

## **Autoimmune thyroid disorders.**

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## **Abstract**

Autoimmune thyroid diseases (AITD) result from a dysregulation of the immune system leading to an immune attack on the thyroid. AITD are T cell-mediated organ-specific autoimmune disorders. The prevalence of AITD is estimated to be 5%; however, the prevalence of antithyroid antibodies may be even higher. The AITD comprise two main clinical presentations: Graves' disease (GD) and Hashimoto's thyroiditis (HT), both characterized by lymphocytic infiltration of the thyroid parenchyma. The clinical hallmarks of GD and HT are thyrotoxicosis and hypothyroidism, respectively. The mechanisms that trigger the autoimmune attack to the thyroid are still under investigation. Epidemiological data suggest an interaction among genetic susceptibility and environmental triggers as the key factor leading to the breakdown of tolerance and the development of disease. Recent studies have shown the importance of cytokines and chemokines in the pathogenesis of AT and GD. In thyroid tissue, recruited T helper 1 (Th1) lymphocytes may be responsible for enhanced IFN- $\gamma$  and TNF- $\alpha$  production, which in turn stimulates CXCL10 (the prototype of the IFN- $\gamma$ -inducible Th1 chemokines) secretion from the thyroid cells, therefore creating an amplification feedback loop, initiating and perpetuating the autoimmune process. Associations exist between AITD and other organ specific (polyglandular autoimmune syndromes), or systemic autoimmune disorders (Sjögren's syndrome, rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, cryoglobulinemia, sarcoidosis, psoriatic arthritis). Moreover, several studies have shown an association of AITD and papillary thyroid cancer. These data suggest that AITD patients should be accurately monitored, for thyroid dysfunctions, the appearance of thyroid nodules, and other autoimmune disorders.

**Keywords:** Autoimmune thyroid diseases, Hashimoto's thyroiditis, Graves' disease, chemokines, CXCL10, cytokines.

## **Introduction**

Autoimmune thyroid diseases (AITD) result from a dysregulation of the immune system leading to an immune attack on the thyroid. AITD are T cell-mediated organ-specific autoimmune disorders [1, 2]. AITD are the most frequent autoimmune disorders, and the most common pathological conditions of the thyroid gland. The AITD comprise two main clinical presentations: Graves' disease (GD) and Hashimoto's thyroiditis (HT), that are both characterized by lymphocytic infiltration of the thyroid parenchyma. The clinical hallmarks of GD and HT are thyrotoxicosis and hypothyroidism, respectively.

The present study summarizes data about epidemiologic, risk factors and immunopathogenesis of HT.

## **Epidemiology**

The prevalence of AITD is estimated to be 5% [3, 4]; however, the prevalence of antithyroid antibodies (ATA) without clinical disease may be even higher [5].

Studies [6-8] that have evaluated the changing epidemiology of HT have shown that: (1) women have a greater risk than men (about 4-10/1, female/male); (2) hypothyroidism from HT becomes more common with advancing age; (3) there are substantial geographic variability in the prevalence and incidence of HT; (4) the prevalences of HT and thyroid antibodies differ with race; (5) ATA frequency increases with age, with a peak around 45–55 years; (6) populations that are iodine-sufficient have higher incidence of HT than those that are iodine-deficient.

In the Wickham study, the prevalence of spontaneous hypothyroidism from HT was 15/1000 in women, with mean age at diagnosis of 57 years, and less than 1/1000 in men [9]. The mean incidence of spontaneous hypothyroidism was 3.5/1000 in women and 0.6/1000 in men. Similar results have been recorded in other geographical areas [6].

The contemporary reported incidence rates of HT and hypothyroidism are higher than in studies previously performed in similar regions [10].

However, it is not possible to know whether this is due to actual increased incidence or to the use of more accurate diagnostic procedures [11].

The HT is a prototypical organ-specific autoimmune disease. However, in many cases, AITD may be associated in the same patient with other organ-specific autoimmune attacks (such as in the case of type II autoimmune polyglandular syndrome), or less frequently with systemic autoimmune syndromes.

## **Risk factors**

The mechanisms that trigger the autoimmune attack to the thyroid are still under investigation. Epidemiological data suggest an interaction among genetic susceptibility and environmental triggers as the key factor leading to the breakdown of tolerance and the development of disease.

