Autoimmunity in Graves' Ophthalmopathy: The Result of an Unfortunate Marriage Between TSH Receptors and IGF-1 Receptors?

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Context: The immunopathogenesis of Graves' ophthalmopathy (GO) is still incompletely understood. Attention has shifted from the TSH receptor (TSHR) to the IGF-I receptor (IGF-1R) as a major autoantigen. This review on the pathophysiology of GO focused on orbital fibroblasts and the question whether autoimmunity against TSHR or IGF-1R is primarily involved.

Evidence Acquisition: Relevant papers on GO were identified by a search on PubMed and scrutiny of their reference lists. In addition, abstracts presented on GO at the 14th International Thyroid Congress in 2010 in Paris, France, were read.

Evidence Synthesis: Orbital fibroblasts (OF) are recognized as the prime target cells of the autoimmune attack in GO. In early stages OF are undifferentiated with low TSHR expression and are stimulated to produce hyaluronan by cytokines (released by activated infiltrating T cells) and not by Graves' IgG. OF lacking the surface glycoprotein Thy-1 (not present in the muscle compartment) may differentiate into adipocytes, associated with increased TSHR expression. Graves IgG stimulate hyaluronan in differentiated OF mostly via non-cAMP signaling pathways for growth, which can also be activated via TSHR. The existence of IGF-1R stimulating antibodies in serum remains dubious. Autoimmunity against IGF-1R is also observed in rheumatoid arthritis and is not specific for Graves' disease. Expression of IGF-1R on T and B lymphocytes may contribute to autoimmunity against fibroblasts.

Conclusion: Autoimmunity against TSHR is most likely initiating the immune response in GO. Autoimmunity against IGF-1R is not specific for Graves' disease but may contribute to ongoing immune reactions. (***J Clin Endocrinol Metab*** **96: 2386–2394, 2011)**

The immunopathogenesis of Graves' ophthalmopathy (GO) remains intriguing. At an international symposium on GO in 1991, attendants were asked whether they thought the TSH receptor (TSHR) was likely the primary autoantigen responsible for GO: only four of the 150 participants answered yes. Opinions had changed at a GO symposium in 2009 also organized in Amsterdam: now most of the 200 participants favored a causal relationship between autoimmunity against the TSHR and GO, although at the same time not excluding a role for the IGF-I receptor (IGF-1R) as another involved autoantigen. What caused this substantial shift in judgment?

Undoubtedly the discovery of a functional TSHR on orbital fibroblasts (OF) changed people's mind. OF are now recognized as the prime target cells of the autoimmune attack in GO, as evident from several studies. First, retrobulbar CD8+ T cells from GO patients recognize autologous OF (but not eye muscle extracts) in a major histocompatibility complex (MHC) class I-restricted manner (1). Second, retrobulbar T cells from GO patients proliferate in response to autologous proteins from OF (but not from orbital myoblasts) (2). Third, OF proliferate in response to autologous T cells dependent on MHC class II and CD40-CD40L signaling (3). And fourth, human leu-

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Abbreviations: GAG, Glycosaminoglycan; GO, Graves' ophthalmopathy; HA, hyaluronan; HLA, human leukocyte antigen; IGF-1R, IGF-I receptor; MHC major histocompatibility complex; OF, orbital fibroblast; PPAR, peroxisome proliferator activator receptor; rhTSH, recombinant human TSH; TBII, TSH-binding inhibitory immunoglobulins; TSHR, TSH receptor; TSHR-Ab, TSHR antibody.

kocyte antigen (HLA)-DR expression is observed on interstitial cells including OF but not on eye muscle fibers (4). Consequently, the autoimmune reaction in GO is directed primarily against OF and not against eye muscle cells (5).

