Update on pathogenesis and immunology of Graves’ ophthalmopathy

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Abstract
Graves’ ophthalmopathy (GO) is an inflammatory autoimmune disorder of the orbital adipose tissue and extraocular muscles, and it is associated with Graves’ disease (GD). GO is triggered by binding and activation of orbital fibroblasts by autoantibodies (TSI) directed against thyroid-stimulating hormone receptor (TSHR) and insulin-like growth factor 1 (IGF-1R), which is highly expressed within the orbit. Moreover, interaction of T cells with orbital fibroblasts that involve T-cell receptor (TCR), autoantigen, and major histocompatibility complex class II (MHC II) molecule, as well as CD40:CD154 signalling, activates p38, ERK 1/2, and JNK pathways. These processes induce fibroblast activation, proliferation, and secretion of chemokines and inflammatory cytokines to maintain inflammation within the orbit. Furthermore, increased hyaluronic acid production and fibroblast differentiation into adipocytes and myofibroblasts leads to development of GO. The elevated number of molecular factors such as PDGF, IL1-β, IL-6, IL10, IL-8, IL-16, HGF, ICAM-1, osteopontin, CTLA-4, and TGF-β are discussed in the paper. Some of them are key markers of disease stage. Better understanding of GO pathogenesis leads to development of new therapeutic options.

Key words: Graves’ disease, Graves’ ophthalmopathy (GO), orbital fibroblast, thyroid-stimulating hormone receptor (TSHR), thyroid-stimulating antibodies (TSI).


Introduction
Graves’ ophthalmopathy (GO) is an inflammatory autoimmune disorder of the orbital adipose tissue and extraocular muscles. The critical clinical signs are retraction of upper eyelid and axial proptosis with variable restriction of eye movements (often extraocular muscles are involved). Conjunctival and corneal inflammatory complications may also occur. It is associated with Graves’ disease (GD) [1, 2].

A major role in the development of this condition is played by autoimmunity of T cells, B cells, macrophages, fibroblasts, and adipose tissue within the orbit. Cytokine-mediated inflammation in the orbit is also an important factor in its development [2]. The most common and important extrathyroidal manifestation of GD is GO [1]. In most cases, it occurs in patients with active or past hyperthyroidism but may rarely develop in patients who are euthyroid or even in a hypothyroid state [3]. About 50-70% of patients with GD have mild (or subclinical) symptoms, whereas 3-5% of patients show sight-threatening symptoms of significant GO with exophthalmos and pain [2, 4]. The latter represents an emergency requiring immediate treatment. Sight loss in those cases may be due to corneal ulceration or to dysthyroid optic neuropathy (DON), which occurs more frequently [5].

The estimated incidence of GO is 16/100,000 women and 3/100,000 men [6, 7].

The molecular mechanism of Graves’ ophthalmopathy
GD hyperthyroidism is caused by autoantibodies (GD-IgG) directed against thyroid-stimulating hormone receptor (TSHR). These autoantibodies activate the receptor and stimulate thyroid follicular hypertrophy, which leads to excessive hormone production [4]. The pathogenesis
of GO is not fully understood. TSHR is highly expressed within the orbit. This points out their potential role in the development of GO [4]. GD-IgG activation of TSHR on fibroblasts, preadipocytes, and adipocytes in the soft tissue of the orbit is considered as a major factor in the pathogenesis of GO. However, GD-IgG may also directly activate IGF-1 receptors (IGF-1Rs) on these cells and support development of GO [8, 9]. GD-IgG and insulin-like growth factor-1 (IGF-1) increase secretion of regulated on activation, normal T-cell expression and secretion (RANTES), and IL-16, which intensify T-cell migration into the orbit. T lymphocytes interact with orbital fibroblasts via a specific CD40:CD154 molecular bridge leading to fibroblast activation, proliferation, and differentiation into myofibroblasts and adipocytes [8-10]. Activated fibroblasts produce GAG in excess, undergo adipogenesis, and secrete pro-inflammatory cytokines including IL-1α, IL-1β, IL-6, IL-8, macrophage chemoattractant protein-1 (MCP-1), and transforming growth factor-β (TGF-β), to maintain inflammation within the orbit (Fig. 1). Molecular

GO is triggered by binding and activation of orbital fibroblasts by autoantibodies called thyroid-stimulating antibodies (TSI) directed against thyroid-stimulating hormone receptor (TSHR), which is highly expressed within the orbit. TSI and insulin-like growth factor-1 (IGF-1) increase secretion of Regulated on Activation, Normal T Cell Expression and Secretion (RANTES) and IL-16, which elevates T-cell migration into the orbit.

