Published in final edited form as:
Surv Ophthalmol. 2010 ; 55(3): 215–226. doi:10.1016/j.survophthal.2009.06.009.

Immunopathogenesis of Thyroid Eye Disease: Emerging Paradigms

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Abstract

Graves disease represents a systemic autoimmune process targeting the thyroid, orbit, and pretibial skin. The thyroid dysfunction is treatable, but no consistently effective medical therapy has yet been described for the orbital manifestations of Graves disease, also known as thyroid-associated ophthalmopathy or thyroid eye disease. Several autoantigens are potentially relevant to the pathogenesis of thyroid eye disease. Activating antibodies generated against the thyrotropin receptor can be detected in a majority of patients, and these drive hyperthyroidism. However, stimulating antibodies against the insulin-like growth factor-1 receptor (IGF-1R) may also play a role in the extra-thyroid manifestations of GD. IGF-1R is over-expressed by orbital fibroblasts derived from patients with TED, while IGF-1R$^+$ T and IGF-1R$^+$ B cells are considerably more frequent in GD. Actions of several cytokines and the molecular interplay peculiar to the orbit appear to provoke the inflammation, fat expansion, and deposition of excessive extracellular matrix molecules in thyroid eye disease. Based upon these new insights, several therapeutic strategies can now be proposed that, for the first time, might specifically interrupt its pathogenesis.

Keywords

Graves ophthalmopathy; immunology; thyroid

I. Introduction

The unique features of Graves disease (GD) have both fascinated and frustrated the medical community for the 200 years since its first description. GD is an autoimmune disease where

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The authors reported no proprietary or commercial interest in any product mentioned or concept discussed in this article.

circulating antibodies cause hyperthyroidism and lead to thyrotoxicosis. These antibodies, originally referred to as long-acting thyroid stimulators, are directed against the thyrotropin receptor (TSHR). They mimic the agonist activity of TSH but are not subject to the normal feedback in the anterior pituitary. GD is approximately 7 to 10 fold more frequent in women, and typically occurs between 20 and 50 years of age.[72]

Clinical manifestations of GD include thyroid enlargement and thyrotoxicosis, inflammation and remodeling of the orbit, and rarely dermopathy. The orbital disease is collectively known as thyroid-associated ophthalmopathy or thyroid eye disease (TED). It is unclear why anatomically unrelated tissues undergo coordinate and selective immune infiltration and remodeling. Furthermore, the mechanistic basis for the self-limited course of the orbital disease is unclear, but identifying these underlying factors could provide insights necessary for the development of effective therapies.

This article summarizes our current understanding of TED, focusing on the fundamental aspects of its molecular pathogenesis. In it we identify attractive potential targets for interrupting the disease.

II. Immunology of GD

Adults normally exhibit tolerance to antigens that are present during fetal life and thus are recognized as “self.” Under certain circumstances, however, tolerance may be lost, leading to immune reactions against self that manifest clinically as autoimmune disease. Proposed mechanisms for autoimmunity include molecular mimicry, abnormal protein modification, release of ordinarily sequestered antigens, and epitope spreading.

Development of disease requires participation of self-reactive helper ($CD4^+$) T cells. These Th1, Th2, and Th17cells can support both cell and antibody-mediated autoimmune responses. It remains likely that common mechanisms for auto antigen generation and both T and B cell activation link several, if not all, autoimmune diseases. Thus, rheumatoid arthritis, type 1 diabetes mellitus, and systemic lupus erythematosis may share pathogenic features with GD. This is the rationale for exploring whether therapeutic agents exhibiting activities in one disease might benefit those with another. While GD is a systemic disease, its manifestations exhibit an anatomic-site selective predilection. Thyroid dysfunction is the principal hallmark of GD and occurs in greater than 90% of patients sometime during the course of their disease.

Hyperthyroidism results from activating antibodies that bind to TSHR on thyroid epithelial cells and mimic the actions of TSH. In addition to stimulating antibodies directed against TSHR (TSAb), those blocking that receptor can also be detected in patients with hyperthyroidism, and a shift in the balance between these two types of antibodies can result in hypothyroidism in as many as 15% of patients.[61] In addition to these pathogenic antibodies, those generated against thyroid peroxidase (TPO) and thyroglobulin (TG) can often be detected. TSAb uniformly belong to IgG_1 subclass, whereas antibodies against other thyroid antigens are not IgG_1 restricted.[98,100] Overall, the clinical manifestations of glandular GD are predictable and can be treated with relative ease in the vast majority of patients.[86] A detailed description of the endocrine derangements associated with GD is beyond the scope of this article, and can be found elsewhere.[47,77,105]