This view is in line with the histopathology of GO, showing an increased amount of fibroblasts and ground substance in the endomysial space and the connective/adipose tissue; there is no increase in number of muscle fibers and no ultrastructural damage to muscle cells except in very advanced cases. Autoimmunity against eye muscle antigens (*e.g.* the occurrence of calsequestrin antibodies) (6, 7) is likely a secondary response to tissue destruction and release of sequestered proteins. The characteristic swelling of extraocular muscles and orbital fat/connective tissue is due to inflammatory edema and accumulation of glycosaminoglycans (GAG), hydrophilic compounds that osmotically attract and bind large amounts of water. Orbital GAG content in GO (predominantly chondroitin sulfate and hyaluronan) is about 70% higher than in controls (8) and contributes greatly to volume expansion. OF are thus also important effector cells in GO, capable of substantial hyaluronan secretion via up-regulation of specific hyaluronan synthases upon appropriate stimulation, *e.g.* by proinflammatory cytokines like IL-1β (9, 10). In the 1990s a full-length functional TSHR was detected on OF, confirmed by several groups (11–13). Expression of the TSHR was also found on fibroblasts in areas of pretibial myxedema (13, 14). The findings were met with great enthusiasm because it provides, by assuming cross-reactivity between thyroidal and orbital/pretibial antigens, an attractive unifying hypothesis for the various phenotypic appearances of Graves' disease, including its extrathyroidal manifestations as well as Graves' hyperthyroidism (15).

Another important development in the last decade originates from a continuing series of often fascinating studies by Smith and coworkers (see below). They suggest involvement of the IGF-1R as a second major autoantigen in GO. Therefore, I will focus on the evidence for and against a role of TSHR and IGF-1R autoimmunity in the immunopathogenesis of GO.

TSHR as autoantigen in GO: *in vivo* studies

The last decade has seen a number of clinical studies all indirectly supporting the hypothesis that autoimmune reactions against the TSHR are the prime cause of GO:

- The prevalence of GO in untreated patients with Graves' hyperthyroidism increases with higher TSH-binding inhibitory immunoglobulins (TBII) levels in a dose-dependent manner, from 14% at TBII 2–10 U/liter or greater to 38% at TBII greater than 40 U/liter (16).
- TSHR antibodies (TSHR-Ab) can be detected in the serum of the vast majority if not all patients with euthyroid GO (17).
- TSHR-Ab (both TBII and thyroid stimulating immunoglobulins) are directly related to the severity and activity of GO (18–20).
- TSHR-Ab have prognostic value for the course of GO, higher levels being associated with worse outcome (21).
- TSHR-Ab rise by 70% in the first 6 months after 131I therapy of Graves' hyperthyroidism, providing a plausible biologic mechanism for the increased risk of developing or worsening of GO after radioiodine treatment; in contrast, TSHR-Ab fall after antithyroid drugs or thyroidectomy, not associated with increased risk of GO (22, 23).
- TSHR expression in orbital fat/connective tissue is higher in the active stage than in the inactive stage of GO, directly related to IL-1β (24).

These studies provide strong circumstantial evidence but no proof that GO is caused by TSHR autoimmunity. As Tweedledee said, "If it was so, it might be; and if it were so, it would be; but as it isn't, it ain't. That's logic."

Evidence against a role of TSHR could be the absence of a single convincing case of neonatal GO, whereas neonatal autoimmune hyperthyroidism due to transplacental passage of TSHR-Ab does happen. One could argue that exposure time to TSHR-Ab *in utero* is too short or that activated T cells are likely the primary mediators of the immune response in the orbit (see below), and T cells do not cross the placenta. The postulated exophthalmos in two newborns with severe congenital hyperthyroidism due to activating germline TSHR mutations is dubious: proptosis in one case was 16 mm at 10 yr of age (25), and in the other case, the suggestion of proptosis (which was slight and not quantified) might have been raised by the upper eyelid retraction (26). But also immunization against the TSHR, which is successful in producing autoimmune hyperthyroidism, has so far failed to induce clinical features of GO in experimental animals, although infiltration of orbital fat with macrophages and lymphocytes is observed (27, 28). However, the orbit of rodents is different from men: the lateral wall is not made of bone but consists of a connective tissue septum. In humans, the immune response causes tissue swelling, intraorbital pressure rises in view of the bony surroundings of the orbit, and mechanical trauma then aggravates the immune response, resulting in further swelling *etc.*, aptly called the cycle of disease (29). The contribution of mechanical trauma is supported by the appearance of Graves' dermopathy not only in the pretibial region but also in other areas of the body when subjected to increased pressure of trauma (30,

31). In rodents the structure of the orbit may hamper the development of GO.