Helper T cells recognise TSHR peptides located on orbital fibroblasts and lead to the activation and ligation of TSHR by TSI. This process induces fibroblast activation, proliferation, and secretion of chemokines, inflammatory cytokines, as well as increased hyaluronic acid production and adipogenesis. Moreover, interaction of T cells with orbital fibroblast that involves T-cell receptor (TCR), autoantigen, and major histocompatibility complex class II (MHC II) molecule as well as CD40:CD154 signalling activates p38, ERK 1/2, and JNK pathways, leading to increased secretion of ICAM-1, NFκB, IL-6, IL-8, and MCP-1, as well as hyaluronan (HA) production, to maintain inflammation within the orbit. Activated orbital fibroblasts proliferate and differentiate into adipocytes and myofibroblasts. Adipogenesis is also induced by IL-1β through an increase of cyclooxygenase-2 (COX-2). IGF-1R, just like TSHR, can be activated by TSI via PI3K/ACT pathways, upregulating peroxisome proliferator-activated receptor-γ (PPAR-γ) expression differentiation and proliferation of adipocytes and accelerate adipogenesis. PDGF increases the TSHR expression on orbital fibroblasts and plays also an adipogenic role.

**Fig. 1.** Pathogenesis of Graves’ ophthalmopathy (GO)
Polymorphism of CTLA-4 gene may lead to autoimmune T-cell surface, is negatively correlated with these cells. One protein called cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), a member with T3 and T4 [25] occurs mainly in GO extraocular muscles, whereas IL-4 and IL-10, Th2-type cytokines, are expressed in orbital fat [14]. The duration of GO plays a role in the predominance of T-cell subsets. Th1 cells dominate in the active phase of GO, and Th2 cells in the late phase [15]. Higher levels of IL-1β, IL-6 [16], and IL-17 [17] are also observed in the active phase compared to the inactive phase. In patients with refractory GO, higher levels of IL-4, IL-6, and IL-10 are seen, compared to those seen in patients in remission [18]. Steroid treatment causes an increase in the level of IL-16 and a decrease of IL-8 [19, 20]. A role in the development of GO may also be played by IL-10 as well as IL-2 polymorphism [20]. The levels of interleukin 2 [21], IL-16 [22], and IL-33 [23] are elevated in the blood of GO patients compared to those of the controls. Serum IL-33 levels are positively correlated with T3 and T4, but they are negatively correlated with TSH [22]. Serum hepatocyte growth factor (HGF) is increased in GO patients compared to that in control subjects, as well as responses to efficient glucocorticoid treatment [19]. Intercellular adhesion molecule-1 (ICAM-1) and soluble vascular cell adhesion molecule-1 (sVCAM-1) are adhesion molecules that play a role in cell/cell or cell/extracellular matrix interaction, activation, and migration. They are increased in the blood of GO patients as compared to those in control patients. Their levels seem also to be responsive to the treatment [23]. Osteopontin [24, 25], a protein involved in inflammation, cell recruitment, cell adhesion, and remodeling, is considered to be involved in GO development. It is inversely correlated with TSH level and positively with T3 and T4 [25]. Another protein called cytotoxic T lymphocyte-associated antigen-4 (CTLA-4), a member of the immunoglobulin superfamily, which is found on T-cell surface, is negatively correlated with these cells. Polymorphism of CTLA-4 gene may lead to autoimmune diseases [26-28]. Moreover, HLA-B8, an MHC class I cell surface receptor, may be associated with GO development, but its role remains to be elucidated [29, 30]. In the orbital fat in smokers with GO elevated levels of IL-1β and IL-6 seem to be associated [31]. Transforming growth factor-β (TGF-β) and fibroblast growth factor (FGF) are elevated in the orbital fat of GO patients, and levels of these factors are correlated with the severity of the disease. Platelet-derived growth factor (PDGF) is probably the most important among all growth factors in the GO pathological events. It is overexpressed in orbital tissue of GO patients, which was observed in several studies [32-34], independently of the activity grade of GO. Specific isoforms of PDGF increase the TSH-R expression on orbital fibroblasts, amplifying the autoimmune response against TSH-R [32]. Drugs blocking PDGF signalling may be new therapeutic options [34, 35]. Some of the latest studies indicate that PDGF plays an adipogenic role by transforming orbital fibroblasts into adipocytes [36]. Adipogenesis is also induced by IL-1β through an increase of cyclooxygenase-2 (COX-2). It is an inflammation modulating enzyme and is anticipated to be a central element of the active phase of GO. Its mRNA and protein levels have been shown to be overexpressed in orbital fibroblasts of GO patients [37], and hyaluronic acid (HA) seems to be involved in its regulation. However, other studies did not confirm any modification of its expression [38]. TGF-β receptor, IGF-1, and insulin-like growth factor binding protein-6 (IGB-6) seem to be downregulated [39].