III. Clinical Course of TED

Approximately 25-50% of patients with GD develop TED, while sight-threatening disease occurs in 5% of patients.[7] Conversely, 10% of those manifesting with TED fail to become hyperthyroid. Regardless of whether thyroid dysfunction or TED develops first, the other becomes apparent within 18 months in 85% of patients with GD. Rundle was the first to divide

the course of TED into active (dynamic) and inactive (static) disease phases. Signs and symptoms of active TED include proptosis, conjunctival injection, chemosis, diplopia, corneal ulceration, and rarely loss of sight from optic nerve compression. The tissue expansion occurs within the relatively fixed volume imposed by the bony orbit and results from inflammation, accumulation of glycosaminoglycans (GAGs), and increased fat content. Compression within the tight orbit can compromise venous drainage, potentially increasing the retrobulbar pressure and leading to chemosis and periorbital edema. Idiosyncratic variations in orbital shape and vessel location may render a subset of patients with GD more susceptible to severe TED.[45] The disease is often asymmetrical. Computed tomography can demonstrate predominant expansion of muscle, fat, or both as illustrated in Fig. 1.

Inactive disease is characterized by stable proptosis, eyelid retraction, and may be accompanied by persistent restrictive strabismus, with resolution of inflammation, usually within 18-24 months of its first appearance. The self-limited nature of TED is peculiar among human autoimmune diseases. Anti-inflammatory therapy, such as corticosteroids are effective only during the active phase, whereas surgical intervention is usually performed once this phase has subsided.

Genetic factors appear to contribute to disease susceptibility, as is suggested by increased incidence of concordance among monozygotic twins.19,[98] Specific genetic alterations peculiar to GD, including polymorphisms, have been difficult to identify across multiple ethnicities; however, candidates include major histocompatibility complex (MHC) class II, protein tyrosine phosphatase-22, CD40, and cytotoxic T lymphocyte antigen 4 (CTLA4).[47,51,98]

Environmental factors, particularly, cigarette smoking, appear to increase the incidence and severity of TED. Moreover, tobacco use reduces the response to therapies.26,103,112 Cawood et al in an in vitro study demonstrated that cigarette smoke extract induced adipogenesis and increased hyaluronic acid production by orbital fibroblasts, and was synergistic with IL-1 in inducing adipogenesis.[26] Tissue hypoxia leading to the formation of superoxide radicals may induce orbital fibroblasts (OFs) from patients with TED to proliferate, synthesize GAGs and undergo adipogenesis.[21,26,87]

Thyroid dysfunction appears to run a clinical course that is independent of TED, but treatment of hyperthyroidism might carry important consequences to the orbital process. Radioiodine therapy can be associated with mild, transient worsening of TED.[71] Routine use of steroids immediately before and following radioiodine therapy remains controversial.[9,114] It may not be necessary in all patients, but is widely recommended for those with severe orbitopathy. Persistence of either hypo- or hyperthyroidism correlates with increased severity of TED.[9] Hence, maintenance of the euthyroid state may be of importance and is therefore strongly advocated.

IV. Immunology of TED

The active phase of TED is characterized by orbital and periorbital inflammation targeting connective tissue and fat.[101,102] Electron and light microscopy suggest that the muscle cells remain intact early in the disease;[59,128] however, intense infiltration between extraocular muscle fibres and in orbital fat of T lymphocytes, mast cells and occasional B cells suggests that connective tissue represents the primary autoimmune target.[134,135]

Immunohistochemical evidence of cytokines, including interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), and interleukin-1α (IL-1α) has been reported in the connective tissues, and their presence is associated with T cell infiltration.[59] These cytokines may be produced by infiltrating mononuclear cells and resident fibroblasts since they are also detected in areas devoid of mononuclear infiltration.55 Specifically, IL-1α is a proinflammatory cytokine

produced by monocytes, macrophages, and fibroblasts that may play a critical role in promoting inflammation and extracellular matrix proteins.48 Extensive deposition of hyaluronan in the interstitium dominates the histological picture of TED, and is associated with orbital tissue expansion.[62,63,84,93,113,128]