TSHR as autoantigen in GO: *in vitro* studies

It is rather easy to isolate OF from fat/connective tissue samples obtained during orbital surgery, and cultured human OF are used widely to elucidate further GO pathogenesis. A subset of OF, called preadipocytes, can be induced by specific culture media to differentiate into mature adipocytes; this process of adipogenesis, also stimulated by IL-1β and IL-6, is associated with increased expression of TSHR on OF, both at mRNA and protein levels (32–37). These *in vitro* findings correlate well with increased TSHR expression in orbital fat of GO but not of non-GO patients (38). The functionality of TSHR on OF has been demonstrated by a modest increase in cAMP upon stimulation with recombinant human TSH (rhTSH), which was greater in differentiated than in undifferentiated OF (33). Transfection of an activating TSHR mutant in human orbital preadipocytes produced a more than 2-fold increase in basal cAMP (39), and up-regulation of hyaluronan synthases and increased hyaluronan (HA) production (40). But the key question is whether Graves' IgG has the same effects. Exposure of orbital preadipocytes of GO patients to thyroid-stimulating immunoglobulins produced only a small (9–24%) albeit significant increase in HA (40).

A recent series of experiments investigated this further using cultured OF originating from various GO patients and Graves' IgG that induced cAMP in a cAMP-responsive luciferase assay to the same extent as rhTSH (41, 42). In undifferentiated OF with low TSHR expression, IL-1β stimulated HA 2-fold. Forskolin induced a 40-fold cAMP and a 2.5-fold HA increase. rhTSH stimulated cAMP by 25–50% but not HA. Graves' IgG, although it slightly up-regulated TSHR expression, had no effect on cAMP or HA production compared with control IgG (41). Relative to nondifferentiated OF, differentiated OF had 4 times higher TSHR expression. Increases in HA were also higher upon stimulation with IL-1β (3.3-fold) and forskolin (11-fold). rhTSH induced a marked cAMP production but little or no HA. In contrast, Graves IgG compared with control IgG induced a moderate cAMP response but a marked HA response (42).

My interpretation of these experiments is that cytokines like IL-1β seem largely responsible for excessive HA production by OF in early stages of GO when most OF will be undifferentiated with low TSHR expression. In later stages with more differentiated TSHR-bearing OF, TSHR-mediated cAMP signaling apparently does not play a pivotal role in Graves' IgG-induced HA synthesis (see Fig. 1). It raises the question how Graves' IgG may act. One possibility is that the TSHR on OF is linked to non-cAMP signaling pathways. Activation of the TSHR via Gαs and adenylate cyclase/cAMP signaling pathways regulate thyroid hormone synthesis. An alternate TSHR effector pathway via Gαq and phopholipase C is most notably for cellular proliferation and survival (43). Some downstream effector molecules are involved in both TSHR-signaling pathways but are also subject to modulation by activation of growth receptors. In this respect it is noteworthy that TSH and insulin/IGF-I have a synergistic effect on growth and proliferation of thyrocytes (44). Indeed, TSHR-stimulating monoclonal antibodies use multiple signaling pathways (45). Differences between TSHR-Ab are another possibility: some TSHR-blocking and TSHR-neutral antibodies are able to generate signals primarily via Gαq cascades inducing cell proliferation (46). Another explanation is that Graves' IgG are heterogeneous, containing also stimulating antibodies against the IGF-1R.

