Etiopathogenesis of Graves’ disease

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Abstract
Graves’ disease is an autoimmune disorder, caused by thyroid-stimulating antibodies (TSAb), which bind to and activate the thyrotpin receptor on thyroid cells, inducing the synthesis and release of thyroid hormones. It is a polygenic and multifactorial disease that develops as a result of complex interaction between genetic susceptibility and environmental and/or endogenous factors. Graves’ disease differs from other autoimmune diseases of the thyroid by specific clinical features, including hyperthyroidism, vascular goitre, ophthalmopathy and – less commonly – infiltrative dermopathy. This article discusses current theories, regarding the etiology and pathogenesis of Graves’ disease, including possible predisposing factors, autoimmune aspects of Graves’ disease, ophthalmopathy, and dermopathy.

Introduction
Graves’ disease is an autoimmune disorder, caused by thyroid-stimulating antibodies (TSAb), which bind to and activate the thyrotropin receptor (TSHR) on thyroid cells, inducing the synthesis and release of thyroid hormones [1–3]. It is polygenic and multifactorial disease that develops as a result of complex interaction between genetic susceptibility and environmental and/or endogenous factors [1–3]. Graves’ disease differs from other autoimmune diseases of the thyroid by specific clinical features, including hyperthyroidism, vascular goitre, ophthalmopathy and – less commonly – infiltrative dermopathy [2–4]. Women are affected 4 to 10 times more often than men, but, before the 10th, and after the 65th year of age, sex difference is significantly less pronounced. The disease may occur in every age, although it is 12 times more frequent in adults than in children [1, 4, 5]. It is estimated that in the world’s population, 2% women and 0.2% men are affected by autoimmune thyroid disorders, whereas subclinical disease, reflected by the presence of thyroid antibodies, is 10-fold higher [6]. On the basis of epidemiological studies, performed in Poland in
1987 – 1990, it appears that about 0.2% of population (women – 0.26%, men – 0.09%) is affected by the disease and the incidence rate is about 4/100.000/year [1, 7]. In Sweden, during the years 1988–1990, the incidence of Graves’ disease was 22.3/100.000/year [8], and it is especially high in Japan [9].

**Predisposing factors**

Genetic, environmental, and endogenous factors are considered to be responsible for the emergence of autoreactivity of T and B cells to the TSHR, leading to the development of Graves’ disease [1–3, 6].

**Genetic factors**

Many authors point to a strong genetic component in the pathogenesis of Graves’ disease [1–3, 6, 10–12]. The importance of genetic factors is suggested by the clustering of the disease within families and by a higher concordance rate for disease in monozygotic (20–60%) than dizygotic (3–9%) twins [10]. Moreover, thyroid antibodies have been reported in up to 50% of the siblings from patients suffering from Graves’ disease [10]. The familial incidence of Graves’ disease is 15-times higher in general population [13]. However, no single gene is known to cause the disease or to be responsible for its development.

Human leukocyte antigen (HLA) alleles have for many years been considered to be well-established risk factors in Graves’ disease [1–3, 6]. The complex of HLA genes is located on chromosome 6 (6p21.3) [2, 12]. HLA gene expression can influence the development of autoimmune disorders in various ways. HLA molecules take part in the clonal selection of T lymphocytes in the thymus. HLA class II modulate the scale of immunological response through inconsistent ability to react with T lymphocyte receptor (TcR) during antigen presentation. This interaction is of great importance in the activation of T helper lymphocytes (Th) [14, 15]. During human life, T helper lymphocyte clones are quite often generated and directed against host cells. If the system of immunological superintendence is efficient, such clones are identified and destroyed. However, if the function of T suppressor lymphocytes is discriminated, then the autoreactive T helper lymphocyte clone persists. A particular set of HLA class II alleles may cause a stronger activation of T-cell receptors on autoreactive lymphocytes, leading to the development of autoimmunization [14, 16].

It is suggested that particular HLA haplotypes may be the primary factor, predisposing to the disease development. It may be associated with low activity of suppressor T lymphocytes or low production of unspecific suppressing factors, such as interleukin-10 (IL-10) or transforming growth factor β (TGF-β) [17]. In patients suffering from Graves’ disease, an increased frequency of the following HLA class II have been shown: DQA1*0501, DR-3, DR-8, DQB1*0302, DRB1*02, DRB1*0304, and DRB1*0301/4 [12, 18, 19, 20, 21]. HLA haplotype DRB1*0304-DRB1*02-DQA1*0501 is associated with the maximal risk of autoimmune thyrotoxicosis [21].

Although most attention has been paid to HLA genes, there are also some other candidate susceptibility genes, including those encoding immunoglobulins and T-cell receptors, cytokines and their modulators, as well as other immunologically important molecules and autoantigens [6]. Three candidates have recently focused attention, namely thyroid stimulating hormone receptor (TSHR; codone 52), cytotoxic T-lymphocyte antigen 4 (CTLA-4; 106bp allele), and the gene encoding interleukin (IL)-1 receptor antagonist [3, 6, 18, 22–24]. The restricted nature of TSHR, stimulating antibody in Graves’ disease, possibly provides the best evidence that crucial immunoglobulin genes could determine whether or not a patient develops these antibodies [25].