The stable phase of TED is defined by resolution of inflammation associated with clinical improvement.[10,11,12] The pattern of Th1 cytokine predominance found in active disease may skew toward Th2 cytokines such as IL-4, IL-5, and IL-13 during the stable phase.[4,49] This shift could alter immune cell trafficking, promote tissue fibrosis, or promote disease resolution.[57,90] Th2 cytokine involvement in the pathogenesis of GD was discovered by chance. Patients diagnosed with the Th1 predominant disease, multiple sclerosis, were treated with a monoclonal antibody against CD52, which depletes >95% of circulating T lymphocytes.[28] Amelioration of that disease appeared secondary to decreasing Th1 T cells. However, 18 months after treatment, patients underwent B cell expansion, presumably due to unopposed Th2 cytokines. One-third of these patients developed GD with detectable TSAb.[28]

Factors underlying the spontaneous resolution of inflammation in TED remain unidentified. The possibilities include declining auto-antigen abundance or reduced antigen presentation.[3,33] The targets of other autoimmune diseases, such as synovial tissue in rheumatoid arthritis, exhibit recognizable lymphoid structures.[25,80,83,127] In contrast, the orbit lacks these structures. Thus, TED is not associated with the lymphoid neogenesis that might be crucial to sustained immune activation.

A. ROLE OF ORBITAL FIBROBLASTS (OF) IN THE PATHOGENESIS OF TED

Several studies have demonstrated that OF, especially those from patients with GD, are unique with respect to how they respond to several proinflammatory cytokines.[27,122,136] The divergent phenotype of these cells may underlie the anatomic site-selective manifestations of GD.[118,119,123] Cao and Smith reported some time ago that OF, unlike dermal fibroblasts, fail to generate adequate levels of soluble IL-1 receptor antagonist. This would allow poorly opposed IL-1β signaling.[23] In comparison to control OF, those from patients with GD over-produce prostaglandin E_2 (PGE_2) in response to IL-1β, CD154, and leukoregulin as a result of the coordinate induction of prostaglandin endoperoxide H synthase-2 (PGHS-2) and the microsomal PGE_2 synthase genes.[23,50] They also exhibit enhanced production of extracellular matrix components such as hyaluronan in response to these cytokines (Fig. 2). Thus, GD OF produce proinflammatory molecules and components of connective tissue that lend themselves to the site-specific tissue remodeling occurring in TED.[62,121]

T cells may also play an important role in OF activation through increased expression of CD40 on the latter.109 CD40 binds CD40 ligand (aka CD154) displayed on the surface of T lymphocytes and provides T cell co-stimulation that results in clonal expansion of naïve T lymphocytes and enhances pro-inflammatory cytokine production, including that of IL-1, IL-6 and IL-8.104 Actions of these in turn activate the expression of PGHS-2, hyaluronan synthase (HAS), and UDP glucose dehydrogenase (UGDH) genes, leading to inflammation and hyaluronan production.[24,125] (Tsui, Chen, and Smith, unpublished observations). Thus, disruption of fibroblast – T cell interactions mediated by CD40-CD40 ligand could represent an important therapeutic target in TED. Administration of therapeutic blocking antibodies against the CD40 ligand already has proven effective in pre-clinical mouse models of diabetes and inflammatory bowel disease.[16,34,89]

Orbital connective tissue comprises a heterogeneous population of OF and this cellular diversity may provide the basis for variations in the clinical presentation of TED. Expression of the surface glycoprotein, Thy-1 has been used to delineate phenotype and function of OF subsets. Those expressing Thy-1, such as perimysial fibroblasts, can differentiate into

myofibroblasts, and their capacity for undergoing adipogenesis may be limited.[68,120,124] Orbital fat and connective tissue contains both Thy-1^+ and Thy-1^- fibroblasts.[131] Thy-1^+ OF differentiate into myofibroblasts when treated with TGF-β.[68] They may promote inflammation and orbital fibrosis through their production of IL-6, IL-8 and extracellular matrix components. Thy-1^- OF can differentiate into adipocytes.[120] An important molecular trigger of adipocyte differentiation is the peroxisome proliferator-activated receptor γ (PPARγ). When activated by agonists, OF and subcutaneous preadipocytes undergo adipogenesis.[1,] 132 When these agents are administered therapeutically to patients with diabetes, they can exacerbate tissue expansion in TED.30،73،[75] A predominance of Thy-1^- fibroblasts could contribute to fat expansion in proptotic disease. Thus, the proximate determinants of fibroblast differentiation might represent targets for disease-modifying therapies.[120]

B. ROLE OF T LYMPHOCYTES IN TED AND ITS THERAPEUTIC IMPLICATIONS

The inflammatory phase of TED is characterized by T cell infiltration, often accompanied by mast cells, B lymphocytes, and macrophages.[65] Endogenous ligation of the T cell receptor (TCR) in the absence of co-stimulation is insufficient to activate T cells, but can lead to T cell anergy, tolerance, or depletion.[6،14] Activated $CD4^+CD45RO^+$ T cells appear numerous in the early orbital infiltrate. They produce cytokines and chemoattractants, which in turn further amplify immune responses.