Contact of T-cell receptor with major histocompatibility complex class II (MHC II) molecule and CD40:CD154 signalling leads to proliferation of orbital fibroblasts. Proliferation of orbital fibroblasts may be inhibited by blocking antibodies to MHC II, CD40, and CD40 ligand (CD154). IFN-γ mediated through Jak2 upregulates expression of CD40 in orbital fibroblasts [16]. Ligation of CD40 with CD154 leads to increased secretion of intercellular adhesion molecule-1 (ICAM-1) [17] and nuclear translocation of nuclear factor-κB (NF-κB) [40], IL-6, IL-8, and MCP-1 in GO orbital fibroblasts compared with normal controls [41]. CD40 upregulates IL-1α secretion, and HA and PGE2 synthesis [42]. Ligation of CD40:CD154 induces all three mitogen-activated protein kinase (MAPK) pathways, p38, ERK1/2, and JNK, which are engaged in gene expression, cellular proliferation, differentiation, and apoptosis.

ICAM expression is mainly P38 MAPK and NF-κB dependent, whereas ERK1/2 and JNK also activate the NF-κB pathway, a transcription factor pathway that regulates genes involved in immune and inflammatory responses [43].

**Orbital fibroblasts**

Orbital fibroblasts have some unique features, including their strong response to cytokines [44], and high levels of inflammatory mediators such as prostaglandins [42, 45-47], lipoxigenase products [48], and chemokines [49]. This may be the background of clinically aggressive GO. They produce a diverse array of both Th1 and Th2 cytokine types [50, 51]. Orbital fibroblasts express all three isozymes of hyaluronan synthase [52] and the upstream enzyme, UDP-glucose dehydrogenase [29, 30]. Those en-
zymes are involved in the biosynthesis of the glycosaminoglycan and hyaluronan. Orbital fibroblasts, especially those from patients with GO, consist of heterogeneous cell populations and are divided into subsets based on the display of the glycoprotein Thy-1 [44, 53, 54]. In regard to the expression of this surface marker, cells can differentiate into mature adipocytes (Thy-1+) and those that can eventually form myofibroblasts (Thy-1+). Thy-1 expression may be, at least in part, responsible for expansion of the orbital connective tissue contents and its extensive fibrosis. However, many studies conducted in order to characterise orbital fibroblasts neglected their phenotypic and functional diversity.

Douglas et al. explored the cellular makeup of the orbit in GO [55]. They identified the increased levels of a subset of circulating CD34+ cells that infiltrate the orbit in GO and express high levels of functional TSHR. Fibrocytes are CD34+ cells that derive from the bone marrow. Normally, fibroblasts inhabiting orbital connective tissue are uniformly CD34-. Fibrocytes in GO appear to partially replace the fibroblasts. They can differentiate into either fat cells or myofibroblasts, which may be responsible for tissue remodelling patterns found in GO [55]. It seems that fibrocytes also infiltrate the thyroid in GD and may be an important link between the orbit and the thyroid.

