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The Pathophysiology of Thyroid Eye Disease (TED): Implications for Immunotherapy

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Abstract

Purpose of Review—Thyroid eye disease (TED) is a poorly understood autoimmune manifestation most commonly associated with Graves' disease. Current nonspecific treatment paradigms offer symptomatic improvement but fail to target the underlying pathogenic mechanisms and thus, do not significantly alter the long-term disease outcome. The purpose of this review is to provide an update of the current understanding of the immunopathogenesis of TED and explore these implications for targeted immunotherapy.

Recent Findings—Orbital fibroblasts are integral to the pathogenesis of TED and may modulate immune responses by production of cytokines and hyaluronan in response to activation of shared autoantigens including thyrotropin receptor (TSHR) and insulin-like growth factor-1 receptor (IGF-R1). Fibrocytes share many of these phenotypic and functional features, suggesting a link between systemic and site-specific disease. Use of targeted immunotherapies in TED is limited, though data from the use Rituximab (RTX), a B cell depleting agent, are encouraging. Sustained clinical response has been seen with RTX in several reports, despite return of peripheral B cell levels to pretreatment levels. Additionally, this response appears to be independent to cytokine and antibody production, suggesting possible modulation of antigen presentation as a mechanism of its effect.

Summary—Progressive advances in the understanding of the immunopathogenesis of TED continue to spur clinical trials utilizing targeted immune therapies. Continued understanding of the molecular mechanisms of disease will expand potential treatments for TED patients and obviate the need for reconstructive surgical therapies.

Keywords

Thyroid eye disease; Graves' disease; fibrocytes; Insulin-like growth factor -1 receptor (IGF-1R); thyrotropin receptor

Introduction

Thyroid eye disease (TED), also known as thyroid associated orbitopathy, is most commonly a manifestation of the systemic autoimmune process known as Graves' disease (GD). This process affects the thyroid gland, pretibial skin and orbit. TED is most commonly associated with hyperthyroidism, however patients may be hypothyroid or euthyroid. Ophthalmic manifestations are present in up to 50 percent of patients with GD, and patients most commonly present in the 3rd to 5th decade of life with women more commonly affected [1]. TED may precede or follow endocrinologic manifestations, however they typically present within 18 months of each other [2]. Ophthalmic manifestations

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include periorbital edema and erythema, eyelid retraction, proptosis, restrictive strabismus, chemosis, increased intraocular pressure, exposure keratopathy and rarely, reduced vision from corneal ulceration or compressive optic neuropathy. The disease has been divided into active and stable phases, with the active phase lasting between 6 months and 2 years. The term “active disease” implies activation of the *immune system* but the association is poorly understood. It may be more appropriate to characterize the clinical manifestations as clinically “progressive” rather than active.

Supportive ophthalmic management is generally indicated for mild orbitopathy, and consists of ocular surface lubrication and prismatic correction of binocular diplopia. With moderate or severe disease, or in cases with reduced vision from compressive optic neuropathy, treatment with corticosteroids, orbital irradiation, or orbital decompression is indicated. Since extraocular muscle and orbital tissue expansion do not regress as disease progresses, rehabilitative surgery is generally instituted once patients enter the chronic or stable phase of the disease. Surgical interventions are typically approached in a staged fashion. When indicated, orbital decompression is performed, followed by strabismus surgery and then eyelid surgery.

Since the molecular underpinnings of TED have been poorly understood, available therapies are nonspecific and target the symptomatic manifestations of progressive disease. Recently the success of immune modulating therapies for allied autoimmune diseases and increased understanding of TED pathogenesis has spurred introduction of these therapies for patients with TED. The ultimate goal of these efforts is to alter the natural course of disease and in turn, reduce the likelihood of sight-threatening complications and obviate the need for surgical rehabilitation. These therapies may also impact health-related quality of life by preventing facial disfigurement and improving ocular function [3-5]. Ultimately, our ability to prevent progression of disease may significantly improve patients’ health-related quality of life.

Pathophysiology of TED

The proximate cause for hyperthyroidism in GD is secondary to activating autoantibodies to TSHR. However, TED can present independent of GD, endocrinologic manifestations or autoantibody formation. Generation of activating antibodies against the TSHR correlates with TED severity, but there is currently no evidence to indicate that autoantibody production is the cause of ophthalmopathy. It appears that the underlying molecular mechanism of TED is far more complex, comprising both environmental and genetic factors. Several genes with immunologic underpinnings are likely central to the process including human leukocyte antigen, cytotoxic T-lymphocyte-antigen 4 (CTLA-4), CD40, and PTPN22 [6-8]. On a cellular level, the interplay of the innate, humoral and cell-mediated immune systems with site-specific fibroblast function may offer potential insights to the process.