### **Genetic susceptibility**

Epidemiological evidence for a genetic susceptibility to AITD has been shown by the familial clustering of the disease (20–30% of AITD in siblings of affected patients), sibling risk ratio (about 17) for AITD, the increased prevalence of thyroid Abs (50%) of siblings of affected subjects [12]. The results of the twin studies show a concordance rate for AITD of 0.3–0.6 for monozygotic, compared to 0.00–0.1 for dizygotic twins [13, 14]. From the twin studies, the heritability of GD has been calculated to be 79% in twin studies, and that of the presence of thyroid Abs about 70% [14].

Several genes have been identified as significantly associated with the AITD and the presence of thyroid antibodies [15, 16].

Among AITD genes detected by traditional case–control studies and tag single nucleotide polymorphism screening:

1- PTPN22 is involved in T-cell signal transduction through interaction with molecules essential for T-cell receptor signalling [17];

2- CTLA4 plays a role in inhibiting T-cell signalling [18];

3- Histocompatibility antigens (HLA) class II molecules play a key part in presenting exogenous antigens for recognition by CD4+ T-helper cells [19];

4- IL2RA encodes CD25 which is expressed on T-regulatory cells and is believed to be important in downregulating T-cell activity [20].

Other AITD genes were detected by case–control studies and confirmed by genome-wide association studies (GWAS):

1- FCRL3 is highly expressed during B-cell maturation and believed to both positively and negatively regulate B-cell signalling [21];

2- HLA class I molecules play a key role in presenting endogenous antigens, such as virally derived antigens, for recognition by CD8+ T cells [19];

3-TSHR is the receptor for TSH and is the primary autoantigenic target in GD [22].

Novel AITD genes have been detected by GWAS and ImmunoChip:

1- GDCG4p14 has been shown to be expressed in CD4+ T helper and CD8+ T cells [23];

2- BACH2 is expressed during B-cell maturation and is believed to control B-cell development and antibody production [24];

3- RNASET2 is expressed in CD4+ T-helper and CD8+ T cells [23];

4- FOXE1 is involved in thyroid gland morphogenesis and binds response elements in the thyroglobulin (Tg) and thyroid peroxidase promoters [25].

There are other AITD genes detected by GWAS and ImmunoChip whose function in AITD is currently unknown [15].

Interestingly among susceptibility genes whose function is known, 7/11 are involved in T cells function, strongly suggesting the importance of T cells in the immunopathogenesis of AITD.

### **Environmental factors**

Environmental factors contribute to the occurrence of AITD for about a 20%. Several environmental factors have been identified: radiation, iodine, smoking, infection, stress and drugs.

The link between environmental factors and autoimmunity is based on the principle that any injury resulting from infectious, chemical, radiological insults, may contribute to the activation of an innate immune response and, in susceptible individuals, to the development of AITD [26].

Radioiodine treatment of toxic goitre may be followed, by the appearance of GD, even Graves' ophthalmopathy (GO) [27]. Children exposed to radiation from Chernobyl showed a greater prevalence of thyroid autoantibody [28].

AITD tend to be more prevalent in areas with iodine sufficiency. Iodine supplementation of populations previously iodine deficient is associated with a transient rise increase of both autoimmune subclinical hypo and hyperthyroidism [29].

Cigarette smoking has been associated with GD and with GO [30, 31]. However, on the contrary, smoking decreases the risk of overt hypothyroidism as well as the prevalence of thyroid antibodies [32].

The thyroid is the organ with the highest selenium content because it expresses specific selenoproteins. After the discovery of myxoedematous cretinism following selenium repletion in iodine- and selenium-deficient children, many researches on links between thyroid and selenium have been published. Small amounts of selenium appear sufficient for adequate activity of deiodinases, however selenium status appears to have an impact on the development of thyroid pathologies. The importance of selenium supplementation in AITD has been emphasized [33].

Stress has been considered as a trigger factor for GD [34].

Among drugs, lithium treatment is associated with an increased prevalence of thyroid antibodies, hypothyroidism and, to a lesser extent, of GD [35].

Thyroid autoimmunity might be relevant in amiodarone induced thyrotoxicosis [36].

The so-called “reconstitution Graves’ disease” has been observed, in patients treated with anti-T cell anti-CD52 Campath monoclonal antibody for multilocular sclerosis, or in AIDS patients treated with antiretroviral therapy [37]. In both cases, GD occurs during the lymphocyte reconstitution phase suggesting the existence of an imbalance towards a Th2-mediated immune response.

Many studies have evaluated the contribution of viruses to the occurrence of AITD, mainly with not fully convincing or negative results [38].

