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## INTERFERON INDUCED THYROIDITIS

Yaron Tomer and

James J. Peters VA Medical New York, NY

Francesca Menconi

Department of Medicine, Division of Endocrinology, Mount Sinai School of Medicine

### Abstract

Interferon-alpha (IFN $\alpha$ ) is used for the treatment of various disorders, most notable chronic hepatitis C virus (HCV) infection. One of the commonest side effects of IFN $\alpha$  therapy is thyroiditis, with up to 40% of HCV patients on IFN $\alpha$  developing clinical or subclinical disease. In some cases interferon induced thyroiditis (IIT) may result in severe symptomatology necessitating discontinuation of therapy. IIT can manifest as clinical autoimmune thyroiditis, presenting with symptoms of classical Hashimoto's thyroiditis or Graves' disease, or as non-autoimmune thyroiditis. Non-autoimmune thyroiditis can manifest as destructive thyroiditis, with early thyrotoxicosis and later hypothyroidism, or as non-autoimmune hypothyroidism. While the epidemiology and clinical presentation of IIT have been well characterized the mechanisms causing IIT are still poorly understood. It is likely that the hepatitis C virus (HCV) itself plays a role in the disease, as the association between HCV infection and thyroiditis is well established. It is believed that IFN $\alpha$  induces thyroiditis by both immune stimulatory effects and by direct effects on the thyroid. Early detection and therapy of this condition are important in order to avoid complications of thyroid disease such as cardiac arrhythmias.

### Keywords

Interferon; thyroiditis; autoimmunity

## INTRODUCTION

Interferon alpha (IFN $\alpha$ ) is a type I interferon that has been widely used as a therapeutic agent mostly, but not exclusively, for infectious and malignant diseases (1). IFN $\alpha$  binds to interferon receptors, and activates various signaling pathways, including the JAK-STAT pathway, the Crk-pathway, the IRS signaling pathway, and the MAP kinase pathway thereby stimulating transcription of target proteins which mediate its immune anti-tumor effects (2–4). One of the major indications for IFN $\alpha$  treatment is chronic hepatitis C. Approximately 50% of patients with chronic hepatitis C, who are treated with IFN $\alpha$  plus ribavirin, will achieve a sustained virologic response (5).

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Correspondence to: Yaron Tomer.

**Address for correspondence:** Yaron Tomer, MD, Department of Medicine, Box 1118, Mount Sinai Medical Center, One Gustave L. Levy Place, New York, N.Y. 10029, Voice: 212-241-6834 Fax: 212-534-3488, Yaron.Tomer@mssm.edu.

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IFN $\alpha$  therapy is associated with many side effects ranging from influenza-like symptoms to hematologic and neuropsychiatric side effects (6). One of the commonest side-effects of IFN $\alpha$  therapy is thyroiditis. The association between IFN $\alpha$  and thyroid disease was first reported more than two decades ago (7), and since the original description of interferon induced thyroiditis (IIT) numerous studies have reported a high incidence of thyroid disease in patients treated with IFN $\alpha$  (8;9). IIT is a major complication of IFN $\alpha$  therapy and can interfere with effective management of chronic hepatitis C. Indeed, some of the manifestations of IIT, especially thyrotoxicosis, can be severe and may result in stopping of interferon therapy (10; 11). Moreover, since the symptoms of hypothyroidism such as fatigue, and weight gain might be attributable to chronic hepatitis C or to IFN $\alpha$  therapy (6), the diagnosis of hypothyroidism in these patients might be delayed leading to development of further complications. In this chapter we will review the epidemiology, etiology, manifestations, and clinical approach to IIT.

## EPIDEMIOLOGY

Based on the epidemiological characteristics of IIT we have recently suggested a new classification of IIT into autoimmune IIT and non-autoimmune IIT (12). Autoimmune IIT can manifest as Graves' disease (GD), Hashimoto's thyroiditis (HT), or the production of thyroid autoantibodies (TAB's) without clinical disease, while non-autoimmune IIT can manifest as destructive thyroiditis, or non-autoimmune hypothyroidism.

### Autoimmune IIT

Hashimoto's thyroiditis (HT) is the commonest clinical manifestation of autoimmune IIT (13–15). The presence of TAB's prior to the initiation of IFN $\alpha$  therapy is a risk factor for the development of autoimmune IIT manifesting as Hashimoto's thyroiditis (9;16–18). Roti et al. calculated that elevated TPO antibodies before IFN $\alpha$  therapy had a positive predictive value of 67% for the development of clinical autoimmune IIT (10). The fact that pre-IFN $\alpha$  treatment TAB's are a risk factor for IIT suggests a genetic predisposition to the development of IIT (12).