Clinically defined autoimmune disease may arise from antigen specific (autoimmune) and/or antigen-independent (autoinflammation) immune activation. Antigen presenting cells such as B cells, dendritic cells, and macrophages, recognize and present antigens in a context that leads to specific recognition by T and B lymphocytes. Aberrations in this process can lead to autoimmunity targeting specific antigens (i.e. TSHR). Humoral and cell mediated antigen-specific immunity is a recent teleological advancement and affords life-long immunologic responses. In contrast, antigen-independent inflammatory responses are typically mediated by conserved bacterial proteins, cytokines and/or chemokines leading to activation and recruitment of effector immune cells, including monocytes, NK cells and granulocytes. The innate immune system is teleologically conserved in mammals, birds and reptiles

comprising the earliest defense against common pathogens. Both antigen specific and autoinflammatory mechanisms are likely required for the clinical manifestations of TED. The active phase of TED is characterized by infiltration of orbital tissues by immune cells, in particular T lymphocytes, mast cells and B lymphocytes [9]. It is unclear whether the *primary* inciting events of TED are antigen dependent or independent, however the production of autoantibodies to the TSHR implicates both humoral and cell mediated immunity.

The explanation for anatomic site-specific manifestations of GD remains uncertain. Fibroblasts appear to be a principal immune target underlying orbital involvement, possibly as a consequence of autoantigen expression, cytokine production and secretion of extracellular matrix. Shared autoantigens from the orbital fibroblasts including TSHR and IGF-1R have been detected on their surface. Activating autoantibodies to the TSHR, called thyroid-stimulating immunoglobulins, drive overproduction of thyroid hormones by thyroid follicular cells [10], while antibodies that bind to the IGF-1R have also been shown to stimulate cytokine production and extracellular matrix [11]. Shared epitopes of these receptors may be critical determinants of the disease process especially since the TSHR and IGF-1R form physical and functional interactions on fibroblasts from GD patients [12].

Orbital fibroblasts from donors with TED have a distinct phenotype and functional capacity compared to orbital fibroblasts from healthy donors [13, 14]. TED fibroblasts also uniquely express several potentially important inflammatory molecules, including CD34, CD40, and many cytokines [15-17]. Bone marrow-derived fibrocytes share many of these phenotypic and functional features with TED orbital fibroblasts and may provide the critical link between the systemic immune response and site-specific disease [18]. Fibrocytes are bone marrow derived and migrate to sites of injury, where they provide antigen-specific T cell stimulation, promote wound healing, and drive fibrosis. During this process, they maintain fibroblast-like morphology [19] and have the capacity to differentiate into myofibroblasts or adipocytes. Fibrocytes are present in increased number when PBMCs are cultured from the circulation of GD patients and can be identified in orbital tissues from individuals with TED. Fibrocytes are absent in healthy orbital tissues [18]. These data suggest that fibrocytes infiltrate orbital tissues in TED mediate inflammation and fibrosis [18]

Fibrocytes have not been previously implicated in antigen specific immune responses. However these cells demonstrate increased expression of TSHR, which was comparable to the levels on thyroid epithelial cells, and when ligated resulted in up-regulation of TNF-α and IL-6 cytokine production [18]. This data suggests that display and possibly binding of the TSHR by TSH or activating antibodies could promote the disease, further implicating the involvement of fibrocytes in TED.

Immunotherapy

Treatment of patients with TED using corticosteroids or other immune modulating therapies has historically been reserved for those with moderate to severe, active disease. As our knowledge of the immunopathogenesis of TED grows, as well as our experience with targeted immunotherapies, there will likely be a paradigm shift in the management of TED patients. Integral to this is the early recognition of patients at risk for progression to moderate or severe disease, allowing for the institution of treatments in early stages that may alter disease course. Much work is being done in this regard, by investigating potential biological markers or clinical indicators that are predictive of disease progression and severity. Examples of this stepwise approach to identify and treat at-risk patients can be seen in other allied autoimmune disorders such as rheumatoid arthritis [20]. The administration of

therapeutic interventions should only be performed if a suitable risk to benefit ratio exists, particularly in early stages when disease manifestations are mild.