IGF-I receptor as autoantigen in GO

IGF-I stimulates the secretion of collagen and GAG by OF (29). Early studies report the ability of TSHR-Ab to immunoprecipitate tyrosine kinase receptors, specifically the IGF-1R (47). Graves' IgG can displace radiolabeled IGF-I from its binding sites on OF (48). These studies from the 1980s and early 1990s were almost forgotten when the group of Smith (49, 50) reported that Graves' IgG stimulated the production of the T-cell chemoattractants IL-16 and RANTES (regulated upon activation, normal T cell expressed, and secreted) and hyaluronan by OF from GO patients; dermal fibroblasts and OF from non-GO patients did not respond (49, 50). Similar results were seen in thyrocytes (51). The effects could be blocked by monoclonal IGF-1R antibodies, suggesting these actions of Graves' IgG are mediated through pathways independent of the TSHR. The authors postulated that a subset of Graves' IgG contains antibodies that stimulate the IGF-1R. Independent confirmation of the existence of such antibodies has thus far not been obtained. To detect IGF-1R antibodies, a luminescent immunoprecipitation assay was developed, using IGF-1R in stably transfected human embryonic kidney cells. IgG isolated from human sera had IGF-1R-Ab concentrations that were not different between GO patients and controls; there was no association between IGF-1R-Ab levels and severity or activity of GO or TSHR-Ab (52). A further study demonstrated colocalization of TSHR and IGF-1R at plasma membranes and also in the cytoplasm, implicating the possibility that both receptors form together a functional complex, both in OF and thyrocytes (53). Cross talk between two receptor systems is known, *e.g.* for interactions between IGF-1R and