Given the diverse roles attributed to T cells, their depletion should attenuate these responses.[54,65] Down-regulating pathogenic $CD4^+$ T cell activity during autoimmune disease has provided an important rationale for work involving anti-CD3 antibodies that bind to the TCR complex. A number of deleterious side-effects associated with this strategy have been overcome by “humanizing” monoclonal antibodies, reducing Fc receptor binding.[115,116,117] These studies have provided encouraging results in type 1 diabetes mellitus.[115,116,117] Preclinical studies by Smith *et al* demonstrate that humanized anti-CD3 [hOKT3γ1 (Ala-Ala)] can either deplete or induce anergy in IL-2 or interferon-*γ* producing T cells (Th1 cells). Conversely, T cells that produce IL-10 or IL-4 (Th2 cells) may be stimulated by anti-CD3.54،64 These effects occur in activated T cells but are absent in their naïve counterparts. hOKT3γ1 (Ala-Ala) was found to improve glycemic control and preserve residual beta cell function during the first year of type 1 diabetes mellitus.54،64 Side-effects of therapy occur in 50-75% of patients but have not proven to be life-threatening.76 A further refinement of this therapeutic strategy, including the generation of a non-mitogenic form of anti-CD3 (IgG_{2a} Ala–Ala), appears to reduce cytokine release but remains equally efficacious.[13,92]

Expression of CD25 and the transcription factor Foxp3 is characteristic of regulatory T cells (Tregs).[20،85] Mutations of *Foxp3* are associated with severe immunopathology.[36,58] Reduced frequency of Tregs can result in particularly severe autoimmune disease while increases may be associated with disease remission.[111] Although details concerning the mechanisms by which Tregs exert immune suppression remain incomplete, $CD4^+$ and $CD8^+$ T cell function appears to be mediated through IL-4, IL-10 and TGF-β.[67]

T cell depletion has yet to be examined as a potential therapy in TED, despite evidence that these cells are critical to cell-mediated responses and antibody production. The prominent role for both in the pathogenesis of GD and its orbital manifestations suggests that this avenue of therapeutic intervention might prove rewarding (Table 1). Interruption of T cell activation mediated through CTLA4 can be achieved with antibodies directed against the protein (CTLA4 Ig). This agent blocks CTLA4 association with CD80 and CD86 on antigen-presenting cells, leading to T cell anergy.[133] Results with CTLA4 Ig have been promising in an open label phase I trial in rheumatoid arthritis and multiple sclerosis.18،97

C. B LYMPHOCYTES IN GD AND THEIR IMPLICATIONS IN THERAPY DESIGN

In addition to their function as precursors for antibody-secreting plasma cells, B cells efficiently present antigen and produce important cytokines. B cell-deficient mice cannot generate T cell responses following immunization with TSHR, and thus these cells are probably essential to the initiation of autoimmune thyroid disease.[5,130] Early plasma cell survival can be mediated by B cell-activating factor (BAFF) receptors that appear critical to the production of autoantibodies.[43,81] Autoantibody generation is also dependent on the complex interplay between B and T cells.[90]

Thus, B cell-depleting therapies and those that interrupt interactions between cognate molecules on B cell surfaces offer great promise in the context of autoimmune disease (Table 2). An important example is rituximab (RTX), a monoclonal antibody that binds the B cell surface antigen CD20. RTX blocks cell proliferation and attenuates CD20-dependent B cell maturation. Plasma cells do not express CD20 and are thus spared from the cell-depleting actions of RTX. Despite this lack of plasma cell depletion, the agent reduces antibody-mediated responses by blocking antigen presentation and cytokine production.[17,82] RTX was developed for the treatment of B cell non-Hodgkin's lymphomas and has been used in rheumatoid arthritis and lupus only relatively recently.[38] In a multi-center, randomized, double-blind study, a short course of RTX provided patients with rheumatoid arthritis symptomatic improvement for 48weeks. The effect was observed when RTX was used as a single agent or in combination with anti-metabolites such as cyclophosphamide.[78] A subsequent dose-escalation study using RTX as monotherapy in 17 patients with lupus found a strong association between reduced disease activity and B cell depletion.[110,129] In these studies, peripheral B cell depletion was associated with reduced levels of rheumatoid factor and B cell activation associated antigens.[110] In addition, T cell expression of CD40 ligand, CD69, and HLA-DR declined following RTX therapy in lupus.[39] Reduction of CD40 ligand levels may be critical since CD40-CD40 ligand interactions are critical to both B and T cell function.[41,108]