Antioxidants

The results of a recently published randomized, double-blind, placebo-controlled trial to determine the effects of selenium and pentoxifylline in patients with mild TED revealed significant improvement in the selenium-treated group in terms of quality of life, reduced progression of eye disease, and improvement in CAS. Patients were treated either one of the two agents or placebo daily for 6 months, and the effect in the selenium group was sustained at 1 year[21].

Corticosteroids

Oral or intravenous corticosteroids have been the mainstay of treatment for patients with severe, acute disease, particularly if vision threatening [22]. However, they are not without significant side effects, including cushingoid features, hypertension, hyperglycemia, weight gain, changes in mood and osteoporosis. While use of intravenous corticosteroids may have reduced side effects as compared to oral corticosteroids, both should be used with caution and close monitoring. Some patients, such as those with uncontrolled diabetes, may be poor candidates for high dose corticosteroid use and others may be intolerant to their side effects. In addition, there remains no consensus regarding the dose or length of treatment with corticosteroids, and prospective studies are ongoing to elucidate the optimal dose of intravenous corticosteroids in patients with moderate to severe TED.

Anticytokine Therapy

Advances in the understanding of TED immunopathogenesis has led to emergence of studies using agents that specifically target B and T lymphocytes, cytokines, and other cell signaling intermediaries [23-29]. Cyclosporin inhibits T cell activation by blocking the function of the enzyme calcineurin and reducing transcription of IL-2. It has been studied both as a single agent and in combination with corticosteroids, and the combination demonstrates improved efficacy compared to either treatment alone [30-32]. A comparison study between the two classes of medications, however, has yet to be performed.

Specific anticytokine therapies, including TNF- α targeting agents, have been evaluated in TED patients. In one recent series of 10 TED patients recieiving Etanercept, a recombinant human soluble TNF-α receptor fusion protein, there was improvement of the clinical activity score (CAS) and severity of TED during the treatment phase. However 3 patients developed exacerbation of inflammation when the drug was discontinued [24]. Two case reports describe beneficial effects of infliximab, a monoclonal antibody against TNF-α, in TED patients [25, 26]. In the first, near complete resolution of inflammation was observed within 72 hours followed by improvement in visual acuity and color vision over the subsequent week [25]. In another, a single dose of infliximab improved inflammatory signs [26]. While these reports show some potential benefit to anticytokine therapy, no randomized controlled trials have been performed. In addition, the side effects of these agents including risk of infection and neoplasms due to depression of normal immune responses must be considered [33]. Other anticytokine therapies including IL-6 receptor blockers and IL-1 inhibitors have been studied in patients with rheumatoid arthritis and other autoimmune inflammatory disorders, but have not yet been used in TED patients [34, 35].

T Cell Targeting Therapy

T cell depletion represents a potential target for TED treatment, based on the diverse immunologic roles of this lymphocyte subclass. Anti-CD3 antibodies that bind to the TCR

complex have been used to down-regulate pathogenic CD4+ T cell activity, and appear to have some efficacy in improving glycemic control in type 1 diabetes mellitus [36, 37]. In addition, anti-CD3+ antibodies may enhance T regulatory cell (Treg) function, and have been shown in an experimental mouse model of autoimmune uveitis to inhibit disease progression and prevent recurrence [38]. CTLA-4 is a regulator of T lymphocyte activation which inhibits T cell responses [39, 40]. Antibodies against CTLA-4 may interrupt T cell activation by blocking its interaction with CD80 and CD86 on antigen presenting cells, resulting in T cell anergy. This therapy has been shown to be promising in the treatment of autoimmune disorders such as multiple sclerosis and rheumatoid arthritis [41, 42]. Other potential therapeutic targets of T cell activation which are yet unexplored in TED patients include the CD40-CD40L, CD80 and CD86 pathways.

B Cell Targeting Therapy

RTX is an anti-CD 20 chimeric humanized monoclonal antibody which depletes mature B cells. Plasma cells are not directly affected by RTX, since they do not express CD20. The rationale for the use of RTX as a clinical treatment of TED includes the depletion of B cells, subsequently altering antigen presentation and cytokine production. In addition, studies have demonstrated that B cell deficient mice are unable to generate T cell responses following immunization with TSHR, indicating their critical role in the initiation of autoimmune thyroid disease [43, 44]. Though plasma cells and thus antibody production are not directly affected, antibody-mediated responses are attenuated by blocking cytokine production and antigen presentation.

