

Heterogeneity of Autoimmune Thyroiditis

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During many decades studies of autoimmune thyroid diseases have provided important information on autoimmune mechanisms in general. In 1956, Rose & Witebsky (64) succeeded in producing experimental autoimmune thyroiditis (EAT) in rabbits by injection of crude thyroid extract together with complete Freund's adjuvant. In the same year, Roitt et al. (62) could demonstrate autoantibodies identified as thyroglobulin precipitins in sera from patients with the fibrous variants of autoimmune thyroiditis, and finally, Adams & Purves (1), in the sera of patients with Graves' disease, isolated a substance with the capacity to stimulate the thyroid gland, which they called long-acting thyroid stimulator, due to the prolonged action when compared with thyrotropin (TSH).

Since then a number of results have indicated that not only humoral but also cellular immune mechanisms are involved in the pathogenesis of thyroid autoimmunity (91). In recent years studies in animals and man seem to indicate a multifactorial influence involving the immune response genes. Moreover, genetic heterogeneity is evidenced in autoimmune thyroid diseases, previously thought to be stages of the same disorder. Therefore, theories concerning the display of organ-specific autoantibody formation have to be considered.

Histological features of autoimmune thyroid diseases

Autoimmune thyroid diseases are inflammatory disorders of the thyroid gland, and can be divided according to thyroid function (Table 1). A general histological feature is the lymphocytic infiltration forming lymphoid follicles with active germinal centres and infiltration of plasma cells. The ultrastructure of the germinal centres is similar to that seen in lymphatic organs (43). In autoimmune thyrotoxicosis (Graves' disease (GD)) the thyroid follicles show epithelial hyperplasia, while the lesions in autoimmune myxoedema are characterized by fibrosis and destruction of the epithelial cells. Two

Table 1
The classification of autoimmune thyroid diseases

Thyroid function	Disease	
	Chronic	Reversible
Hyperthyroidism	Graves' disease Hashimoto's disease	Silent thyroiditis
Euthyroidism	Symptomatic autoimmune thyroiditis	Subacute thyroiditis
Hypothyroidism	Hashimoto's disease Atrophic thyroiditis	

variants of autoimmune myxoedema can be distinguished: One with massive lymphocytic infiltration and slight fibrosis (Hashimoto's thyroiditis (HT)) and one with more prominent fibrosis (atrophic thyroiditis (AT)). However, all variants of thyroiditis are seen, including generalized and focal lesions as well as goitrous and atrophic variants. Separation of HT from focal lesions by morphological methods is impossible when the infiltrates are pronounced, although immunohistochemical studies have revealed differences in the number of immunoglobulin-containing cells (42). Also rare cases with evidence of a combination of active GD and HT have been reported, i.e. Hashitoxicosis (21, 45). Moreover, a form of thyroiditis found in otherwise normal individuals has recently been demonstrated and described as symptomless autoimmune thyroiditis (4, 31, 41).

In all these variants of thyroiditis the histological lymphocytic infiltration is chronic and progressive. In contrast, the histological features in subacute thyroiditis (de Quervain) and silent thyroiditis are reversible without development of germinal centres (42). Whether these autoimmune thyroid diseases constitute a broad spectrum caused by a single pathological process, or are separate disease entities, has not been clarified.

Experimental autoimmune thyroiditis (EAT)

The understanding of the pathogenic events in autoimmune thyroiditis has evolved primarily from animal studies. In EAT in rabbit injection of either altered forms of thyroglobulin or unaltered thyroglobulin together with complete Freund's adjuvant, lipopolysaccharide, or bacterial antigens, lead to lymphoid infiltration of the thyroid gland (30, 64, 65), while omission of polyclonal activators results in appearance of autoantibodies without thyroid lesions. In general, the reactions are unspecific and disappear when the immune stimulation is terminated. EAT could only be produced in apparently normal animals, and neither athymic mice nor mice that have been thymectomized or irradiated develop EAT after immunization until reconstitution with syngeneic T cells (65, 83).

Furthermore, it is possible to transfer EAT to normal animals with thyroglobulin-sensitized lymphoid cells (12). The development of EAT thus seems to depend on presence of intact T helper cells in the immune system, and the immune response is probably mediated by T cells.

EAT has served as a model for autoimmune diseases in general and has given rise to a number of results on the interactions of antigen and antibody in the immune response (83). In contrast to the human chronic autoimmune thyroiditis, plasma cells or germinal centres do not usually develop in the thyroid gland (39), and EAT does not resemble the lesions in HT, but rather the lesions of subacute thyroiditis. However, in various strains of mice, marked differences were found in their susceptibility to EAT, with a striking correlation to the H-2 genotype and with a closer resemblance to human chronic autoimmune thyroiditis (65).