Experience with B cell depletion in TED has been limited to uncontrolled studies but remains encouraging. Two case reports describe reduction in the clinical activity in patients with TED unresponsive to steroids.[15,108] A prospective, controlled study demonstrated sustained remission of hyperthyroidism in GD patients treated with RTX, even though the drug failed to influence autoantibody levels. In another open, non-randomized study of patients with TED, RTX was compared to intravenous glucocorticoid therapy. Patients receiving RTX demonstrated greater improvement of the clinical activity score with fewer side effects (33% vs. 45% of patients) than those treated with glucocorticoids. Thyroid function and TRAb levels were unaltered following RTX treatment. Adverse effects related to RTX include transient hypotension, cough, itching, mild temperature elevation, multifocal leucoencephalopathy and potentially, infection.[22,29] However, most studies have failed to demonstrate significantly increased infection rates.[8,38,123] Thus, RTX appears to represent a promising therapeutic agent in a subset of patients with TED.[91] Well-controlled, prospective, and adequately-powered studies remain essential to fully evaluate its role.

D. AUTOANTIGENS IN TED

The search for relevant antigenic triggers in GD and TED has broadened considerably in the wake of findings that other autoimmune processes involve multiple autoantigens. Both genetic and environmental factors have been implicated. The role of TSHR is firmly established in the pathogenesis of hyperthyroidism in GD. But the other facets of this disease, including those occurring in the connective tissue are not easily reconciled with TSHR as the single pathogenic antigen. IGF-1R has been implicated in the pathogenesis of TED by our research group.[88]

Other potential autoantigens expressed by extraocular muscles include tropomodulin, G2s, which is the terminal 141 amino acids of the winged-helix transcription factor FOXP1, and the calcium binding protein calsequestrin. Antibodies to each of these proteins have been detected in patients with GD and their levels may correlate with myopathy.37 TG and TPO have also been proposed; however, levels of anti-TG and anti-TPO antibodies do not correlate with the presence, clinical activity, or severity of TED.[79] TG shares physical attributes with acetylcholinesterase (ACHE), prompting the question of whether a shared epitope might provide the link between thymus nd orbit.[60] Anti-ACHE antibodies were detected in 8% of sera from patients with TED, but their levels failed to correlate with disease activity.37,46 Multiple non-pathogenic autoantibodies are frequently detected in autoimmune disease, generated as a consequence of tissue damage. Thus, a role for any of these proteins and the antibodies directed against them in TED remains to be demonstrated.

E. ROLE OF TSHR

The role of TSHR and its antibodies in the pathogenesis of TED remains uncertain. Several interesting correlations between antibody levels and disease activity have been reported. TSHR expression in human fat tissue was first suggested when TSH was found to mediate lipolysis in fetal and newborn adipocytes but not in adult adipocytes.[42,56,126] TSHR mRNA has been detected in orbital tissues and OF, albeit at extremely low levels.[129,131] Undifferentiated fibroblasts fail to respond to rhTSH;[2,131,132] however, functional TSHR appears following differentiation into adipocytes where rhTSH modestly enhanced cAMP.[44] The role of TSHR in T cell activation is unclear. Two of eighteen T cell lines derived from orbital tissue of patients with GD exhibited increased migration following treatment with TSH, suggesting the absence of an important role for TSHR in orbital T cell activation.[40,52,74] Clearly additional studies will be required if we are to establish an important role for TSHR in the pathogenesis of TAO.

F. ROLE OF IGF-1R

The IGF-1/IGF-1R pathway has been implicated in the pathogenesis of many malignant and autoimmune diseases. Crohn disease, pulmonary fibrosis, and multiple sclerosis are examples of presumed autoimmune diseases where IGF-1R might be over-expressed. More than 20 yrs ago, IGF-1 immunoreactivity was demonstrated on the surface of extra-ocular muscle and orbital fat cells from 2 patients with TED.[101] Subsequently, the fraction of $IGF\text{-}1R^+$ fibroblasts cultured from the orbit, skin, and thyroid of patients with GD was found to be increased.[99,100,101] Treatment of these fibroblasts with either IGF-1 or GD-IgG results in the synthesis of two powerful T cell chemoattractants, IL-16 and RANTES, as well as the generation of hyaluronan.[101,119,123] Importantly, neither IGF-1 nor GD-IgG elicited these responses in fibroblasts from individuals without autoimmune disease. These findings suggest that the increased levels of IGF-1R may play a role in the pathogenesis of GD; however, serum IGF levels are normal in euthyroid patients with GD. Elevated IGF-1 levels in orbital tissues appear to be independent of serum IGF-1.[70] Anti-IGF-1R antibodies were detected in most patients with GD, but in few individuals without the disease.[31]

