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Graves' Disease - The Interaction of Lymphocytes and Thyroid Cells

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1. Introduction

Human autoimmune thyroid disorders (AITD), Graves' disease (GD) and Hashimoto's thyroiditis, are characterized by reactivity to self-thyroid antigens. Graves' disease is the archetype for organ-specific autoimmune disorders, very important to our understanding the mechanisms responsible for progression of autoimmunity.

It has been known for years that hyperthyroidism in Graves'disease is induced by immunological reaction, in which TSH receptor antibodies bind to the receptors on the surface of thyrocytes, activate them and initiate thyroid hormone production independent of the hypothalamic-hypophyseal control. It is known nowadays that, probably for environmental or endogenous reasons, Graves'disease may develop in genetically predisposed individuals [Weetman, 2004].

2. Antigen presentation

A small number of antigen presenting cells (APCs) as CD1a+ presenting dendritic cells (DC) were observed in the thyroids without AITD, but their number was significantly higher in the thyroids from Graves' disease patients [Ben-Skowronek et al., 2007, 2008]. There are indications that such DCs are able to proliferate, which indicates that not all of the thyroid DCs need to have recently immigrated with the blood stream [Quadbeck et al. 2002]. CD1a antigen has the structure of an α-chain connected with β-microglobulins and is characteristic for immature APCs [Brigl & Brenner, 2004]. Thyroidal DCs are often in close contact with thyrocytes; they are clearly in an immature state and often show monocyte marker characteristics. The presence of positive reaction to CD1a protein in the granules of the apical part of some thyrocytes suggested that the thyrocytes may probably be antigen presenting cells in the thyroid autoimmune reactivity [Ben-Skowronek et al., 2007,2008]. The investigations of transgenic mice by Kimura et al. [Kimura et al., 2004] indicated that expression of class II MHC molecules on epithelial thyroid cells is not required for the initiation of an autoimmune attack to the thyroid. The initiation, then, seems to be mainly mediated by the professional antigen presenting cells in the lymphoid tissue. The antigen can be presented to CD4+ cells by conventional antigen presenting cells, particularly dendritic cells and also by B-cells and activated T-cells, and less effectively by thyrocytes. The antigen presentation by thyroid epithelial cells sustains the autoimmune reaction.
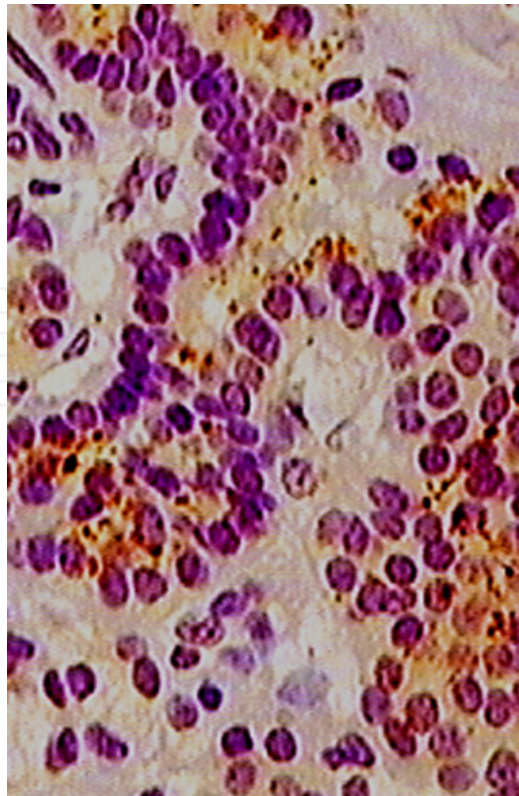
Fig. 1. The thyrocytes are antigen presenting cells and show reaction with the CD1a monoclonal antibody. Magn. 400x

While analyzing the process of antigen presentation in thyroids sampled from patients, the treatment process should be taken into account. Metimazole and carbimazole change the presentation of antigens by thyrocytes. Thionamides have been reported to influence the expression the antigens of the major histocompatibility complex class I, IL-1 (interleukin-1), IL-6 (interleukin- 6), prostaglandins E2 produced by thyrocytes [Zantut-Wittmann et al., 2001]. The expression of major histocompatibility complex class II is unchanged by thionamides [Dedecjus et al. 2010].