It should also be mentioned that the loci associated with susceptibility to Graves’ disease (designated GD-1, GD-2, and GD-3) have been identified by linkage analysis on 14q31, 20q11.2, and Xq21.33–22 chromosomes [18, 26–28]. Recently, an evidence for new Graves’ disease susceptibility locus at chromosome 18q21 has been provided [29]. Therefore, Graves’ disease, like most autoimmune diseases, is inherited as a complex multigene trait.

**Environmental and endogenous factors**

The following environmental factors that damage thyroid cell may be associated with the risk of development of Graves’ disease: environmental toxins, bacteria, viruses, humoral factors, stress or excessive iodine uptake [1–3, 5, 6]. Infections have for many years been an attractive susceptibility factor but there is no clear evidence that infection directly induces Graves’ disease. It seems that, except of retroviruses and foamy viruses, due to a direct influence on genome and an indirect effect through interferon-γ (IFN-γ), and *Yersinia enterocolitica*, the bacteria in which antigen protein in cellular membrane shows similarity to TSHR of thyroid follicular cell, and therefore, may be etiological factors of some importance, the remaining above mentioned factors may only promote development of the disease in persons with genetic susceptibility [1–3, 6, 30]. However, it should be mentioned that the role of *Yersinia enterocolitica* in the etiology of Graves disease has been recently neglected [5]. The similarity of some bacterial and viral antigens to TSHR [31] and changes in the receptor structure (especially TSHR) in thyroid follicular cells, caused by its mutation or bio modification by drugs, chemical compounds or inflammatory mediators [32–37], may underlie the origin of thyroid autoantibodies and the development of Graves’ disease.

It has already been mentioned that the risk factor for Graves’ disease is higher in females than in males, probably in result of the modulation of autoimmune response by estrogens [3]. Nutritional factors in early stages of life seem to be also of some importance because low birth weight is associated with an increased prevalence of thyroid antibodies [38].
Autoimmune aspects of Graves’ disease

**The role of TSH receptor and antibodies against this receptor**

TSHR is the main antigen, inducing the generation of autoantibodies. TSHR is a G protein-coupled receptor with the characteristic seven membrane spanning regions. Along with FSH and LH receptors, TSHR molecule is a membrane-bound glycoprotein and has a similar structure of transmembrane domain and, what is more important, of a large extracellular domain which confers the ligand binding specificity. Particular extracellular epitopes of TSHR in humans are homologous in 7–85% with the responding fragments of LH receptor and, in 20–85%, with that of FSH receptor [39, 40]. TSHR has two unique insertions. The first insert of 8 residues is required for mature receptor to be expressed at the cell surface, the second insert of 50 residues is the probable site of TSHR cleavage, and is highly immunogenic [41]. Antibodies directed against TSHR mimic the effects of TSH, stimulating the function of thyroid follicular cells and causing hyperthyroidism. These TSAb are detected in circulating plasma of all patients suffering from Graves’ disease. TSAb bind to conformational epitopes in the extracellular domain of the TSHR, which make up discontinuous segments that overlap the binding site for TSH [3, 42, 43]. The production of thyroid stimulating antibodies is dependent on T cells and circulating T cells recognize multiple epitopes of the TSHR [3, 44]. Hyperthyroidism is caused by the ability of TSAb to increase the production of intracellular cyclic AMP, leading in consequence, an excessive production of thyroxine and triiodothyronine [3].

**The role of lymphocytic infiltration**

Activated T cells, directed against thyroidal and nonthyroidal antigens, are present in peripheral blood of patients with Graves’ disease [5, 45]. However, lymphocytic infiltrate is also present in the thyroid, consisting predominantly of activated T lymphocytes, but also in a smaller number of B lymphocytes, dendritic cells, and macrophages, occasionally in association with germinal centers [2, 3, 5, 46]. The degree of infiltration is highly variable [5]. Many activated T lymphocytes contain IFN-γ, a strong stimulator of the inflammatory process and immunological response [2, 45]. However, other cytokines and growth factors are also present and give impetus for the local proliferation of glandular tissue [3, 5, 47].

**The role of thyroid cells**

Thyroid cells play a very important role in the initiation of Graves’ disease. As already mentioned, thyroid follicular cells are the source of thyroid antigens and target of TSAb but also, in response to T cell-derived cytokine – IFN-γ, they express HLA class II molecules and therefore, allow the cell to present its antigens to activated T lymphocytes, what results in the development of autoimmunization [3, 6, 35, 48, 49]. It seems that in the initiation of Graves’ disease, B lymphocytes and dendritic cells play also some role because these cells express costimulatory molecules CD80 and CD86 that are of crucial importance for naive T lymphocytes [3, 50]. The autoimmune process may further be exacerbated by the expression of other molecules by thyrocytes, such as IL-1, IL-6, CD40, and CD54 [3].