The development of Graves' disease secondary to IFN $\alpha$  therapy is less common (10;19). A retrospective review of 321 patients with hepatitis B or C treated with IFN $\alpha$  found 10 patients who developed clinical thyrotoxicosis and of them six had classical signs of GD (19). In all cases of GD the thyrotoxicosis did not resolve after discontinuation of IFN $\alpha$  therapy (19). In most reported cases of autoimmune IIT manifesting as GD the disease did not go into remission when IFN $\alpha$  therapy was completed or stopped (16;19;20). One case report of Graves' ophthalmopathy secondary to IFN $\alpha$  treatment for hepatitis C was also reported (21).

The most common form of thyroid autoimmunity is the presence of thyroid antibodies [including thyroid peroxidase antibodies (TPO-Ab), and thyroglobulin antibodies (Tg-Ab)], without clinical disease (22). The presence of TAB's is usually a pre-clinical phase of AITD (23), and is genetically determined (24). TAB's without clinical disease commonly develop during or following IFN $\alpha$  therapy. TAB's can develop de novo during IFN $\alpha$  therapy, or their levels can increase during IFN $\alpha$  therapy if they were positive prior to treatment. Thus, it seems that IFN $\alpha$  can induce thyroid autoimmunity de novo, as well as exacerbate pre-existing thyroid autoimmunity (16;18). The incidence of de novo development of TAB's is about 10–40% (10;16–18;25). TAB's develop more frequently in women than in men treated with IFN $\alpha$ , and they are also associated with increasing age (26). The majority of individuals who develop "de novo" TAB's on IFN $\alpha$  therapy remain TAB positive after the end of treatment (15).

## Non-Autoimmune IIT

Non-autoimmune IIT is also common and is seen in up to 50% of IIT cases. Non-autoimmune IIT usually manifests as destructive thyroiditis. Destructive thyroiditis is a self-limited inflammatory disorder of the thyroid gland characterized by an early thyrotoxic phase, caused by the release of preformed thyroid hormones, and a late hypothyroid phase, with complete resolution in most cases (12). Since many cases of destructive thyroiditis secondary to IFN $\alpha$  are mild or subclinical, it is possible that destructive thyroiditis occurs more frequently than reported. Permanent hypothyroidism is unusual and develops in less than 5% of cases (27). Destructive thyroiditis in patients receiving IFN $\alpha$  therapy is diagnosed based on negative TSH-receptor antibodies (TRAb) and low thyroid radioactive iodine uptake (12). On re-treatment with IFN $\alpha$  patients frequently develop recurrent thyroiditis, and therefore, thyroid functions should be carefully monitored if treatment with IFN $\alpha$  is resumed (28). While most cases of destructive thyroiditis due to IFN $\alpha$  resolve spontaneously, some patients may develop complications, such as rapid atrial fibrillation, requiring thyroid ablation prior to re-treatment with IFN $\alpha$ . Moreover, a subset of patients with destructive thyroiditis may progress to permanent hypothyroidism (11). The presence of TAB's prior to the initiation of IFN $\alpha$  is a significant risk factor for developing permanent hypothyroidism due to autoimmune thyroiditis. Interestingly, one group from France reported 3 patients that developed destructive thyroiditis followed by hypothyroidism, and a few months later by recurrent thyrotoxicosis due to Graves' disease (29). Of note all 3 patients had positive TAB's during the DT episode again demonstrating that IFN $\alpha$  triggers autoimmune thyroiditis in genetically predisposed individuals.

Non-autoimmune IIT can also manifest by hypothyroidism without TAB's (20). Frequently the hypothyroidism is transient and resolves spontaneously upon completion of IFN $\alpha$  therapy (10;14–16).

## ETIOLOGY

Most of the beneficial effects of IFN $\alpha$  in infectious and malignant diseases are due to its effects on the immune system. Therefore, it was assumed for many years that the side effects associated with IFN $\alpha$  therapy including thyroiditis are due to immune dysregulation. However, while, immune mechanisms must play a role in the development of IIT, the predilection to the thyroid, and the non-autoimmune manifestations of IIT suggested that direct thyroid effects of IFN $\alpha$  play a major role in the etiology of IIT (Figure 1).

## Immune mechanism

IFN $\alpha$  receptor binding results in activation of the JAK-STAT pathway (30), leading to activation of a large number of interferon-stimulated genes (ISGs) including cytokine and adhesion molecule genes (31;32). These combined effects can contribute to the development of thyroid autoimmunity. IFN $\alpha$  increases the expression of MHC class I antigens on cells. As expected, IFN $\alpha$  was shown to increase the expression of MHC class I antigens on thyroid epithelial cells (10). Over-expression of class I antigens can activate cytotoxic T cells, thereby leading to tissue damage and inflammatory response (31).