Numerous investigations indicate that adhesion molecules are engaged in the process of migration of lymphocytes to the thyroid and lymphocyte adhesion [Arao et al., 2000]. Adhesion molecule ICAM-1 (Inter-Cellular Adhesion Molecule 1) belonging to the superfamily IgG is a natural ligand of antigen located on lymphocytes LFA-1 (Lymphocytic function-associated antigen - 1). This antigen belongs to the integrin-β2 superfamily [Springer, 1990]. ICAM-1 is located on different cells: fibroblasts, endotheliocytes, and thymocytes. It was identified on thyrocytes as well [Weetman et al., 1989, Martin et al., 1990, Springer,1990].The expression of ICAM-1 is regulated by proinflammatory cytokines: interferon γ, interleukin 1β (IL 1β) and TNF-α (Tumor Necrosis Factor -1) [Dustin et al., 1986, Martin et al., 1990, Springer 1990, Bagnasco et al., 1991]. In Graves' disease, the ICAM-1/LFA-1 pathway plays a key role in migration and settlement of lymphocytes in the thyroid, and particularly in the process of adhesion of lymphocytes to thyrocytes [Arao et al.,2000]. In vitro experiments have shown that thyrocytes behave like antigen presenting cells and can induce lymphocyte migration [Estienne et al., 2002].

Expression of HLA DR II and the immunoglobulin Fc receptor (FcγRIIB2) has been found on the basal and apical surfaces of thyrocytes [Botazzo et al., 1983, Wu et al., 1999]. The

presentation of the latter antigen is dependent on the low level of androgens, which is probably connected with higher prevalence of AITD in women [Estienne et al., 2002]. Presentation of antigens by thyrocytes without the costimulatory molecule B7 does not lead to activation of T-cells [Marelli-Berg et al., 1997]. The expression APC characteristic antigens are dependent on TSH [Todd et al., 1987, Estienne et al., 2004]. Thyrocytes may produce HLA I under the influence of cytokines of lymphocytes present in the thyroid. In this way, the autoimmunologic reaction is sustained [Catalfamo et al., 1999].

3. The development of autoimmune reaction

When immune tolerance to thyroid antigens is broken, the endothelial cells of regional postcapillary venules are activated, allowing extravasation of blood leukocytes. In Graves' disease, the lymphatic tissue arranged in lymphoid follicles containing T- cells may be formed in the thyroid. T-cells form infiltrations and lymphatic follicles but do not damage thyrocytes [Kuby et al., 2007].

Graves' disease patients seem to have mixed Th1/Th2 profiles. The lymphocyte subsets produce signal interleukin: Th1 – IL2 and Th2- IL4.The immunological response proceeds via T-cell receptor (TCR) antigen recognition, followed by activation of the T- cell through a combined effect of antigen recognition and co-stimulatory signals, including interleukin -1 (IL-1) action leading to T- cell IL 2 secretion and IL-2 receptor expression and, subsequently, to proliferation of the T- cell into an active clone. [Janeway et al., 2001 Janeway & Medzhitov 2002]

In Graves' disease, the increased percentage of CD4+ T helper cells, in comparison to non-AITD, leads to development of humoral autoimmune response. Antigens of self-thyrocytes are presented in such a way that they are recognized by self – T-helper CD4+ lymphocytes. T-helper cells CD4+ sporadic occurred in thyroids of children from the control group, seldom in the simple goiter and slightly more often in the nontoxic nodular goiter. The number of T-helper cells in Graves' disease was the largest [Ben-Skowronek et al., 2007, 2008].