## **HCV**

However, recently, several studies have confirmed an association of hepatitis C virus (HCV) infection with AITD both in adults [39, 40], such as in children [41].

The thyroid disorders observed in patients with chronic hepatitis C (CHC) is characterized by a high risk of autoimmune thyroiditis (AT) and hypothyroidism in females, and high levels of anti-thyroperoxidase antibodies (AbTPO).

Recently, several studies have confirmed a high frequency of AT in patients with mixed cryoglobulinemia and hepatitis C (MC+HCV) and CHC.

In a case-control study serum AbTPO, and/or AbTg, and subclinical hypothyroidism were significantly more frequent in MC+HCV patients than in HCV-negative controls [42].

Moreover, a high prevalence of papillary thyroid cancer (PTC) has been observed in CHC patients, and more recently in MC+HCV patients, overall in the presence of AT [43-46].

The presence of HCV in the thyroid of chronically infected patients has been demonstrated [47, 48].

More recently, it has been shown that HCV can infect a human thyroid cell line (ML1) *in vitro*. These findings suggest that HCV infection of thyrocytes may play a role in the association between CHC and thyroid diseases [49].

Recent data have confirmed a strong association of AITD with interferon(IFN)- $\alpha$  therapy in patients with CHC. HCV and IFN- $\alpha$  can act in synergism to trigger AITD in patients. Approximately 40% of CHC patients develop thyroid disorders while receiving IFN- $\alpha$ . IFN-induced thyroiditis can manifest as destructive thyroiditis (or non-autoimmune hypothyroidism), or AT (with clinical features similar to those of GD or HT). IFN- $\alpha$  can induce thyroiditis via both immune stimulatory, such as direct toxic effects on the thyroid cells [50-52].

## **Endogenous factors**

The marked predominance of AITD in female [53] suggests that estrogens have a significant role in AITD. The complex immunological changes associated with pregnancy and their postpartum regression are important factors. However, the female predisposition to AITD is also present in nulliparous women. Microchimerism, the presence of small populations of cells from one subject in another genetically distinct individual (microchimerism), has also been considered as one of the endogenous factors linked to AITD [14].

### **Immunopathogenesis**

The common pathological feature of AITD is the presence of lymphocyte infiltrates within the thyroid. AT is characterized by lymphocytic infiltration, mainly of T cells, that may progressively replace thyroid tissue. Lymphoid infiltrates are also present in GD glands. Variable thyroid follicular cell atrophy and fibrosis are characteristic of thyroiditis, while in GD thyroid follicles are hypertrophied [54].

CD8<sup>+</sup> T cells is decreased in peripheral blood of patients with GD, HT and postpartum thyroiditis, just as in patients with other autoimmune diseases. Consequently, the CD4/CD8 ratio is increased. Also, activated T cells expressing HLA-DR are increased. In the thyroid tissue, T cell infiltrates associate CD4<sup>+</sup> and CD8<sup>+</sup> cells, often in the activated state. CD4<sup>+</sup> may be predominant in Hashimoto glands [55].

B cell numbers are normal in circulation in AITD. In HT, B cells are found within the thyroid tissue, typically organised in secondary lymphoid follicles, sometimes with germinal centres. Intrathyroid B cells have been shown to produce antibody, suggesting that the thyroid is the main source of autoantibodies *in vivo*. Bone marrow and juxta-thyroid lymph node B cells are also a source of antibodies.

The prevalence of AbTg in patients with HT is 25–50%, while is 90% for AbTPO [56]. In the young patients with thyroiditis, however, AbTg may be present in the absence of AbTPO.

AbTg, predominantly IgG1 and 4, do not activate complement and are not pathogenic [57].

AbTPO are a sensitive marker of AITD, both in thyroiditis and GD. AbTPO are markers of thyroid dysfunction [58], in fact their presence is predictive of the subsequent occurrence of thyroid failure in AITD patients with subclinical hypothyroidism.

TSH receptor antibodies (TRAbs) are pathognomonic of GD. Indeed, the stimulating TRAbs are responsible for the hyperthyroidism of GD. TRAbs are present in more than 90% of the GD patients. TRAb radioimmunometric competition assays detect TRAbs through their capacity to bind to the TSH receptor; they provide no indication on the biological activity of the antibodies, stimulating, blocking or, neutral. The identification of the bioactivity of TRAbs

requires a bioassay using cellular systems carrying functional TSH receptors [59]. Blocking antibodies are detected using a modified bioassay [60, 61]. Blocking TRAbs are mostly detected in a fraction of patients with AT.