Another effect of IFN $\alpha$  that could trigger autoimmune IIT is switching of the immune response to a Th1 mediated pattern (33). This causes production of IFN- $\gamma$  and IL-2, two potent proinflammatory cytokines (34). Indeed, hepatitis C patients, treated with IFN $\alpha$ , that developed IIT showed Th1 polarization of their immune response (35). However, Graves' disease, which is generally believed to be a Th2 mediated disease, is one of the manifestations of autoimmune IIT (36;37). Since IFN $\alpha$  is associated with Th1 switching it is unclear how IFN $\alpha$  can induce

GD in some patients. One explanation of this paradox comes from recent studies by Rapoport and colleagues suggesting that the initiation phase of GD may be Th1 mediated (38).

IFN $\alpha$  enhances the activity of lymphocytes, macrophages, and NK cells (1;31;39), and it also activates neutrophils and monocytes (31). IFN $\alpha$  can induce the release of potent cytokines, such as IL-6 (31), a cytokine that has been associated with autoimmune thyroiditis (40). Additional effects of IFN $\alpha$  include alteration of immunoglobulin production and decrease in T regulatory cell function, which can contribute to the development of autoimmune responses (41;42).

### Direct effects of interferon alpha on the Thyroid

The predilection of the autoimmune effects of IFN $\alpha$  to the thyroid and the occurrence of non-autoimmune IIT in up to 50% of patients strongly suggest that IFN $\alpha$  exerts direct effects on the thyroid. Few studies to date examined the direct effects of IFN $\alpha$  on thyroid cells. IFN $\alpha$  was shown to inhibit TSH-induced gene expression of thyroglobulin (Tg), TPO, and sodium iodide symporter (NIS) in cultured human thyrocytes (43). We have recently tested the expression levels of the TSHR, Tg, TPO, and NIS genes in a rat thyroid cell line. Our results showed an early (24 hours) increase in the levels of TSHR, Tg, TPO, and NIS with a later decrease (at 48 hrs) in the levels of TPO and NIS, but not TSHR (44). Moreover, we have shown increased thyroid cell death induced by IFN $\alpha$  (44). Increased thyroid cell death was also recently reported by another group (45). Combined, these data demonstrate a direct toxic effect of IFN $\alpha$  on thyroid follicular cells. Such effects can explain the non-autoimmune manifestations of IIT.

## DIAGNOSIS AND TREATMENT (12)

The diagnosis of IIT is not always simple and straightforward. Since the patients have a plethora of symptoms associated with chronic hepatitis C and interferon alpha treatment, symptoms of hypo- or hyper-thyroidism may be attributed to their underlying disease and not to a thyroid abnormality. For example, classical symptoms of hypothyroidism such as weight gain, lack of energy, depression, or hair loss could be caused by the liver disease or interferon alpha.

### Diagnosis of IIT

Since IIT can cause severe hyper- or hypo-thyroidism (10;11;21;26;46;47), it is now recommended that all patients receiving interferon alpha therapy for hepatitis C have a baseline TSH level measured and repeat TSH measured at regular intervals during therapy (12). Clinicians should routinely examine for signs of thyroid dysfunction such as tachycardia or bradycardia, heat or cold intolerance, and unexpected weight change.

In addition, we recommend screening all hepatitis C patients for thyroid disease prior to starting IFN $\alpha$  therapy. Baseline screening should include at least TSH levels but we recommend screening also for thyroid antibodies (TAB's) (TPO-Ab, Tg-Ab) since positive TAB's are a significant risk factor for IIT (9). If the TSH level is normal and TAB's negative, TSH levels should be monitored every three months until completion of IFN $\alpha$  course. If TSH levels are normal, but TAB's are positive we recommend monitoring TSH levels every two months since clinical thyroid disease is much more likely to develop. Currently there are not tests to predict the development of IIT in patients starting IFN $\alpha$  course. However, a recent study from Italy showing a significant association between lower serum CXCL10 levels and the development of IIT, suggested that this might be a useful predictive test (48). Since pre-treatment TAB's also have a high predictive value for the development of autoimmune IIT (10), it would be interesting to test in the future the predictive value both of these tests combined.

If the patient develops abnormal thyroid functions while on IFN $\alpha$  a full workup needs to be completed. For thyrotoxicosis, in order to discern between GD and destructive thyroiditis,

workup should also include TSH receptor antibody (TRAb), and TPO-Ab, and Tg-Ab levels. If antibodies are negative I-123 uptake and scan may be performed. For hypothyroidism workup should include full thyroid functions and antibodies (TPO-Ab, and Tg-Ab).

