured fibroblasts, when exposed to radiation, express cell-surface antigens differently. In theory, radiotherapy might alter the inflammatory phenotype of the orbital fibroblast to more closely resemble that of the extraorbital fibroblast. Alternatively, radiotherapy may destroy or inactivate local antigen-presenting cells such as tissue macrophages and dendritic and mast cells.

The inflammatory events occurring in TAO are complex and incompletely understood. Currently, no pharmacologic agents are available to specifically reverse either the systemic or orbital manifestations of Graves disease. Glucocorticoids are powerful modulators of immune function that appear to act at several levels of the inflammatory cascade. While they attenuate many of the signs and symptoms of disease, they are associated with adverse effects. Less toxic and more specific agents are clearly needed. Nonsteroidal anti-inflammatory agents act by inhibiting cyclooxygenases. Inhibitors of the inflammatory cyclooxygenase 2 have been introduced to the marketplace recently and are purported to be less toxic than traditional inhibitors. Although less effective than glucocorticoids, their lower toxicity makes them potentially valuable therapy for the mild, acute-phase disease. Clearly, well-controlled studies examining their efficacy in TAO are warranted.

**TREATMENT RECOMMENDATIONS**

On the basis of our current understanding of TAO and its pathogenesis, the following therapeutic recommendations can be made. Early identification of the glandular and orbital manifestations of Graves disease is invaluable. Restoration of a euthyroid state is probably of considerable importance in minimizing orbital inflammation. Profound and prolonged intervals of hypothyroidism with associated elevations of serum thyrotropin levels should be avoided. When recognized early, orbitopathy might be effectively treated with nonsteroidal anti-inflammatory drugs. When the inflammation is advanced, and certainly in the presence of compressive optic neuropathy, glucocorticoids administered orally or by orbital injection are required to control the soft tissue features. Patients with Graves disease should be strongly encouraged to discontinue smoking, whether or not they have orbitopathy. Radiotherapy has a defined therapeutic role in the treatment of TAO, and we strongly hold that it abbreviates the acute phase of the orbitopathy. As a general rule, the acute phase will usually resolve within 3 to 6 months after radiotherapy, as compared with 1 to 3 years in untreated cases. Radiotherapy is strongly recommended in patients with compressive optic neuropathy. That intervention may reduce the effective dose and duration of corticosteroid therapy. Moreover, surgical decompression may be avoided. When required to relieve residual proptosis, decompression after radiotherapy is simplified by the absence of acute inflammation. We also recommend radiotherapy for the unusual case in which inflammation progresses rapidly. It should be avoided in patients with underlying vasculitis, in those with concomitant diabetic retinopathy, and when the orbital inflammation has remitted spontaneously. When used properly, radiotherapy in acute TAO should limit surgery in the acute phase of disease to the rare instance. We advocate relegating most surgery to reversing the residual clinical consequences of orbital fibrosis and fatty expansion, at a stage when the disease has stabilized.

**CONCLUSION**

Thyroid-related orbitopathy is characterized by clinical paradoxes that continue to challenge the clinician and intrigue the scientist. The thyrotropin receptor has attracted substantial attention in our search for a single molecule that might explain the anatomic localization of
Graves disease to specific tissues. This receptor, which is expressed by fibroblasts throughout the body, may serve as a conduit for molecular communication between connective tissues and the immune system in TAO. Additional self-antigens, particularly those displayed by fibroblasts, may well be involved in cell activation through their recognition by disease-specific immunoglobulins. Thus, the overlooked fibroblast may orchestrate a complex immune cascade that initiates, perpetuates, and eventually attenuates the clinical disease. This proposed mechanism might explain some of the clinical features of the disease, including adipose accumulation in the orbit, within the muscles, and on the face. It may also underlie age-related differences in disease presentation, the worsening disease in states of hypoxia, and responses to radiotherapy. Many questions concerning TAO remain to be addressed. New technology is allowing us to probe and dissect aspects of its pathogenesis that likely result from genetic and acquired factors. Avances for further investigation include the characterization of the specific mediators of the immune cascade, development of clinically useful tests to determine disease activity, and identification of the earliest cells initiating inflammatory responses in the orbit.

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