### **Cytokines, chemokines, and AITD**

Recent studies have shown the importance of cytokines and chemokines in the pathogenesis of AT and GD. In thyroid tissue, recruited T helper 1 (Th1) lymphocytes may be responsible for enhanced IFN- $\gamma$  and TNF- $\alpha$  production, which in turn stimulates CXCL10 (the prototype of the IFN- $\gamma$ -inducible Th1 chemokines) secretion from the thyroid cells, therefore creating an amplification feedback loop, initiating and perpetuating the autoimmune process (**Fig. 1**).

The IFN- $\gamma$ -inducible protein 10 (IP-10/CXCL10) was initially identified as a chemokine that is induced by IFN- $\gamma$ . CXCL10 exerts its function through binding to chemokine (C-X-C motif) receptor 3 (CXCR3) [62].

CXCL10 and its receptor, CXCR3, appear to contribute to the pathogenesis of many autoimmune diseases, organ specific [such as type 1 diabetes (T1D), GD and GO], or systemic [such as systemic lupus erythematosus (SLE), MC, Sjögren's syndrome (SS), sarcoidosis, psoriasis or systemic sclerosis (SSc)] [63-68].

The secretion of CXCL10 by (CD)4+, CD8+, and natural killer is dependent on IFN- $\gamma$ . Under the influence of IFN- $\gamma$ , and with synergism with TNF- $\alpha$ , CXCL10 is secreted by thyrocytes [69].

Determination of high level of CXCL10 in peripheral fluids is therefore a marker of a Th1 orientated immune response [62].

High levels of circulating CXCL10 have been shown in patients with AT, in particular in the presence of a hypoechoic ultrasonographic pattern, which is a sign of a more severe lympho-monocytic infiltration, and in those with hypothyroidism [69].

For these reasons, it has been postulated that CXCL10 could be a marker of a stronger and more aggressive inflammatory response in the thyroid, subsequently leading to thyroid destruction and hypothyroidism. Further studies are needed to investigate whether CXCL10 is a novel therapeutic target in AT.

Moreover, CXCL10 appears to contribute to the pathogenesis of GD and GO (**Fig. 1**). Under the influence of IFN- $\gamma$ , CXCL10 is secreted by thyrocytes (in GD), fibroblasts and preadipocytes (in GO) [70-72].

Circulating CXCL10 is associated with the active phase of GD in both newly diagnosed and relapsing hyperthyroid patients. Methimazole reduces CXCL10 secretion by isolated thyrocytes, decreases serum CXCL10 levels, and promotes a transition from Th1 to Th2 dominance in patients with GD active phase [73].



In GD patients the decrease of CXCL10 after thyroidectomy and radioiodine strongly suggests that this chemokine is mainly produced by the thyroid itself. In GO patients the increased concentrations of CXCL10, at least in part, reflect the activity of orbital inflammation [74, 75].

A significant reduction in CXCL10 serum concentrations during corticosteroids and/or radiotherapy treatments, as compared both to control group and to basal values in GO patients, suggests that this chemokine could serve as a guideline in therapeutic decision-making in patients with GO [76, 77].

Further studies are needed to evaluate whether CXCL10 is a novel therapeutic target in HT, GD and GO [78, 79].

### **Other autoimmune diseases associated with thyroid autoimmunity**

Associations exist between AITD and other organ specific, or systemic autoimmune disorders.

Among these syndromes, polyglandular autoimmune syndromes (PAS) are rare polyendocrinopathies characterized by the failure of several endocrine glands as well as nonendocrine organs, caused by an immune-mediated destruction of endocrine tissues.

In a study [80] of more than 15,000 adult patients with endocrine diseases, who have been screened, 360 patients with PAS have been found. T1D, GD, HT, Addison's disease, vitiligo, alopecia, hypogonadism, and pernicious anemia were observed in 61%, 33%, 33%, 19%, 20%, 6%, 5%, and 5%, respectively. The most common disease combination was T1D and AITD. In most patients, T1D was the first manifestation of PAS (48%).

Patients with PAS had significantly higher frequencies of the human leukocyte antigens A24, A31, B8, B51, B62, DR3, and DR4 (relative risk, 2.35, 2.74, 2.47, 7.17, 2.22, 1.94, and 2.46) vs. controls, and for A31, B15, B52, B55, DR2, DR11, and DR13 (relative risk, 2.51, 7.96, 3.99, 5.36, 4.46, 2.89, and 3.26) vs. T1D patients without PAS. This study suggests that patients with autoimmune endocrine disease should be followed on a regular basis, if clinical disease is present, and serological measurement of organ-specific antibodies should follow [80].