The subset of CD4+cells includes the regulatory lymphocytes - Tregs, which play a fundamental role in modulation of immunological response through their inhibitive effect on autoreactive T-cells [Piccirillo & Shevach,2004, Piccirillo & Thornton, 2004, Shewach, 2006]. The mechanism of this suppression is unknown, but many investigators consider it to be dependent on the contact between lymphocytes and independent of secretion of IL-10 and TGFβ [Piccirillo et.al. 2002,2003]. In the remission phase during thyrotoxic treatment, the subsets of lymphocytes were not different from the control group and from children with the simple goiter and nontoxic goiter [Bossowski et al. 2003]. The cells were characterized by expression of CD25 (the α-chain of IL2) and intracellular expression of FoxP3 (Forkhead winged helix box3). Only the subset of CD4+cells with maximal expression of CD25 (CD4+CD25+high) is responsible for the suppressor – regulatory effect of these lymphocytes [Cao et al., 2003, Baecher-Allan et al., 2001, 2003, Bossowski 2010]. The CD4+CD25+ cells can occur natural or can be induced – they are generated in the lymphatic tissue from CD4+CD25+ cells by different stimulant agents: by immature dendritic cells, IL-10, TGFβ, supply of vitamin D3 or dexamethasone, anti-lymphatic treatment or small doses of antigens. The Treg cells not need costimulation of CD28-B7 for their development or activity. They play a pivotal role in sustenance of immunologic tolerance [Piccirillo & Shewach, 2004, Piccirillo & Thornton, 2004]. TGF-β is assumed to be necessary for the

regulatory function of Treg cells; it also prevents activation of lymphocytes and autoimmune reactions [Bommireddy et al., 2008]. The quantity of lymphocytes in this subset is decreased in Graves' disease [Deshun et al., 2009].

An increase in T-helper lymphocytes, especially in Th1 lymphocytes, results in activation of B lymphocytes and their transformation into plasma cells which produce thyroid antibodies, predominantly TRAB (TSH receptor antibody), TSI (TSH stimulated immunoglobulin), and also TPO Ab (Antithyroperoxidase antibody) and TG Ab (Antithyroglobulin antibody).

T cells CD8+ are observed in the thyroid more often in Graves' disease than in non-AITD; they have a regulatory T-cell function. Electron microscopy examinations did not demonstrate any damage to thyrocytes, but CD8+ lymphocytes frequently entered the thyroid follicles through the basal membrane [Ben-Skowronek et al., 2009].

The T-suppressor-cytotoxic CD8+ cells were observed in thyroid follicles between thyrocytes, in mononuclear infiltrations and in lymphatic follicles in the mantle zone. In light microscopy, CD8+ T-cells and adherent normal thyrocytes were visible in high magnifications. Bossowski et al. have found a correlation between expression of costimulatory molecules CTLA-4 and CD28 on T-cells and the level of antibodies against the TSH receptor [Bossowski et al., 2005]. The investigations of Negrini et al. [Negrini et al., 2006] indicate a possibility of presentation of GITR receptors on the surface T-cells CD8+ characteristic for Treg cells. Own observations have confirmed this character of CD8+ T-cells, because they are located between thyrocytes and do not cause apoptosis.
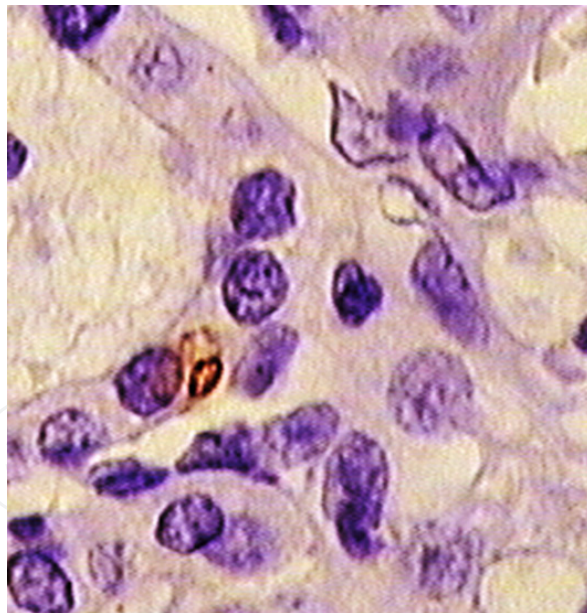