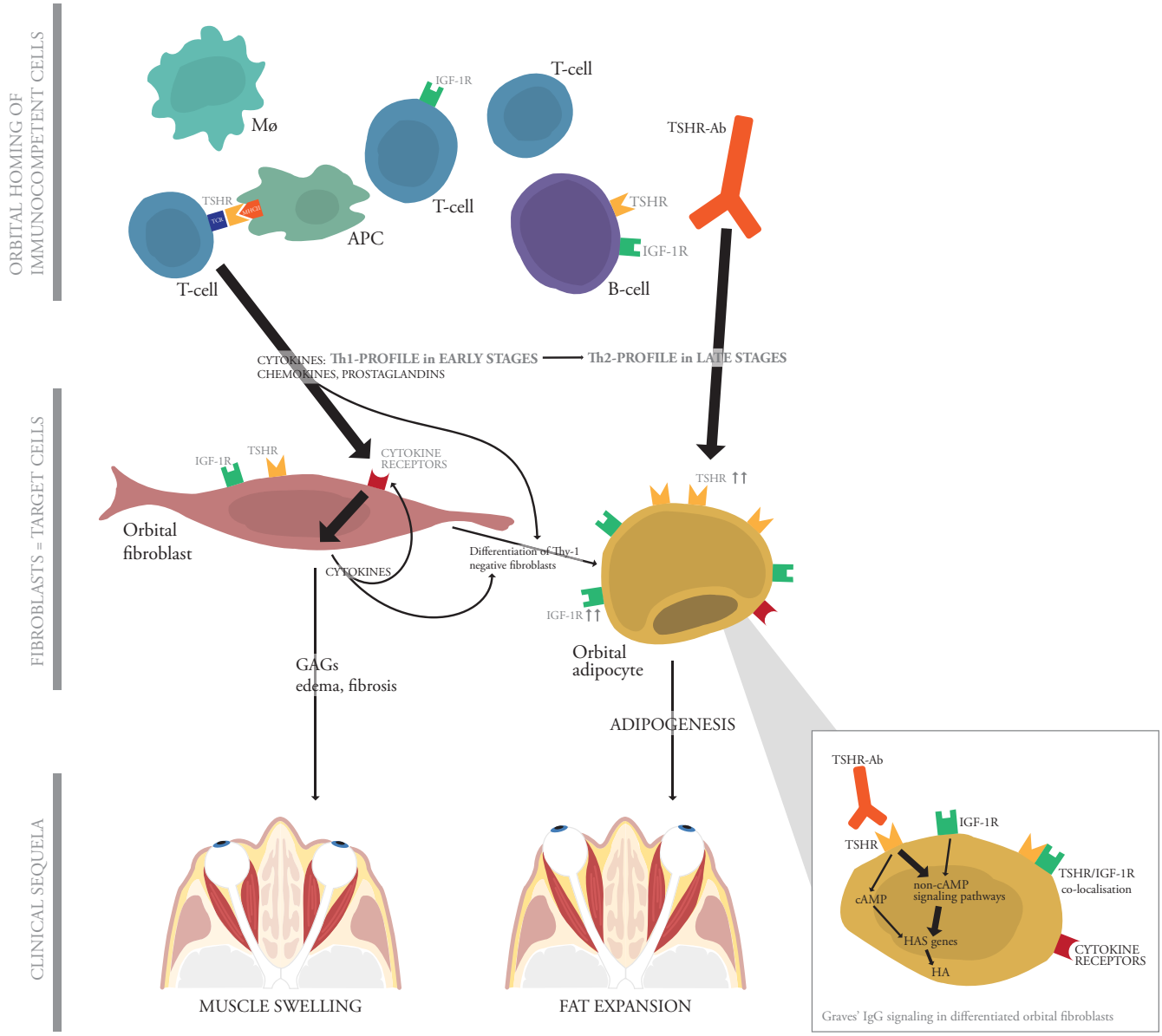

FIG. 1. Simplified model of the immunopathogenesis of GO. Homing of immunocompetent cells to the orbit is facilitated by the cytokine-induced expression of HLA and adhesion molecules on vascular endothelium. Graves' IgG induce OF to secrete T cell chemoattractants. A disproportionally large fraction of peripheral blood and orbital T and B lymphocytes of Graves' disease patients express IGF-1R, which may contribute to the immune response. Macrophages (Mϕ) and B cells may act as antigen-presenting cells (APC) that in the setting of MHC class II molecules present TSHR to T-cell receptors (TCR). T cells are able to recognize OF. Activated T cells release a variety of inflammatory cytokines, chemokines, and prostaglandins, causing inflammatory edema. The cytokine profile in the early stages of GO is predominantly Th1 derived, inducing OF to secrete cytokines and excessive amounts of GAG, which, due to their hydrophilic nature, cause swelling of orbital tissues, especially of extraocular muscles. A subset of Thy-1-negative OF called preadipocytes (present in orbital fat but not in muscles) differentiates into adipocytes under the influence of particular cytokines. This process of adipogenesis is associated with an increased expression of TSHR and contributes in later stages of GO to further expansion of orbital fat and exophthalmos. TSHR-Ab bind to TSHR on OF, resulting in the up-regulation of hyaluronan synthase (*HAS*) genes and excessive production of HA, one of the prevalent GAG in the orbit. Ligation of TSHR with TSHR-Ab induces GAG production mostly via non-cAMP signaling pathways, which overlap with signaling pathways downstream the IGF-1R. Evidence that Graves' IgG contain IGF-1R-stimulating antibodies is inconclusive. TSHR and IGF-1R may colocalize at the plasma membrane and in the cytoplasm; its functional significance is unknown.

epithelial growth factor receptor, which may be mediated at multiple levels, either through a direct association between the two receptors, by mediating the availability of each other's ligands, or indirectly via common G protein-coupled receptors or downstream signaling molecules (54). The latter seems operative for the interaction between TSHR and IGF-1R in OF. The monoclonal TSHR-stimulating antibody M22 (like an IGF-I analog) enhances phosphorylation of Akt, which is inhibited by a monoclonal IGF-1R antibody (55). Likewise, activation of ERK in thyrocytes by rhTSH is blocked by a monoclonal IGF-1R antibody (53). One wonders whether there would not be

more interactions between growth receptors as also platelet-derived growth factor-BB and TGFβ stimulate cytokine and HA production by OF (56–58).

Another study reports stimulation of OF by IgG from patients with rheumatoid arthritis and conversely stimulation of synovial fibroblasts by IgG from patients with Graves' disease; the responses were supposedly mediated by IGF-1R pathways (59). Thus, IGF-1R stimulating activity of IgG, if any, is not specific for Graves' disease.