The above mentioned study underlines the importance of a common genetic susceptibility in patients with AITD and T1D, as confirmed also in other studies [81].

Thyroid function abnormalities and thyroid autoantibodies have been frequently described in patients with systemic rheumatologic autoimmune diseases, such as SS, rheumatoid arthritis (RA), SLE and SSc [67, 82, 83].

A recent study showed that, despite contradictory results in the literature, there is a greater prevalence of the association between AITD and rheumatic diseases, highlighting the possibility of common pathogenic mechanisms among them [84].

Furthermore, more recently, a first study [85] has evaluated longitudinally the incidence of new cases of thyroid autoimmunity and dysfunction in 179 female patients with SSc, and 179 matched control subjects, with similar iodine intake (median follow-up 73 months in patients with SSc vs. 94 months in control subjects). A high incidence of new cases of hypothyroidism, thyroid dysfunction, AbTPO positivity, and appearance of a hypoechoic thyroid pattern in sclerodermic patients (15.5, 21, 11, and 14.6 of 1000 patients per year; respectively) vs. that in control subjects was shown. A logistic regression analysis showed that in patients with SSc, the appearance of hypothyroidism was related to a borderline high initial TSH level, AbTPO positivity, and a hypoechoic and small thyroid. This study shows a high incidence of new cases of hypothyroidism and thyroid dysfunction in female sclerodermic patients, suggesting that these patients should have periodic thyroid function follow-up [85].

Furthermore, new associations of AITD are being uncovered, for examples with MC, sarcoidosis, or psoriathic arthritis [86-88].

Many studies underline the importance of a common genetic susceptibility in patients with AITD and systemic autoimmunity.

The participation of the HLA of the haplotypes HLA-B8 and DR3 in both AITD and primary SS (pSS) has been suggested, because of the high frequency of those haplotypes in Caucasian patients with those diseases [89].

Genetic influence has been suggested in a study of 35 families with several cases of SLE concomitant with AITD, in which a gene of susceptibility was identified in 5q14.3-q15 (major locus of susceptibility for SLE, also found in AITD). That locus can be shared by patients with SLE and AITD, evidencing a potential genetic link between both diseases [90].

Another study has assessed the frequency of ATA and the genetic association with HLA class II antigens in 85 patients with scleroderma. Individuals with anti-TPO had a higher frequency of the HLA-DR15 allele than patients without those antibodies, suggesting that the HLA-DR15 allele can be a marker of immunogenicity for the formation of anti-TPO [91].

Even environmental factors could be implicated in the association of autoimmune disorders.

Recent reports that have shown that the serum and/or the tissue expressions of CXCL10 are increased in organ specific autoimmune diseases, such as AT, GD, T1D, and/or systemic rheumatological disorders like RA, SLE, SSc, MC, underline the importance of a common immunopathogenesis of these disorders, that are characterized by a Th1 prevalent autoimmune response in the initial, and/or active phases of these diseases [63, 92, 93].

### **The association of AITD and thyroid cancer**

Several studies have shown an association of AITD and PTC [94].

A recent study [95] analyzed the frequency of PTC, TSH levels and thyroid autoantibodies in 13738 patients [9824 untreated and 3914 under l-thyroxine (l-T(4))]. The frequency of PTC was significantly higher in nodular-HT than in nodular goiter and was associated with increased levels of serum TSH. Treatment with l-T(4) reduces TSH levels and decreases the occurrence of clinically detectable PTC [95].

However, other studies have found that both thyroid autoimmunity and increased TSH represent independent risk factors for malignancy [96].

A high prevalence of PTC has been observed in CHC patients, and more recently in MC patients, overall in CHC or MC patients with AT [43, 44, 46].

The increased prevalence of PTC in AITD patients is clinically relevant since about 10-30% of these patients may have an aggressive disease, requiring systemic treatments [97-99].