Fig. 2. The CD8+ T-cell between thyrocytes in thyroid follicle wall. The thyrocytes are active and present no signs of apoptosis or cell damage. Magn. 400x.

In vitro investigations and observations of the thyroid tissue in electron microscopy indicate the possibility of formation of the so-called immunological synapse of a character of a tight junction between lymphocytes and thyrocytes with participation of adhesive proteins. This physical contact may result in establishment of an immunological synapse able to stimulate intra thyroid T lymphocyte proliferation and differentiation.
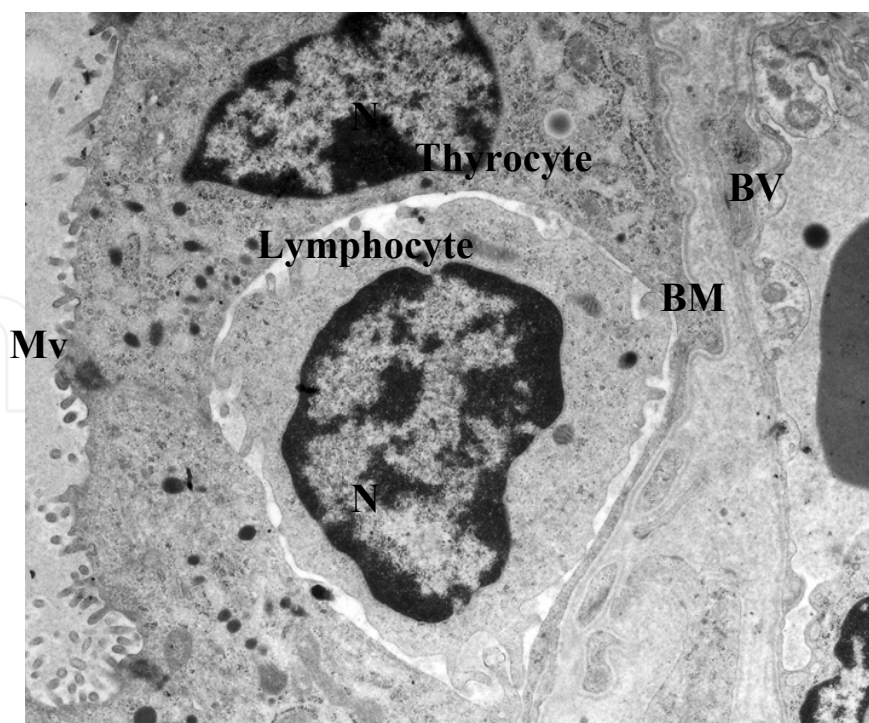
Fig. 3. T cells among thyrocytes in the thyroid epithelium. The thyrocytes are active without destruction signs. N- nucleus, Mv – microvilli, BM – basal membrane, BV – blood vessel. Transmission Electron Microscopy Magn. 15 000x.