TSHR

TSHR plays a major role in the hyperthyroidism associated with GD. However, the role of the stimulatory antibodies directed against TSHR, often referred to as thyroid-stimulating antibodies (TSI or TSAb), in initiating or sustaining orbital tissue remodelling in GO has not been well established yet. A lot of circumstantial evidence suggests that TSHR and TSAb may be involved. General correlation appears to exist between levels of TSAb and the severity and activity of GO [56-58]. Higher cell surface levels of TSHR are found in orbital tissues from active disease and are displayed by orbital fibroblasts from these patients, especially following induction of adipogenesis [59]. These findings generally support the participation of TSHR. Detection of TSHR mRNA in orbital tissues was first reported by Feliciello et al., who found the transcript in healthy tissues and those coming from GO [60].

Parmentier et al. accomplished molecular cloning of the TSHR gene [61]. They isolated a 4.9 kb cDNA encoding a 744 amino acid peptide. The receptor protein represents a classical seven-membrane spanning, rhodopsin-like, G-protein-coupled protein. Its structure has been solved with crystallisation studies by the laboratory group of Reese-Smith [62, 63]. TSHR is a family member of cell surface receptors that includes luteinising hormone (LH) and follicle-stimulating hormone (FSH) [64]. It comprises a multimeric structure [65, 66] with the ligand-binding site located in the amino-terminus [67]. One gene encodes the receptor, which is translated into a single peptide undergoing cleavage into constituent subunits connected by a disulphide bond. The extracellular TSHR domain is cleaved by a cell surface metalloproteinase, the identity of which remains uncertain [68]. This cleaved fragment is particularly immunogenic, and its characteristics are likely to proximally underlie generation of TSI. The multimeric structure of the TSHR drives affinity maturation of the pathogenic autoantibodies in GD.

Helper T cells recognise TSHR peptides, leading to their activation and ligation of TSHR by TRAb, which induces secretion of chemokines and inflammatory cytokines, adipogenesis, and increased hyaluronic acid production. Enhanced production of connective tissue results in extraocular muscle enlargement and orbital fat expansion [69] (Fig. 1).

Levels of TSI correlate with the severity and clinical activity of the disease [57, 58] and high TRAb levels in early GO predict a poor prognosis [59].

Many investigations provide data showing that TSHR mRNA and protein are detectable in both GO and normal orbital tissues and fibroblast cultures. However, considerably higher levels of TSHR are found in GO cells [69-71]. It has been also proven that levels of TSHR mRNA in GO orbital adipose tissue correlate with the activity of the disease, indicating a potential role of TSHR in the development of the disease [72].

Zhang et al. introduced bovine TSH or two different monoclonal TRAbs into normal and GO fibroblast cultures and demonstrated increased HA production in normal fibroblast cultures, but not in GO fibroblasts [73].

They also introduced an activating mutant TSHR into normal and GO orbital fibroblasts and observed enhanced adipocyte differentiation [73]. Nevertheless, transfecting GO orbital fibroblasts with an activating mutant TSHR leads to elevated HA production due to induction of hyaluronan synthases 1 and 2, compared with control transfected cells.

In another study, conducted by Kumar et al., of GO orbital fibroblasts treated with either bovine TSH or a potent stimulatory TSI (termed M22), elevated levels of cAMP, pAkt, and HA were found [74]. These effects could be blocked by co-treatment with a small molecule TSHR antagonist, termed C-1 [75]. Activation of this receptor leads to changes in the cellular characteristic of GO.

However, these associations between levels of anti-TSHR and disease activity/severity do not constitute proof of a causal relationship. Currently, a potential role of additional molecular determinants such as IGF-1R is being considered as a participant in the disease process [8].

The signalling downstream from TSHR is complex. It involves several distinct pathways known to crosstalk. Better apprehension of post-receptor signalling would allow identification of additional therapeutic targets. These include the potential role of proteins binding with TSHR.
Among these are the β arrestins [76, 77], versatile adaptor proteins that are involved in receptor internalisation and desensitisation, assisting receptor uncoupling from downstream targets, and facilitating receptor interactions with clathrin-coated pits. β-arrestins are capable of protein complex formation, which is thought to be involved in the transduction of post-receptor signalling [76, 77].