### Treatment of IIT

**Thyrotoxicosis**—In most cases thyrotoxicosis is caused by destructive thyroiditis (DT) or by Graves' disease (GD). If the TRAb and TAB's are negative and the radio-iodine uptake is low the patient most likely has DT, and should be treated with a beta-blocker, if symptomatic. Patients with DT should be monitored for the development of hypothyroidism, which usually follows the hyperthyroid phase within a few weeks. Corticosteroids, while helpful in subacute thyroiditis, are generally contraindicated in hepatitis C patients. In most cases IFN $\alpha$  therapy can be continued. However, if severe symptomatic thyrotoxicosis develops withholding IFN $\alpha$  therapy should be considered in consultation with the hepatologist (19). In addition, re-challenge with IFN $\alpha$  may result in a recurrence of DT (28), and, therefore, patients need close monitoring of thyroid functions if they are re-treated with IFN $\alpha$ . In cases of IIT that manifest as Graves' disease (GD), thyroid ablation with radioactive iodine and/or surgery is preferred (49). We do not recommend treating patients with interferon-induced GD with anti-thyroid medications since they can worsen the liver dysfunction.

**Hypothyroidism**—Patients are treated with thyroid hormone replacement, with no need to stop IFN $\alpha$  therapy. However, close monitoring of thyroid functions, at least every two months, should be performed since the disease may progress leading to increased T4 requirements. Moreover, T4 replacement requirements may increase if patients are treated with a second course of interferon, or may decrease or end altogether after completion of IFN $\alpha$  course (14; 26).

### IS THERE A GENETIC SUSCEPTIBILITY TO IIT?

GD and HT have a strong genetic predisposition (reviewed in (50;51)). Therefore, one hypothesis on the pathogenesis of IIT is that IFN $\alpha$  triggers thyroiditis in genetically predisposed individuals (12). Support for a genetic predisposition for IIT comes from epidemiological observations showing variations in the prevalence of IIT in different ethnic populations. In one study Asian origin was an independent predictor of thyroid dysfunction in patients receiving IFN $\alpha$  (52). Like in AITD there is a female preponderance in IIT (8). The female predisposition to IIT could be due to an X-chromosome susceptibility locus, or due to the effects of estrogens (53).

The presence of TAB's before initiation of IFN $\alpha$  therapy is a strong risk factor for the development of clinical IIT (9;10;16). Since the presence of TAB's is a pre-clinical stage of AITD and represents a marker for genetic predisposition to AITD (23), this finding also supports the notion that IFN $\alpha$  may trigger thyroiditis in genetically predisposed individuals. We have studied the genetic predisposition to IIT in the thyroiditis-prone NOD-H2h4 mouse (54). When we treated NOD-H2h4 mice with IFN $\alpha$  for eight weeks the interferon-injected group showed increased frequency thyroiditis and/or thyroid antibodies, compared to the saline-injected group, (46.2% vs. 30.8%); however, this difference was not statistically significant and more studies are needed to examine the effects of IFN $\alpha$  on thyroiditis in NOD-H2h4 mice (54;54).

In recent years several susceptibility genes for thyroid autoimmunity have been identified (55), including HLA-DR (56;57), CTLA-4 (58–60), PTPN22 (61;62), thyroglobulin (63) and TSHR (64). It is likely that some of these genes also contribute to the genetic susceptibility to IIT. Indeed, two small studies showed HLA associations of IIT (46;65). We recently tested several candidate genes for association with IIT. Our preliminary data, in a small cohort,

showed evidence for association of IIT with polymorphisms in the CTLA-4 and CD40 genes (66). Taken together, this preliminary evidence supports a genetic role in the etiology of IIT.

## DOES CHRONIC HEPATITIS C VIRUS INFECTION CONTRIBUTE TO THE PATHOGENESIS OF IIT?

IIT has been reported in patients receiving IFN $\alpha$  for various diseases (67). However, by far IIT is most common in patients with chronic HCV infection. Could HCV infection play a role in the etiology of IIT? In fact, there is strong evidence that infectious agents may trigger thyroid autoimmunity (68). Among the possible infectious triggers of AITD, HCV has received much attention (69).