**Goitre in Graves’ disease**

Goitre in Graves’ disease may be induced by TSAb, as well as by activated lymphocytes infiltrating the thyroid gland [2, 3, 36, 51, 52]. TSAb probably stimulate the proliferation of thyroid follicular cells, although the precise mechanism of this proliferation is not clear. It could be a result of the activation of phospholipase A2 (and C) and/or adenylate cyclase which is the second signal necessary for TSH-stimulated thyrocyte proliferation [32, 51, 52]. Cyclic AMP is recognized as the basic regulator of thyroid cell proliferation [53]. The proliferation of thyroid cells might also be induced by activated lymphocytes, infiltrating the thyroid because they are the source of various cytokines and growth factors which stimulate cell proliferation [54].

**Thyroid-associated ophthalmopathy**

Thyroid-associated ophthalmopathy, usually called Graves’ ophthalmopathy, is a well-described but poorly understood component of Graves’ disease [55–58]. The eye complications in Graves’ ophthalmopathy range from discomfort and lid distraction to proptosis (the main clinical manifestation of the disease), dislopa, and sight loss, and are clinically evident in 20–50% of patients with Graves’ disease, although only in 5–15% with moderate to severe manifestations [55, 56, 58]. Graves’ ophthalmopathy is characterized by an enlargement of the extraocular muscles and an increase in the retrobulbar fat, and can be classified as non-infiltrative, called congestive subtype (including oedema of lids, periorbital tissues and conjunctiva, conjunctival injection and eye pain, irritation and a sensation of grittiness) and infiltrative, called ocular myopathy subtype (including infiltration, inflammation and enlargement of extraocular muscles) [56, 59, 60]. Although the pathogenetic mechanism of Graves’ ophthalmopathy is still unclear and the nature of the involved autoantigens is not known (though a number of candidates have been suggested), recent studies support the hypothesis of autoimmune response against one or more shared or cross-reactive thyroid-orbit autoantigens [61, 62].

Some authors believe that extraocular connective tissue is the main location of the initial reaction [63, 64, 65]. Infiltrative process, caused by autoantibodies, leads to a local accumulation of stimulated T lymphocytes which may secrete cytokines (such as IL-1α, IL-2, IFN-γ, tumor necrosis factor-α and –β (TNF-α and –β), and leukoregulin) which activate orbital fibroblasts and cause overproduction of collagen and glycosaminoglycans. In consequence, the accumulation of glycosaminoglycans causes tissue oedema, leading to a disproportion between orbital capacity and orbital tissue volume.
Others propose that the eye muscle is the primary target of the autoimmune reaction, while orbital fibroblast stimulation and congestive changes are of secondary importance [65, 66, 67].

Early, the active phase of Graves’ ophthalmopathy is associated with a cell-mediated immune response (Th1-like cytokines: IL-2, INF-γ, and TNF-β), inducing an expression of adhesion molecules on endothelial cells leading to the recruitment of activated leukocytes from blood vessels. The migration of leukocytes into the retrobulbar tissue is intensified by the expression of leukocyte function-associated antigen-1/inteacellular adhesion molecule-1 (LFA1-/ICAM-1) and very late antigen-4/vascular cell adhesion molecule-1 (VLA-4/VCAM-1). In addition, Th1-like cytokines induce the expression of certain immunomodulatory proteins (HLA-DR, adhesion molecules, heat-shock proteins) on orbital fibroblasts, adipocytes, and eye muscle cells. The late inactive phase is associated with a stimulation of...
humoral reaction and secretion of IgG, IgM, and IgE by Th2-like cytokines (IL-4, IL-5, IL-10, IL-13) [61, 68].

Proinflammatory Th1-like cytokines may play a role in the development of eye muscle component of Graves’ ophthalmopathy in the acute stage, whereas anti-inflammatory Th2-like cytokines may be protective in the chronic stage of the disease [69].

Dermopathy and acropachy

An uncommon manifestation in Graves’ disease is a local pretilial oedema—a dermopathy which occurs in 1–2% of patients and is, sometimes, associated with acropachy [2, 3]. Dermopathy is characterized by lymphocytic infiltration of the dermis, the accumulation of glycosaminoglycans, and oedema. The overproduction of glycosaminoglycans (mainly hialuronic acid) by fibroblasts is the primary cause of pretilial oedema and acropachy [56, 70, 71]. Although the presence of distinct pretilial oedema and acropachy is rarely observed in patients with Graves’ disease (1% and 4%, respectively), detailed morphological studies of forearm skin sections reveal discrete dermopathy also in patients without oedema [56, 72]. The intensity of lymphocytic infiltrations in subcutaneous tissue is, however, significantly lower than that observed in retroocular tissues, although the histological patterns of both tissues are very similar [73].

Concluding remarks

Despite a significant progress in the understanding of Graves’ disease, especially of its etiology and pathogenesis as well as of underlying immune system abnormalities, many problems are still to be solved; the current mechanisms, involved in the pathogenesis of Graves’ disease, are presented in Figure 1.