Recent investigations have suggested that a crucial role in peripheral tolerance or autoreactive T- cells is played by T regulatory subsets (Tregs) divided into two populations: naturally occurring and inducible [Wieczorek et al., 2009]. Tregs so far identified as participating in the pathogenesis of Graves' disease include naturally occurring CD4+,CD25+T cells , C8+CD122+T cells and natural killer cells [Bossowski et al., 2010]. Comparison of immunohistochemical localization of CD4+ T cells in ultrastructural investigations has shown that lymphocytes CD4+T were small cells with large nuclei and a small amount of cytoplasm in contact with thyrocytes and other lymphocytes [Ben-Skowronek et al., 2009].
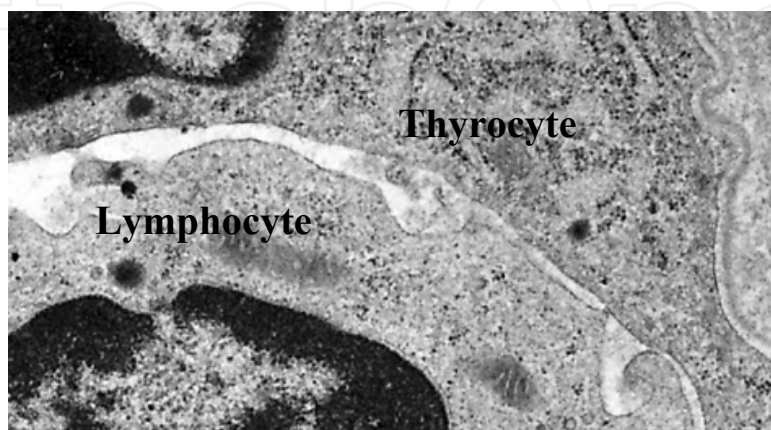

Fig. 4. The immunological synapse between T-cells and thytrocytes in Graves' disease. Transmission Electron Microscopy Magn. 20 000x

Rifa'i et al. [Rifa'i et al., 2004] have described subsets of naturally occurring Tregs CD8+CD25+. It is possible that CD8+T cells in contact with thyrocytes play the role of Tregs in the pathogenesis of Graves' disease. The investigations of Negrini et al. [Negrini et al. 2006] have characterized a subpopulation of CD8 T suppressor lymphocytes able to inhibit both cell proliferation and cytotoxicity; they have observed that glucocorticoid–induced TNF-like receptor (GITR) is expressed on such CD8 T suppressor cells. The papers of Nakano et al. [Nakano et al., 2006] and Nagayama [Nagayama et al., 2007] suggest a preventive role of Tregs in autoimmune reaction in the thyroid with AITD.

Patients with Graves' disease have an increased number of circulating B-cells but plasma cells predominate in the thyroid. The close contact with T-cells (probably Th2 cells) and plasma cells has been frequently observed only in Graves' disease and sporadically in the non-AITD and suggested the regulation function of the T-cells stimulating plasma cells to produce autoantibodies [Ben-Skowronek et al., 2008].