Like fibroblasts, T and B cells from patients with GD exhibit a striking phenotypic skew toward the $IGF\text{-}1R^+$ phenotype.[31,32] Notably, $CD45RO^+$ T cells, representing memory T cells, exhibit remarkable IGF-1R skew, especially those with the $CD8^+$ phenotype.[129] Display of IGF-1R imparts a growth advantage and protects from Fas mediated apoptosis among T cells and is associated with the production of anti-TSHR antibodies in B cells.[32] These findings suggest that IGF-1R may participate in the development of GD. Evidence that TSHR and IGF-1R might be functionally linked was strengthened recently when these proteins were found to co-localize.[129] These receptors may form both physical and functional complexes since TSHR signaling to ERK activation could be attenuated by an IGF-1R blocking antibody.[53,95,107]

Several strategies for disrupting IGF-1R signaling have been developed recently and are currently being evaluated as therapy for cancer. These include several small molecules and antibodies. CP-751,871 (Pfizer) is an anti IGF-1R antibody currently undergoing phase III clinical trials in patients with non-small cell lung cancers. Phase I trials with IMC A-12 (Imclone), a human monoclonal antibody against IGF-1R, has also shown promise.[69]

G. ROLE OF CYTOKINES AND IMMUNE MEDIATORS

TNF-α levels may be elevated during the inflammatory phase of TED.[96,106] Disruption of this pathway has become a major and highly successful approach to the therapy of rheumatoid arthritis and Crohn's disease.[35,66] Three biological anti-TNF-α agents are currently in wide clinical use including the monoclonal antibodies infliximab and adalimumab. Etanercept, a recombinant human soluble TNF-α receptor fusion protein, binds and inhibits TNF-α activity. Two separate reports of infliximab use in patients with TED suggest that it might reduce inflammation and improve visual function without side effects.[35] In the first study, nearly complete resolution of inflammation was observed within 72 hours following drug administration and improvement in visual acuity and color vision occurred over the subsequent week.[94] In another, Paridaens *et al* found that the clinical activity score was reduced by 60% among 10 patients with TED, although 3 exhibited a disease flare following therapy withdrawal. No serious adverse event was noted during a mean follow-up of 18 months.[94]

V. Conclusion

Despite intensive study, identity of the proximate antigenic target initiating TED and the relationship between the orbital disease and the other components of GD remain uncertain. Lack of a preclinical disease models continues to plague our efforts to better understand this disease. Important insights concerning the pathogenesis of allied autoimmune diseases and increasing knowledge about their successful treatment should shed new light on the fundamental factors underlying TED and facilitate development of therapies for this particularly vexing process.

VI. Method of Literature Search

The primary search was performed on the accessible literature as of September, 2008. The MeSH database was used to target the search of Medline/PubMed and included available reports of Graves disease and thyroid eye disease. Various synonyms and eponyms of TED were searched. Additional MeSH terms included “autoimmune disease” and “thyroid” which were combined with “TED” to identify relevant citations. Full-text manuscripts of relevant English-language abstracts were reviewed. Additional references were identified by examining the bibliographies of retrieved articles and relevant textbooks of ophthalmology and immunology. English language abstracts for non-English language articles were included and referenced where relevant.