One recent prospective study of 12 patients reported reduction in the clinical activity score (CAS) in patients with moderate-to-severe TED treated with RTX at dosages used in the treatment of rheumatoid arthritis (2 doses of 1g, 2 weeks apart) [27]. This improvement was seen at 1 month, and sustained at 1 year of follow up [27]. No infusion reactions or adverse events were noted in this series [27]. Of further interest was the lack of recurrence of active disease during the follow up interval, despite persistently elevated TSI and stabilization of B lymphocyte levels in the peripheral blood, indicating that RTX may confer long-term effects that are not directly related to humoral reactions. Vannucci *et al* analyzed the effects of RTX in 10 patients receiving a similar dose of RTX, and demonstrated no significant effect of RTX on thyroid autoantibodies [45]. In addition, production of IL-6 and its soluble receptor (sIL-6R) was unchanged in response to RTX, suggesting that its effect in TED may be related to inhibition of B cell antigen presentation rather than humorally or cytokine mediated responses. In another retrospective review of 6 patients with severe, progressive TED unresponsive to corticosteroids, rapid and sustained resolution was seen following treatment with RTX [29]. Proptosis and strabismus, however, were unimproved [29]. A previous report of 9 patients, of which 7 had active disease, reported statistically significant improvement in CAS, NOSPECS grade and proptosis [28]. Response to therapy in this series was related to initial peripheral B cell depletion, and no patients had recurrence of active disease at 1year follow up despite return of peripheral B cells levels after 4-5 months [28]. Analysis of the side effect profile of RXT in 10 patients receiving the drug revealed adverse effects in 3 patients and gastrointestinal symptoms in 2 patients [46]. Of the 3 patients with adverse effects, 2 developed serum sickness-like reactions within 2 weeks of the first infusion, one of which also developed low-grade colon inflammation and iritis [46]. A third developed systemic polyarthritis and ulcerative colitis [46]. While past and present experience with RTX remains encouraging, there has yet to be any randomized controlled trials to clearly delineate the efficacy of RTX in a standardized fashion, or to establish effective treatment dosages. Adverse effects, though not common according to published literature, have been demonstrated, indicating the judicious use of RTX in select patients

with moderate to severe active disease who may be intolerant or poorly responsive to conventional therapy.

Autoantigen Targeting Therapy

Both TSHR and IGF-1R have been implicated in the pathogenesis of TED, and recent studies suggest these receptors co-localize and form functional complexes [12]. Stimulation of the IGF-1R with IGF-1 or GD-IgG has been shown to increase production of IL-6 and RANTES, as well as hyaluronan (HA) [11, 47, 48]. Consequently, it is reasonable to assume that disruption of the IGF-1R signaling pathway may ameliorate disease by reducing the production of pro-inflammatory cytokines and HA. Figitumumab (CP-751,871) is a blocking anti-IGF-1R antibody currently undergoing phase III clinical trials in patients with non-small cell lung cancers, and IMC-A12 (Imclone), a human monoclonal antibody against IGF-1R, which has also shown promise in the treatment of other IGF-1R bearing neoplasms [49, 50]. Their use in the treatment of TED has yet to be evaluated.

Conclusion

Thyroid eye disease is a complex autoimmune disorder that may result in significant ocular morbidity. Established treatment paradigms, while successful in addressing disease manifestations, do not ultimately alter the course of the disease. Expanding knowledge of the immunopathogenesis of TED has led to the use of novel treatments that have shown some promise in patients who are otherwise poor candidates or resistant to established therapies. As experience with these treatment modalities increases, further studies to assess the short and long term efficacy, weighed against potential adverse effects, will be critical. Parallel to these efforts, identification of patients who are at risk for progressive, severe disease may guide the early use of these targeted immunotherapies in the future.

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Key Points

- Both antigen-specific and antigen-independent pathways play important roles in the pathogenesis of TED.
- Emerging reports reveal that B cell depletion with Rituximab may provide sustained clinical effects in reducing severity of TED, and this response may be independent of antibody or cytokine production
- Prospective trials evaluating the efficacy of targeted immune therapies, weighted against their side effect profiles, are needed to further refine their use in TED patients.