The plasma cells in Graves' disease penetrate between thyreocytes; nevertheless, they caused no destruction of thyroid follicles and epithelial cells. Ultrastructural changes in plasma cells were observed in patients with Graves' disease: a large, active nucleus with a nucleolus, a well-developed rough endoplasmic reticulum in which antibodies were
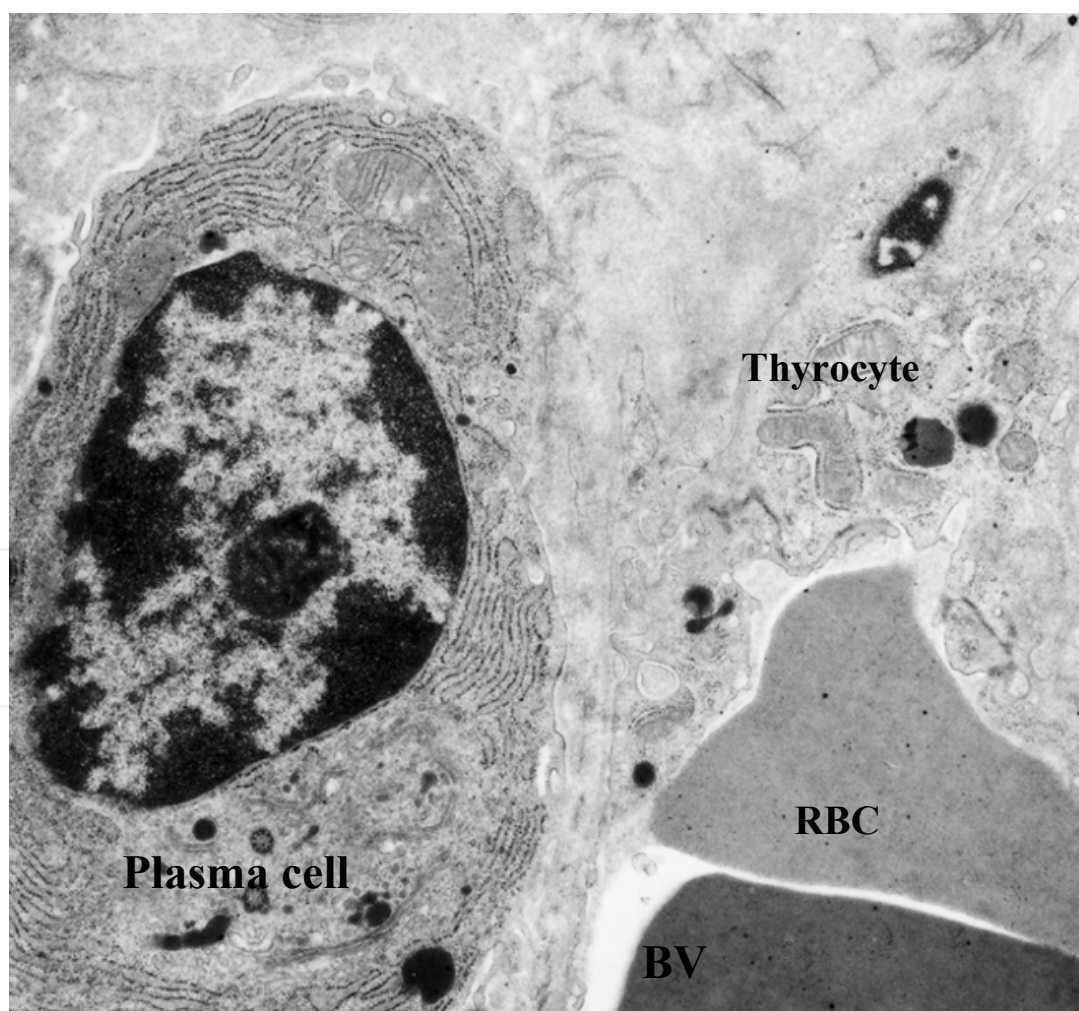

Fig. 5. The plasma cell producing antibodies in contact with thyrocytes. RBC-red blood cell, BV- Blood vessel. Transmission Electron Microscopy Magn. 15.00x

produced. The number of plasma cells in the thyroid was inversely proportional to time of treatment, which proved the immunomodulant activity of thyrostatic drugs [Ben-Skowronek et al., 2009].