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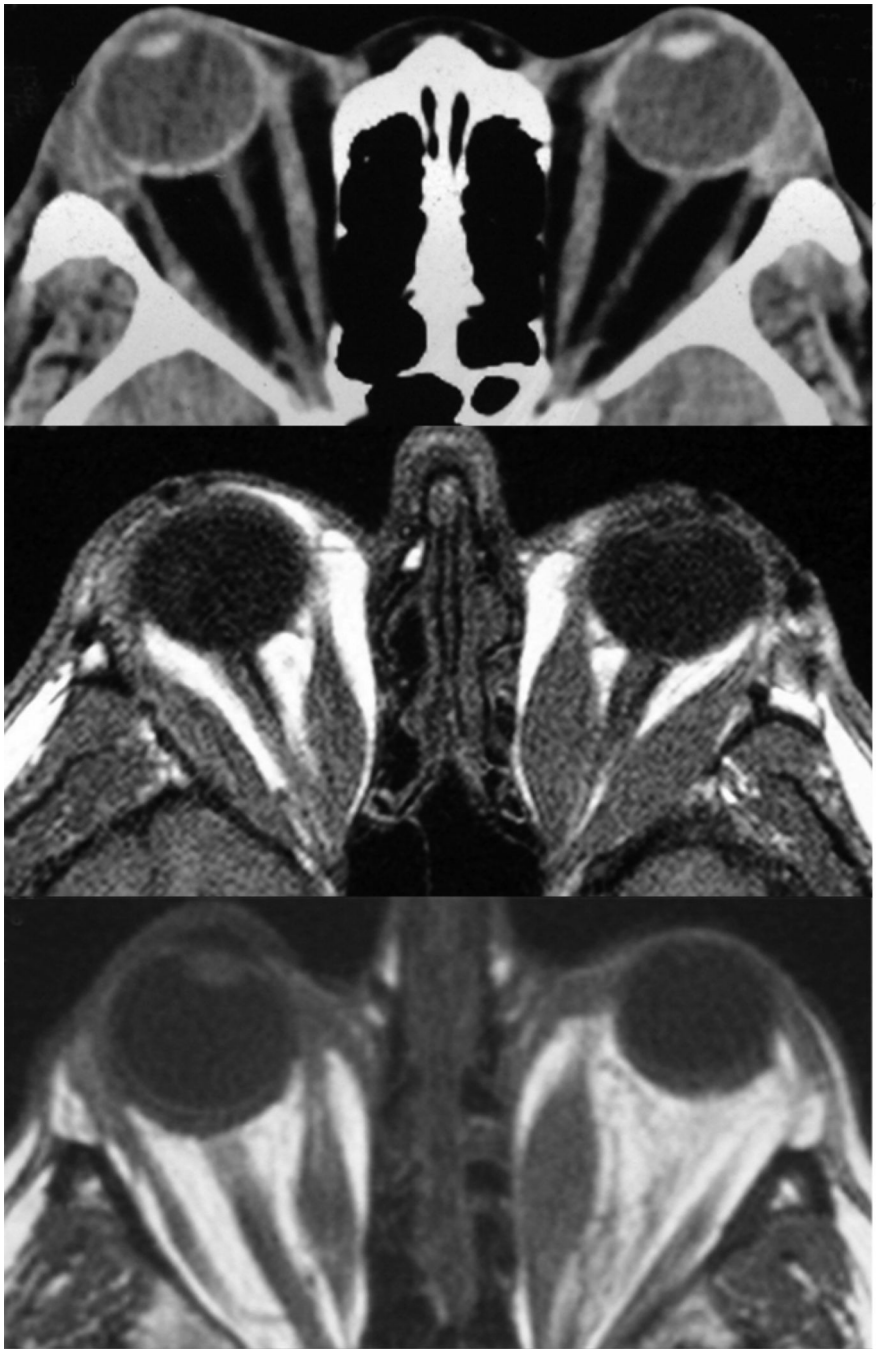

Figure 1.
The three predominant forms of soft tissue involvement in TED. Predominantly fat expansion (top), predominantly muscle enlargement (middle), or a combination of both (bottom).