Crosstalk between TSHR and IGF-IR

IGF-I and its cognate receptor, IGF-IR, are family members of a group of molecules that play critical roles in diverse biological functions such as growth, cellular metabolism, and immunity [78]. IGF-IR is a tyrosine kinase receptor that spans the plasma membrane and connects with several down-stream signalling pathways, taking part in the regulation of many target genes [79, 80]. Pritchard et al. noticed that GD-IgGs, but not those from healthy controls, could upregulate the expression of chemokines in orbital fibroblasts [81]. That study indicates that IGF-IR was over-expressed in orbital fibroblasts from patients with GD. Moreover, the FRAP/Akt/mTOR/p70S6k pathway was involved in downstream signalling and the activation by GD-IgG of chemokine expression in orbital fibroblasts from these patients, including IL-16 and regulated on activation, normal T cell expressed and secreted (CCL5, RANTES) [82]. The specific antagonist 1H7 could attenuate activation by rTSH and IgGs of the downstream kinase Erk.

The same results could be achieved by transfecting cells with a dominant negative IGF-IR [81]. It has been many years since Ingbar et al. investigated the relationship between the TSHR and IGF-IR pathways. They found that IGF-I could enhance or abrogate certain actions of TSH in cultured thyroid epithelial cells [83]. However, the molecular basis for the interactions between the two pathways is still is still uncertain. Tsui et al. reported that TSHR and IGF-IR form a physical and functional complex in thyroid tissues, orbital fat, and in fibroblasts [60]. IGF-IR, just like TSHR, can be activated by TSI via PI3K/ACT pathways, upregulating peroxisome proliferator-activated receptor-γ (PPAR-γ) expression, differentiation, and proliferation of adipocytes and enhancing adipogenesis [84]. This same group found what appears to be a fragmentation of IGF-IR into polypeptide sequences containing the alpha and beta subunits [85]. IGF-IRβ co-localises with TSHR and seems to mediate the signalling initiated by TSHR, which leads to downstream activation of the Erk and FRAP/mTor/Akt/p70s6k pathways [60]. The actions of TSH, TSI, IGF-I, and GD-IgG can be attenuated with IGF-IR inhibiting antibodies. A confirmatory study of TSHR-initiated signalling on IGF-IR was conducted recently by Krieger et al. [86].

Teprotumumab, the fully human IGF-IR blocking antibody, is a newly developed therapy for GD and GO. This antibody has recently been evaluated for safety and efficacy in the treatment of moderate to severe active GO in a phase 2 double-masked, placebo-controlled, prospective, multicentre trial [67]. It has been shown to be capable of blocking the actions of IGF-1 and both TSH and pathogenic TSIs in bone marrow-derived fibrocytes in vitro [87]. There is still the unsolved issue of the potential for side effects. These can occur frequently because of the wide array of normal physiological function that this pathway is involved in regulating, including growth and metabolism. The structural similarities shared by IGF-IR and the insulin receptor make the selective modulation of each difficult but not impossible.

Newly developed molecules for directly interrupting TSHR function

Development of small molecules as cell-surface receptor antagonists can offer specific advantages as potential therapeutics. The inverse TSHR agonist NCGC00161856 inhibits in a competitive way basal and TSH-dependent cAMP generation in HEK-EM 293 cells [88]. The molecule is able to attenuate constitutive expression of TSHR, thyroperoxidase, thyroglobulin, and sodium iodide symporter in thyroid epithelial cells and is one of the first discovered small molecule reverse agonists for TSHR. It was also shown that the agonist could inhibit basal levels of cAMP, pAkt, and hyaluronan accumulation in orbital fibroblasts [89]. Other studies, also in orbital fibroblasts, have revealed that the antagonist NCGC00229600 could block the actions of TSH and M22, the monoclonal mAb TSHR agonist [90]. NCGC00229600 attenuated the increased cAMP generation provoked by M22 and TSH in orbital fibroblasts that had been differentiated into adipocytes.

Conclusions

Nowadays, anti-inflammatory treatment is mainly based on corticosteroids. Better understanding of GO pathogenesis leads to the development of new therapeutic options, e.g. biologic agents (rituximab, infliximab). There are some reports with small series of patients, in which biologic agents were used off-label. This approach showed some promising results. However, there is still much that needs to be investigated.

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