In Graves' disease, the immunological deposits observed in the basal membrane of the thyroid follicles lead to thickening of this membrane and probably to changes in polarization of cell membranes. The thyrocytes in this region are columnar, with signs of increased activity (big nuclei; active, enlarged mitochondria; a big number of granules in the apical pole; long microvilli). [Ben-Skowronek et al., 2008,2009]. The antibody deposits do not damage thyrocytes but enhance their activity and metabolism by activation of the THS receptors, and lead to hyperthyroidism.
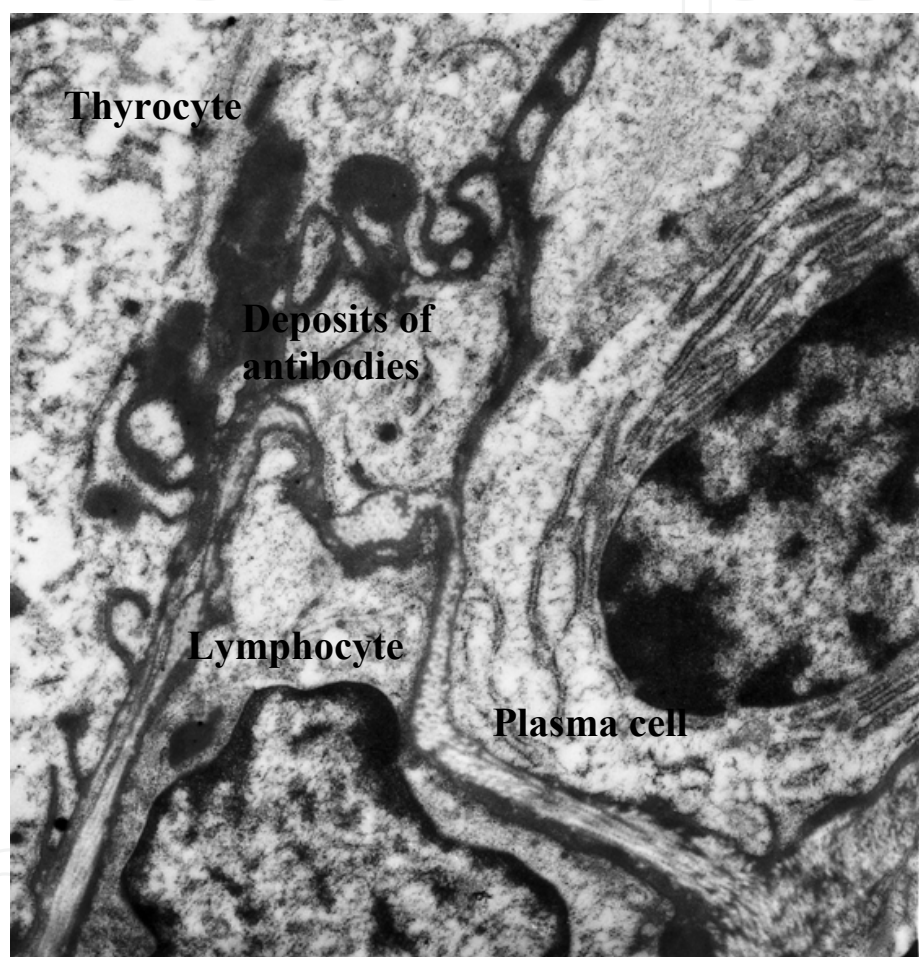

Fig. 6. The late phase of development of antibodies deposits in the basal membrane of the thyrocytes. Transmission Electron Microscopy Magn. 20 00x

Numerous reports have shown that Th-1 cell activating the antibody-dependent cellular cytotoxicity (ADCC) can be detected in Graves' disease, although the response is usually weak and not present in many patients [Guo et al., 1997, Metcalfe et al., 1997]. ADCC of thyroid cells is induced by anti TPO antibody positive sera, but other unknown antibody-antigen systems and methimazole therapy also contribute. Large granular lymphocytes – phenotypic NK cells - are rarely present in the lumen of the thyroid follicle. Here, degenerative changes in the thyrocytes were observed by electron microscopy [Ben-Skowronek et al., 2009].

Antibodies may be produced against the TSH receptor (TSH receptor stimulating antibodies – TS Ab, TSH binding inhibiton immunoglobulins – TBII, TSH stimulation blocking antibodies – TSBAb), against thyroperoxidase (TPO Ab), against thyroglobulin (TG Ab), against megalin [Marino et al., 1999], against the iodine symporter, against thyroid's DNA, against components of external eye muscles and fibroblasts, against parietal cells and against platelets [Weetmann, 2004].

The stimulating antibodies (TSAb) react with the TSH receptor and initiate activity of adenyl cyclase and phospholipase A2of the receptor, thus stimulating production of thyroid hormones and growth and division of thyrocytes [Orgiazzi et al.,1976, DiCerbo et al., 1999, Ewans et al.,1999, Morshed et al., 2009]. The blocking antibodies act like weak agonists of the TSH receptor [Lenzner et al., 2003, Schwarz-Lauer et al., 2002].

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