Spontaneous autoimmune thyroiditis (SAT)

Different animal models are found in the spontaneously developed autoimmune thyroiditis (SAT) in which the B cells and their antibodies seem to play a decisive role in the initial phases of the disease. In contrast to EAT, neonatal thymectomy does not prevent development of SAT and results in even more severe thyroid lesions (88). The preponderance of plasma cells and occurrence of numerous germinal centres are characteristic features of SAT that parallel the findings in human chronic autoimmune thyroiditis, but are in contrast to the observation in EAT (39).

While development of EAT by immunization with appropriate antigens and adjuvants depends on the presence of T helper cells, the mechanism initiating SAT is still unknown. Also the B cells and their products, i.e. antibodies, play a primary role in the pathogenesis, and the effector cells may be under separate genetic control determining the severity of the thyroid lesions (65). It is therefore possible that the defect lies in the suppression of the effector cells (88). These models of SAT have provided strong evidence for the importance of antigen

in both the induction and maintenance of the autoimmune response (59, 65, 83, 88).

Lymphocyte function in thyroid autoimmunity

Several abnormalities in number and/or function of the lymphocytes have been encountered in autoimmune thyroid diseases, and Volpé and co-workers (70, 91) have suggested that thyroid autoimmunity in man is linked to a deficiency of the T suppressor cells. The development of monoclonal antibodies recognizing the different lymphocyte subsets has provided evidence for a decreased number of OKT₈ positive cells in HT (67, 74), and functional *in vitro* tests have shown defective suppressor cell function when exposed to thyroid antigens (3, 60, 77). However, some investigators found normal conditions in HT (17, 47, 82). In other studies excess of T helper cells (18) and evidence of hyperresponsiveness of the B cells have been demonstrated (5). Antibody-mediated mechanisms such as an increase of K cells (2, 15) and natural monocyte-mediated cytotoxicity (66, 73) have been shown. In subacute thyroiditis, Wall & Chartier (82) found increased suppressor cells, probably reflecting a non-specific effect of the possible viral infection, which has been supported by a recent study of plaque-forming cells (84). Mononuclear cells have been identified as sites of antibody production against thyroglobulin, microsomal as

well as thyroid cell membrane antigens (49, 50), and the immune cells within the thyroid showed greater ability to secrete autoantibodies than peripheral cells and included a larger proportion of B cells (51, 79).

In a recent review Strakosch et al. present data in favour of an organ-specific and not a general defect in the suppressor cells in thyroid autoimmunity (70). Whether this deficiency is primary in the initiation of the disease or a consequence of the disease is not clear, but recent findings (35) seem to indicate that a T lymphocyte sensitization persists for years after therapy, at least in GD. Thus, no definite conclusions concerning the initiation of the autoimmune process can be drawn at present.

Thyroid autoantibodies

The pattern of autoantibodies in autoimmune thyroiditis is complex and their role is not fully clarified. Several antigen-antibody systems can be distinguished (Table 2). Thyroglobulin antibodies were first identified (62), but this was soon followed by the discovery of antibodies against the microsomal fraction of thyroid epithelial cells, and antibodies against the second colloid antigen and epithelial surface antigen (19). Thyroglobulin antibodies have been claimed to be responsible for initiation of the autoimmune process in HT as indicated by experimental studies (88). The thyroglobulin autoantibodies are directed against a limited number, possibly two to four, of epitopes on the molecule of the colloid glycoprotein, thyroglobulin. In the majority of sera from patients with HT the autoimmune response is directed towards the same epitopes (56). Due to the limited epitope density the corresponding immune complexes are generally not complement-activating (28, 78) though they contain IgG subclasses able to fix complement (34).

Thyroid-stimulating antibodies, present in most cases of GD, have been suggested to be responsible for the thyrotoxic state of this disorder. These antibodies are directed against components of the thyroid cell membrane involving the TSH receptor, and mimic TSH in various ways. This has been used in methods

Table 2

Antigen-antibody systems related to the thyroid gland

Antigens	Antibodies
Thyroglobulin	Thyroglobulin antibodies
Microsomes	Microsomal antibodies
Second colloid	Colloid antibodies
Surface antigens	Surface antibodies
TSH receptor	TSH binding inhibiting antibodies Thyroid-stimulating antibodies Thyroid growth-stimulating antibodies Antibodies blocking TSH receptor, adenylate cyclase and thyroid growth

for measuring these antibodies (8, 10, 61). Also antibodies which inhibit thyroid adenylate cyclase activity and TSH stimulation have been demonstrated (9). Recently, these antibodies have also been demonstrated in patients with HT (11, 14), and during the acute phases of subacute thyroiditis (69, 81). Autoantibodies, that might stimulate the growth of the thyroid gland have been detected in patients with goitre (22), and in primary myxoedema antibodies blocking the trophic effect of TSH have been reported (23).