A recent study demonstrates that the fraction of peripheral blood T cells expressing IGF-1R is larger in Graves' disease patients than in controls (48 *vs.* 15%), resulting in part from expansion of CD45RO$^+$ memory T cells (60). The up-regulated IGF-1R expression might stimulate proliferation and inhibit Fas-mediated apoptosis of T cells. A similarly skewed B cell population expressing IGF-1R is observed in the blood, orbit, and bone marrow of Graves' disease patients, which might be related to increased B cell expansion (61). Twin studies clarified that the increased fraction of T and B cells expressing IGF-1R in Graves' disease cannot be attributed to genetic determinants; it must therefore be acquired (62). The latest study reports on fibrocytes (hematopoietic stem cells) that carry IGF-1R. IGF-1R$^+$ fibrocytes are generated from peripheral blood mononuclear cells more readily in Graves' patients than in controls (63). Tissue-infiltrating fibrocytes express TSHR *in situ* and comprise a subpopulation of OF in GO, likely participating in local tissue injury and remodeling (64).

How should all these findings on IGF-1R be interpreted? First, one should take into account that IGF-I does seem to play a role in autoimmunity. In a number of experimental models of autoimmune disease, low IGF-I/IGF-1R expression is associated with worse outcome and IGF-I administration with better outcome (65–67). Second, the reported IGF-1R data are not specific for Graves' disease in view of similar findings in rheumatoid arthritis and possible other autoimmune diseases as well (59). Third, IGF-I production by the liver accounts for 80% of total serum IGF-I; the remainder is synthesized in the periphery, usually by connective tissue cell types. Serum IGF-I, IGF-II, and IGF-binding protein concentrations are completely normal in GO patients (68). It is therefore more likely that local production of IGF-I, acting in an autocrine or paracrine fashion, is involved in autoimmune reactions. Fourth, after tissue or cell injury, there is a wave of IGF-I synthesis to stimulate replication of reparative cells (69). Other growth factors involved in repair (like platelet-derived growth factor, fibroblast growth factor, epithelial growth factor) also stimulate local IGF-I synthesis. There is good evidence that oxidative stress plays a role in GO:OF of GO patients have higher contents of malondialdehyde, superoxide anions, and hydrogen peroxide than control OF (70), urinary 8-OH-2′-deoxyguanosine (marker of oxidative DNA damage) is increased in GO patients and correlated with disease activity (71), and serum oxidative stress markers are higher in Graves' patients with GO than without GO (72). Inflammatory responses in orbital tissues of GO patients might induce local IGF-I production. Fifth, IGF-1R are ubiquitous present, and both thyrocytes and thyroidal fibroblasts produce IGF-I (50). In the process of sensitization against self-antigens (like the TSHR), immunocompetent cells are induced to express TSHR but perhaps also IGF-1R. In this respect it is intriguing that immunization against TSHR in experimental animals also produced IGF-1R-Ab but that immunization against IGF-1R did not produce TSHR-Ab (73). The expression of IGF-1R on T and B cells will likely aggravate immune reactions directed against OF. The existence of functional IGF-1R stimulating antibodies in Graves' disease remains doubtful (52); activation of IGF1-R-dependent growth pathways in OF can also be mediated by TSHR (55) (see Fig. 1).

Fibroblasts and orbital fat

OF are found in the fat/connective tissue compartment and in the interstitium between the muscle cells (74). Fibroblasts from other sites (skin, abdomen) respond in general less to stimuli than OF. Phenotypic differences also exist within the population of OF. OF derived from perimysium express the cell surface glycoprotein Thy-1 uniformly (like in the skin). OF derived from the fatty/connective tissue compartment can be either Thy-1$^+$ or Thy-1$^-$ (75). Both OF subsets produce IL-6 after stimulation with IL-1β or the CD40 pathway. Thy-1$^+$ OF produce higher levels of prostanoids and display higher CD40 levels than Thy-1$^-$ OF, whereas Thy-1$^-$ OF produce more IL-8 (75, 76). Only the Thy-1$^-$ OF have the capacity to differentiate into mature adipocytes, associated with increased TSHR expression. Several genes are involved in orbital adipogenesis. One is secreted frizzle-related protein-1 (77); another is peroxisome proliferator activator receptor (PPAR)-γ (36, 77). PPARγ is elevated in orbital fat from GO patients relative to control samples (36). Exposure of OF to rosiglitazone, a PPARγ agonist, stimulates expression of PPARγ, TSHR, and differentiation in adipocytes (79). Exacerbation of GO has been described in a patient upon prescription of pioglitazone (80), and treatment with pioglitazone in diabetic patients increases proptosis by about 2 mm (81).

