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Rationale for therapeutic targeting insulin-like growth factor-1 receptor and bone marrow-derived fibrocytes in thyroid-associated ophthalmopathy

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Summary

Development of medical therapy for thyroid-associated ophthalmopathy has lagged behind that for many other autoimmune diseases, in large part because its pathogenesis has not been understood. Recent insights into the nature of the main target of the disease, orbital connective tissues, have led to a greater understanding of how and why this ocular manifestation of Graves' disease might occur. Emerging from this work are the identities of potential drug targets. We believe that these findings will help pave the road toward an acceleration of therapy development.

Keywords

ophthalmopathy; autoimmune; Graves' disease; orbit; immunity

Introduction

Clinical management of thyroid-associated ophthalmopathy (TAO) fails to offer definitive medical therapies that reliably and unambiguously benefit patients with moderate to severe disease. A major barrier to the development of better drugs is the uncertainty surrounding its pathogenesis and the details underlying the development of its parent malady, Graves' disease (GD). Recent insights into how the disease might occur have now set the stage for progress in diminishing the severity and altering the natural course of TAO, thus potentially reducing the need for surgery aimed at rehabilitating disfigurement and visual impairment.

Identifying the insulin-like growth factor-1 receptor (IGF-1R) as a participant in TAO

IGF-1R is a tyrosine kinase receptor that mediates the actions of IGF-1, a factor critical to normal growth and development (1). Many years ago, the pioneering work of Ingbar and his colleagues revealed a synergistic relationship between IGF-1 and thyrotropin (TSH) and its

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receptor (TSHR)(2). This interplay between the TSHR and IGF-1R has been characterized subsequently by several different laboratory groups, including our own (3–5). Connecting GD and TAO to the IGF-1 pathway came considerably later when Kendall-Taylor and her colleagues demonstrated that antibodies from patients with TAO could displace radiolabeled IGF-1 from unidentified binding sites on orbital fibroblasts (6). These relationships prompted our research group to inquire whether IGF-1R and TSHR might share some physical and functional relationships. Initially we found that IGF-1R was over-expressed in orbital fibroblasts derived from individuals with TAO (7). Antibodies circulating in the sera of these patients were found to induce the expression of two powerful chemokines that target T cells. Further, they confirmed that these antibodies could displace IGF-1 binding directly to IGF-1R rather than to one of the several known IGF-1 binding proteins. GD-specific antibodies were also found to induce hyaluronan accumulation in orbital fibroblasts, effects which could be attenuated by an IGF-1R blocking antibody (8). Subsequent studies have revealed that TSHR and IGF-1R form a physical and functional complex in orbital fibroblasts and thyroid epithelial cells. They revealed that IGF-1R functions as a critical molecular conduit for mediating certain components of the signaling downstream from TSHR (4). Besides orbital fibroblasts, T lymphocytes were found to over-express IGF-1R (9) while IGF-1R$^+$ B cells become more numerous in GD (10). Thus, alterations in IGF-1R expression and activities were implicated in GD and TAO using a variety of different investigative strategies. It thus seemed to us that this pathway and its interface with TSHR might prove to be a therapeutic target.

Realization that bone marrow-derived fibrocytes infiltrate the orbit in TAO

Among the earliest observations made when orbital fibroblasts were first examined in the laboratory was that these cells exhibited marked heterogeneity and were particularly responsive to inflammatory cytokines (11). Their morphologies in monolayer were quite variable and agents that increase intracellular cAMP provoked substantial changes in their appearance (12). Initial studies of cell surface markers demonstrated two distinct populations of cells based on the expression of a glycoprotein CD90 (Thy-1) (13). More recently, subsets of orbital fibroblasts from individuals with TAO displayed CD34, a progenitor cell marker, as well as CXCR4 and collagen I whereas another population failed to exhibit cell-surface CD34 (14). In contrast, orbital fibroblasts derived from tissues of healthy donors were uniformly CD34$^-$. Because the CD34$^+$CXCR4$^+$Col1$^+$ phenotype strongly resembles that of circulating fibrocytes, peripheral blood mononuclear cells were interrogated for the abundance of these cells. Patients with GD were found to have substantially elevated numbers of these cells. Given the findings in animal models of fibrosis, it is likely that the CD34$^+$ orbital fibroblasts found in the TAO orbit derive from circulating fibrocytes.

Once we had substantial evidence that fibrocytes might be infiltrating the TAO orbit, we asked a fundamental question, namely what impact these cells might be imposing on the tissues they inhabit. For instance, it has long been suspected that the low level TSHR expression found in orbital tissues (15) and in orbital fibroblasts (16) might inform us about the target of antigen-dependent infiltration by T cells in TAO. Could fibrocytes and their derivatives account for the ectopic expression of TSHR in the orbit? In examining more closely the array of genes expressed by fibrocytes, we unexpectedly detected relatively high

levels of TSHR mRNA and abundant TSHR protein displayed on their surface (14). These levels were comparable to those found on thyroid epithelial cells. In contrast, TSHR was found to be expressed at substantially lower levels in orbital fibroblasts. In inventorying other thyroid related proteins that fibrocytes might express, we were surprised to detect the molecular medley necessary for thyroid hormone synthesis, including functional thyroglobulin, sodium/iodide symporter, and thyroperoxidase (17,18). In contrast these proteins were essentially undetectable in TAO orbital fibroblasts. We then postulated that if $CD34^+$ orbital fibroblasts were derived from fibrocytes, $CD34^-$ fibroblasts might be expressing an inhibitory factor(s) that suppresses the fibrocyte phenotype. To test this hypothesis, the mixed fibroblast population from TAO orbits was subjected to cytometric cell sorting into pure $CD34^+$ and $CD34^-$ subsets which were then re-cultured. The $CD34^+$ fibroblasts exhibited a remarkable phenotypic shift toward that of fibrocytes including the substantially increased levels of thyroid protein expression (17,18). Thus, these observations strongly suggest that residential $CD34^-$ produce a factor(s) that down-regulates the inflammatory phenotype associated with fibrocytes. Identifying its nature may provide important insights into the design of “smart” therapies for TAO.

How might we utilize the recent advances in understanding the pathogenesis of TAO to better serve patients with TAO?

Mapping out the underlying molecular and cellular events that underlie TAO is well and good. But do these insights provide a roadmap for the way forward as we strive to better treat our patients? The majority of drug candidates currently used or those under consideration for use in TAO are repurposed from other diseases. They have yet to be rigorously examined for efficacy, including corticosteroids. Newer biologics such as anti-CD20 monoclonal antibodies that target mature B cells have recently undergone pilot clinical trials involving single centers and have yielded divergent results (19,20). The emergence of greater insight into the immunological basis for TAO should inform the most promising targets. In the case of IGF-1R, the experimental evidence generated from basic laboratory studies resulted in the organization of a multicenter trial which is nearing completion. This study exams the impact of a fully human monoclonal antibody, teprotumumab, which specifically and efficiently blocks IGF-1R, on active, recent-onset TAO [http://clinicaltrials.gov/show/NCT01868997]. Studies conducted *in vitro* have established the efficacy with which this agent attenuates the induction by both TSH and TSI of the proinflammatory cytokines implicated in TAO (21,22). Future studies might involve inhibitors of fibrocyte differentiation or interrupting the chemokine pathways associated with their infiltration of orbital tissue. In any event, I believe that we are entering a new and promising era in the clinical care of this disease, one where treatment development is evidenced-based and targets aspects of disease pathogenesis that make sense.

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