It is thus evidenced that several different thyroid autoantibodies exist with relation to the clinical state. Some of these act on thyroid stimulation by increasing cyclic AMP similar to the native hormone, some act on thyroid growth by either stimulation or inhibition, and some are able to compete with the native hormone for the receptors without stimulating the thyroid adenylate cyclase or even blocking the receptor function.

In addition to all these autoantibodies, possibly also anti-idiotypic antibodies towards the hypervariable regions of IgG can be found. Roitt et al. (63) have proposed that a disturbance of this region towards thyroglobulin might be present in HT. Studies in obese strain (OS) chickens, however, have indicated that this phenomenon is probably secondary (59).

Circulating immune complexes have been detected in sera from patients with both HT and GD (14, 16, 40, 48). Recent data have indicated that the composition of these immune complexes is heterogeneous with respect to antigenic content, ratio of antigen to antibody as well as complement dependent properties (14, 36, 48), and might represent a wide spectrum just like the antibodies (80).

The pathogenic potential of thyroid autoantibodies has been supported by the studies of symptomless thyroiditis. Thyroid antibodies of low titres are frequently present in otherwise symptomless individuals (41). When studied at necropsy, the presence of thyroid autoantibodies was paralleled by focal lymphoid infiltration in the thyroid gland (92), in accordance with animal studies showing a relation between antibody response and degree of lymphocytic

infiltration of the thyroid (44). The clinical implications of this was evidenced by the risk of developing hypothyroidism in long-term follow up studies. When only thyroid antibodies were present, the risk was 7.8% per year, while the annual incidence was much higher (25%), when also serum TSH was elevated (31). This agrees with the concept that symptomless autoimmune thyroiditis appears as a graded process of thyroid alterations eventually resulting in hypothyroidism (4), whereas the genetic predisposition in this condition is not known.

Silent thyroiditis and subacute thyroiditis are reversible conditions with transitory presence of thyroid autoantibodies (37). A number of studies have evidenced a viral pathogenesis (90), but also autoimmunity may be involved in the development of the diseases, possibly as a secondary immune response to the inflammatory release of the antigen.

Genetic aspects in animals

It has been shown that immune response genes linked to the major histocompatibility complex (MHC) may be important in determining the susceptibility of mice to EAT induced by thyroglobulin with adjuvants. Rose et al. (65) have proposed that at least three genetically determined defects participate in the pathogenesis. Two genes, located to the H-2 complex, predispose to an altered immune response to thyroid components, and diminish the ability of T cells to suppress an auto-immune response, while in EAT complete adjuvant may partly overcome the need for genetic predisposition. In OS chickens an abnormal thyroid function with hyperresponsiveness to very low levels of TSH has been demonstrated before hatching and signs of thyroiditis (88). This same abnormality was seen in Cornell Strain birds (46) with much lower incidence of thyroiditis. These findings support the theory

of a genetic organ-specific defect. In OS chickens also the thymus appears immunologically hyperresponsive to thyroid gland, which may be important for disease development (72). Moreover, the concept of a thyrotropic viral induction of thyroid abnormality in a genetically predisposed individual has been proposed, and C-type virus-like particles in OS chickens have been demonstrated, but needs further confirmation (87). Recently, it has been possible to convert low-responder inbred strains of mice to high-responders by cyclophosphamide treatment, suggesting that the suppressor activity influences the lesions (89).

Genetic aspects in man

The MHC in man analogous to the H-2 complex in mice is the HLA complex. Several studies have emphasized the influence of HLA upon many diseases (27, 71). These diseases can be divided into those primarily associated with the serologically defined HLA-A, B, C antigens, and those with stronger associations with the antigen of the D locus identified by mixed lymphocyte culture (D antigens) or serologically on B lymphocytes (D-related or DR antigens). These disorders are generally autoimmune diseases. It has therefore been suggested that susceptibility for development of organ-specific autoimmunity could be linked to certain HLA-D/DR alleles, or that HLA-D/DR could themselves act as immune response genes.