The process of adipogenesis increases fat volume, contributing to proptosis. Clinical experience tells us that sometimes GO patients present with an increase of only orbital fat, not of extraocular muscles. In a recent series of

95 consecutive untreated GO patients, it occurred in 5.3% (82). The reasons for differential enlargement of orbital fat and muscle compartments are incompletely understood. Possibilities are: 1) polymorphisms in the PPARγ gene (proptosis is 2 mm lower in carriers of Pro12Ala single nucleotide polymorphism) (83); 2) different cytokine profiles in muscles and fat (Th1-like cytokines predominate in extraocular muscles, with wide interindividual variation in Th1- and Th2-derived cytokines in fat) (84, 85); 3) modulation by cytokines of 11β-hydroxysteroid dehydrogenase-1 activity (the enzyme increases cortisol bioavailability and has greater activity in OF from GO patients than from controls, thereby enhancing adipogenesis and limiting proliferation) (86); and 4) smoking (exposure of OF to cigarette smoke extract greatly enhances adipogenesis in a dose dependent manner) (37). In a recent clinical study in GO patients, however, smoking did not influence orbital fat volume, but current smokers had larger extraocular muscles volume than ex- and never-smokers (87). Fat volumes were larger in patients with GO duration longer than 1 yr compared with duration less than 1 yr, The data suggest that adipogenesis is a rather late phenomenon in the pathogenesis of GO, in keeping with the notion that when the disease starts the expression of TSHR on OF is low (see Fig. 1).

Synopsis

With the present knowledge, I favor the hypothesis that autoimmunity against the TSHR (and not the IGF-1R) is the initiating event in the immunopathogenesis of GO. Orbital infiltration of immunocompetent cells is enhanced by high expression of HLA-DR and adhesion molecules on vascular endothelium in retrobulbar tissues (88). Homing is facilitated by smoking and Graves IgG, the latter also inducing release of T cell chemoattractants by OF (51). The numerous macrophages (89, 90) but also the few B cells in the orbit may act as antigen-presenting cells. Their relevance is indirectly supported by the success of treatment with rituximab in GO (91): the direct action of this anti-CD20 antibody, targeting the CD20 transmembrane receptor found on all B cells, is related to decrease in activation of $CD4^+$ and $CD8^+$ T cells by a lack of antigen presentation by B cells and by inhibition of antigen presentation by macrophages. Antigen-presenting cells may expose linear TSHR peptides to T cells (92). Activated T cells release inflammatory cytokines inducing HA synthesis and release by OF and may bind to OF further stimulating cytokine production. In this view GO is initiated mostly by cell-mediated immunity, in keeping with the predominant Th1 profile in the early stages of GO, whereas in later stages, Th2 profile is predominant (93). A nice review on the complicated interplay between cytokines, chemokines, and prostanoids has been published recently (78). The role of Graves' IgG becomes more prominent in later stages because adipogenesis gradually develops associated with increased TSHR expression.

Involvement of IGF-1R expression is likely to occur in early stages in view of IGF-1R expression on T cells, B cells, and fibrocytes also in Graves' patients without GO (60–64). It might enhance autoimmune reactions against fibroblasts. The existence of specific IGF-1R-stimulating antibodies in serum remains dubious (52, 59). TSHR-Ab may signal to the same growth pathways as activated by direct ligation of the IGF-1R (55). I favor the idea of colocalization of TSHR and IGF-1R (53), which may have functional consequences. The fascinating story of IGF-1R autoimmunity deserves further study. Could it be viewed as collateral damage?

When I started studies on GO in the early 1980s, I was rather convinced I would see resolvement of the immunopathogenesis of GO within my professional lifetime. That does not seem to happen.

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