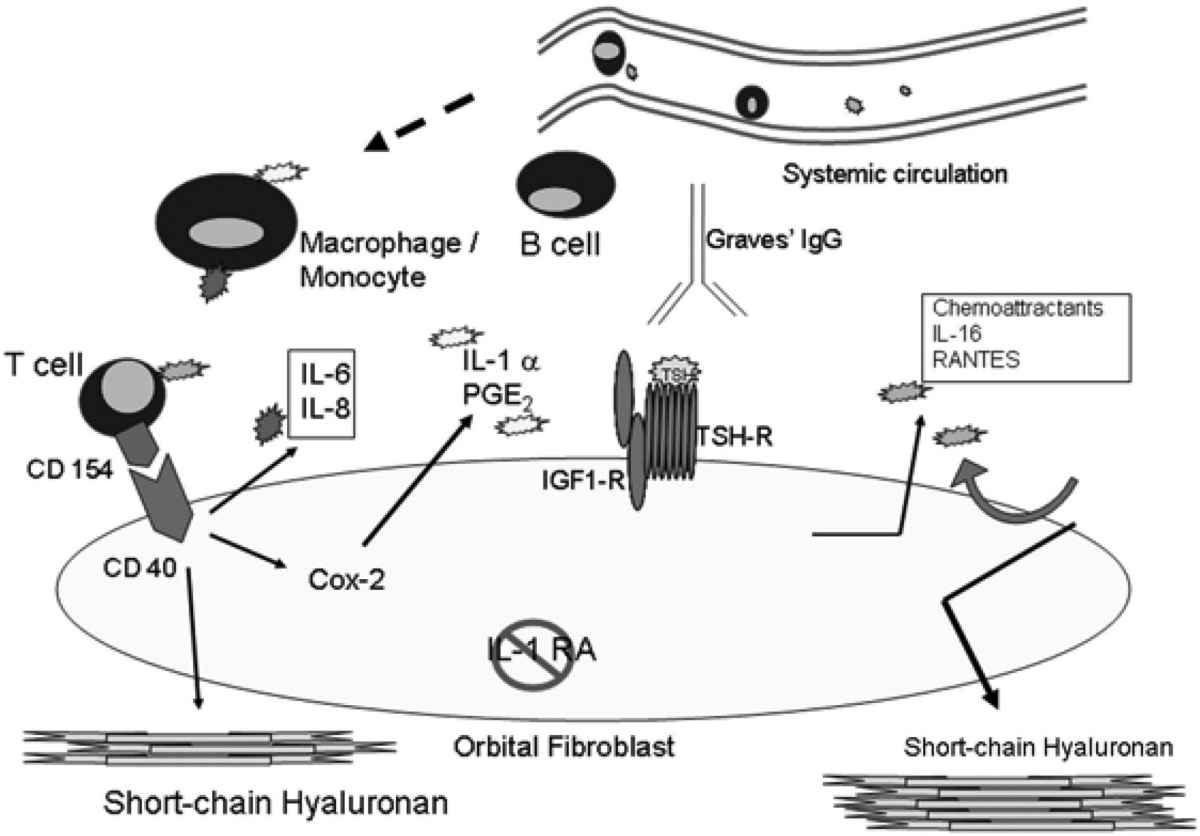

Figure 2.

Cartoon of our current model for the interaction between orbital fibroblasts and members of the professional immune system and the small molecules they produce. Chemoattractant molecules such as IL-16 and regulated on activation, normal T cell expressed (RANTES) are generated in response to Graves disease-IgG (GD-IgG) acting on the fibroblast. This in turn leads to the recruitment of T cells and other mononuclear cell members of the immune system. When activated, these cells produce a number of proinflammatory cytokines such as IL-1a, IL-1b, CD154 (CD40 ligand), and IL-6. Cytokines in turn activate proinflammatory genes such as those encoding prostaglandin endoperoxide H synthase-2 (PGHS-2), IL-6, IL-8, hyaluronan synthase (HAS), and UDP glucose dehydrogenase (UGDH). The major factor thus far identified as explaining the exaggerated responses to cytokines concerns the low levels of IL-1 receptor antagonist (IL-1RA) expressed by orbital fibroblasts. In addition, IL-4 and IL-13 induce 15-lipoxygenase exclusively in orbital fibroblasts from patients with GD, perhaps accounting for the different patterns of inflammation found in TAO.

Table 1

Immunotherapy for Thyroid Eye Disease

Therapy	Target Tissues	Agents
B-cell targeted therapy	Membrane proteins, Survival factors, or ligands	Eprantuzumab, Belimumab, Abatacept, LJP394
T-cell targeted therapy	CTLA4	CTLA4 Immunoglobulin
Cytokine mediated therapy		Etanercept

Table 2

B Cell–Targeted Agents in Autoimmune Disease.

Agent	Target	Target characteristics	Mode of action
Rituximab	CD-20	Membrane protein	Cytolysis through antibody dependent cellmediated cytotoxicity, complement, and=or apoptosis
Eprantuzumab DT2219	CD-22 CD-19 and CD-22	Membrane protein Membrane proteins	Cytolysis with or without agonist is inhibitory Cytolysis through immunotoxin bispecific binding to CD19 and CD22
Belimumab TACI-immunoglobulin	BAFF BAFF and APRIL	B-cell survival factor B-cell survival factors	Sequestration and=or neutralization Sequestration and=or neutralization
Abatacept	CTLA4-immunoglobulin	Negative cell-surface costimulatory ligand	Modulation of costimulatory pathways
LJP394	BCR	Cell-surface ligand	Antigen decoy to induce tolerance