A number of studies in relatives of patients with autoimmune thyroid diseases have indicated a genetic component in the pathogenesis, but there was also a high incidence of apparently non-immunological thyroid diseases in those families, indicating influence of factors relating to the thyroid gland itself, analogous to the findings in animal studies (32, 33). An association between the HLA system and autoimmune thyroiditis was first demonstrated in GD in which the frequency of HLA-D/DR3 was increased (7, 71). At the same time a highly increased frequency of HLA-Bw35 was found in subacute thyroiditis, while this disease was apparently not associated with HLA-D/DR (6, 57, 58). This further strengthens the concept that

the immune response in this disease was possibly secondary to a viral infection, and not of autoimmune origin, and it has been proposed that the HLA antigens may act as receptors for infectious agents involved in the pathogenesis (27). Recently, by combining with present data, Farid & Bear (27) suggest that DR5 may be increased secondary to Bw35, and they postulate that the autoimmune process is restricted by Bw35 and is determined by an Ir gene in linkage disequilibrium with DR5 (27).

It was not possible to show any deviations of the frequencies of HLA antigens in the chronic autoimmune thyroiditis (25, 38, 53) until recently, when Moens et al. (54) demonstrated an association between DR3 and AT, and Weissel et al. (85) between DR5 and HT. These findings indicated a genetic distinction between the two variants of autoimmune thyroiditis (Table 3) and have later been confirmed by others (26, 76). Preliminary findings have also shown an increase in the prevalence of DR5 in silent thyroiditis occurring post partum and of DR3 in silent thyroiditis unrelated to pregnancy (27).

As the HLA system might be important for control of the events responsible for antibody formation, the relationship between HLA alleles and the pattern of autoantibodies in autoimmune thyroiditis was of interest. In subacute thyroiditis a relation between HLA-Bw35 and an increase of IgA has been shown (58), and in GD an association between HLA-DR3 and IgG has been demonstrated (13), but no clear relation to thyroid autoantibodies. A significantly greater lymphocyte blast transformation in response to thyroglobulin in DR3 positive patients has been demonstrated in GD (68). In HT a relation between absence of D5 and thyroglobulin antibodies (29), thyroid-stimulating antibodies (11) and immune complexes (40) has been found, while similar relations to D5 were not present in AT (86). It was remarkable that the D5 gene, which seems to be associated with the susceptibility to develop HT, was negatively associated with the formation of most organ-specific autoantibodies, which probably play a pathogenic role in the development of the disease. However, the same pattern has been encountered in patients with pernicious anemia,

Table 5
The HLA-antigens associated with autoimmune thyroiditis

Disease	HLA
Graves' disease	D/DR3
Atrophic thyroiditis	D/DR3
Hashimoto's thyroiditis	D/DR3
Subacute thyroiditis	Bw33
Silent thyroiditis	D/DR3 - D/DR5?

another D5-associated disease, in which intrinsic factor antibodies were decreased in D5-positive individuals (75).

Farid et al. (26) have proposed a relationship between DR5 and autoantibodies promoting goitre formation as an explanation of the association of this allele in HT and not in AT. Accordingly, it has been demonstrated that thyroid-stimulating antibodies, which were also present in HT, might have growth-stimulating capacity (55). However, an association between antibodies with growth-stimulating capacity and D/DR5 in HT remains to be established.

These findings suggest a HLA-D restriction and genetic specificity of the proliferative response to the relevant antigens as was proposed by Farid & Bear (27). In analogy to animal studies there might be genetically determined low- and high-responders with respect to organ-specific autoantibodies. The antibodies of the D5-positive individuals might be of higher affinity, or the D5 might function as receptor for these antibodies, resulting in more rapid disappearance. The mechanisms initiating the development of the disease were probably dependent on multiple genes as well as environmental factors.

Concluding remarks

Recent progress now seems to indicate that autoimmune thyroiditis comprises several variants with genetically different predisposition. Furthermore, a genetic distinction between goitrous and non-goitrous autoimmune thyroid-

itis is evident, and therefore HT and AT should be regarded as separate disease entities and not as different stages of the same disorder. Antibody formation is probably under genetic control, and a different relationship between autoantibodies and the HLA-D alleles has been demonstrated in these variants. Moreover, a genetic distinction exists between the chronic and reversible form of autoimmune thyroiditis, as the latter is not associated primarily with the HLA-D, but instead with the HLA-B antigen. This suggests that there could be a difference in the pathological process in these disorders rather than a common organ-specific abnormality, although it is evident that disease development is due to an interplay of several different factors. Studies of the full spectrum of autoantibodies in organ-specific autoimmune diseases and their relation to HLA-D antigens are needed for further progress in this field.

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