## **Conclusion**

Autoimmune thyroid diseases (AITD) result from a dysregulation of the immune system leading to an immune attack on the thyroid. AITD are T cell-mediated organ-specific autoimmune disorders. AITD are the most frequent autoimmune disorders. The AITD comprise two main clinical presentations: GD and HT, that are both characterized by lymphocytic infiltration of the thyroid parenchyma. The clinical hallmarks of GD and HT are thyrotoxicosis and hypothyroidism, respectively. The mechanisms that trigger the autoimmune attack to the thyroid are still under investigation. Epidemiological data suggest an interaction among genetic susceptibility and environmental triggers as the key factor leading to the breakdown of tolerance and the development of disease. Several environmental risk factors have been identified: radiation, iodine, selenium, smoking, infections, stress and drugs.

The common pathological feature of AITD is the presence of lymphocyte infiltrates within the thyroid. Recent studies have shown the importance of cytokines and chemokines in the pathogenesis of AT and GD. In thyroid tissue, recruited Th1 lymphocytes may be responsible for enhanced IFN- $\gamma$  and TNF- $\alpha$  production, which in turn stimulates CXCL10 (the prototype of the IFN- $\gamma$ -inducible Th1 chemokines) secretion from the thyroid cells, therefore creating an amplification feedback loop, initiating and perpetuating the autoimmune process.

Associations exist between AITD and other organ specific, or systemic autoimmune disorders [100]. Many studies underline the importance of a common genetic susceptibility in patients with AITD and systemic autoimmunity.

Moreover, recent reports that have shown that the serum and/or the tissue expressions of CXCL10 are increased in organ specific autoimmune diseases, such as AT, GD, T1D, and/or systemic rheumatological disorders like RA, SLE,

SSc, MC, underline the importance of a common immunopathogenesis of these disorders, that are characterized by a Th1 prevalent autoimmune response in the initial, and/or active phases of these diseases.

Several studies have found that both thyroid autoimmunity and increased TSH represent independent risk factors for thyroid malignancy.

The above mentioned data suggest that AITD patients should be accurately monitored, for thyroid dysfunctions, the appearance of thyroid nodules, and other organ specific or systemic autoimmune disorders during the course of the disease.

**Integrity of Research and Reporting**

The authors declare that they have no conflict of interest.

**Conflict of Interest**

The authors declare that they have no conflict of interest.

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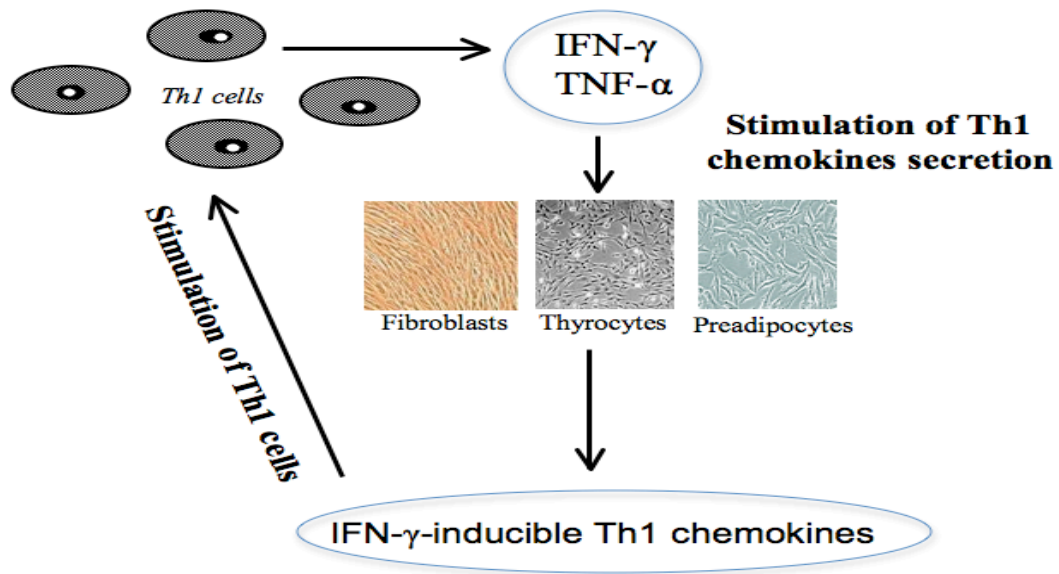
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## Figure Captions

**Fig. 1** In thyroid (and orbital tissue of GO patients), recruited Th1 lymphocytes may be responsible for enhanced IFN- $\gamma$  and TNF- $\alpha$  production, which in turn stimulates CXCL10 (the prototype of the IFN- $\gamma$ -inducible Th1 chemokines) secretion from the cells, therefore creating an amplification feedback loop, that initiates and perpetuates the autoimmune process.



**Fig. 1**