Earlier studies of patients with hepatitis C that never received IFN $\alpha$  showed mixed results. Some studies did not show a correlation between hepatitis C infection and the presence of thyroid antibodies (70–72). On the other hand, other studies have shown a significant association between hepatitis C infection and thyroid disorders (17;73–76). Some of the weaknesses of earlier studies included the use of less sensitive TAb assays and the lack of control for factors, which may affect the development of thyroid autoimmunity, mainly iodine intake. However, a recent well-controlled study demonstrated that both hypothyroidism and thyroid autoimmunity were significantly more common in patients with hepatitis C compared to controls (69;76). Similarly, Indolfi et al found that the prevalence of non autoimmune hypothyroidism, as well as the presence of Tg-Ab, were higher in untreated children with HCV compared to healthy non-HCV infected controls. This increased prevalence was not associated with other parameters (family history of autoimmune diseases, duration of HCV infection, viral genotype, viral load or liver function) except active HCV infection (77). Moreover, pooling of data from all studies on HCV infection and thyroid autoimmunity demonstrated a significant increase in the risk of thyroiditis in HCV patients (78). Therefore, we conclude that HCV infection is most likely a risk factor for thyroiditis both autoimmune and non-autoimmune.

Could HCV trigger thyroiditis by infecting thyroid cells? A recent study demonstrated HCV virions inside thyroid follicular cells (79) suggesting that this could be a potential mechanism. However, even if HCV cannot infect thyroid cells, viral proteins that are shed from virions may also have important physiological consequences. For example, it was shown that HCV E2 proteins can induce apoptosis (80;81), and upregulate the pro-inflammatory cytokine interleukin 8 (IL-8) (82). These data suggested that HCV envelope proteins themselves could significantly impact the thyroid environment and contribute to thyroid dysfunction. Indeed, we have recently shown that HCV E2 protein can bind to CD81 molecules on thyroid cells and trigger IL-8 secretion (83). Thus, a potential mechanism exist whereby HCV itself infects thyroid cells, or its envelope proteins bind to thyroid cells, triggering cytokine secretion that can activate resident T-cells and, in genetically susceptible individuals, result in thyroid autoimmunity through a bystander mechanism.

## CONCLUSIONS

Interferon induced thyroiditis (IIT) is a common complication of IFN $\alpha$  therapy of HCV patients (84). IFN $\alpha$  can induce thyroiditis by at least two mechanisms: (1) Immune dysregulation resulting in activation of T-cells which, in genetically predisposed individuals, will trigger AITD; (2) Direct thyroid toxic effects resulting in thyroid inflammation which, in genetically predisposed individuals, can cause autoimmune thyroiditis by bystander mechanisms. HCV infection most likely has a synergistic effect in the triggering of thyroiditis by IFN $\alpha$ . IIT has very high prevalence and all patients with chronic hepatitis C receiving IFN $\alpha$  therapy should undergo routine thyroid screening. In most cases IIT can be treated without discontinuing IFN $\alpha$  therapy, but occasionally the manifestations are severe requiring halting IFN $\alpha$  therapy.

### CLINICAL PRACTICE POINTS

- Interferon induced thyroiditis (IIT) is a common complication of interferon alpha (IFN $\alpha$ ) treatment of chronic hepatitis C with up to 10% of patients developing clinical thyroiditis and up to 30% developing subclinical autoimmune thyroiditis.
- The main clinical manifestations of IIT can be divided into: (1) autoimmune IIT, which can manifest as Hashimoto's thyroiditis, Graves' disease, or the development of thyroid antibodies; and (2) non-autoimmune IIT which can manifest as destructive thyroiditis or non-autoimmune hypothyroidism.
- While most cases of IIT are mild, in some cases the thyrotoxicosis can be severe and require discontinuation of IFN $\alpha$  therapy.
- The etiology of IIT is unknown, but both immune effects and direct thyroid toxic effects of IFN $\alpha$  have been shown to play a role. Genetic factors also play an important role.
- The hepatitis C virus infection itself contributes to the development of IIT.
- All patients with hepatitis C starting an IFN $\alpha$  course should have a baseline level of TSH and thyroid antibodies, and then TSH levels should be monitored every 2–3 months.
- If clinical IIT develops in a patient on IFN $\alpha$  therapy it should be treated based on the clinical presentation. IFN $\alpha$  therapy can be continued in most cases, but if thyrotoxicosis is severe clinicians should consider stopping IFN $\alpha$  therapy.

### RESEARCH AGENDA

- Genetic studies to identify the genetic factors contributing to the development of IIT in order to develop prediction algorithms and prevention strategies.
- In vitro and in vivo basic studies to identify the mechanisms by which IFN $\alpha$  causes thyroiditis, focusing on the immune effects and direct thyroid toxic effects of IFN $\alpha$ . These mechanistic studies will enable development of preventive therapies.
- Prospective studies to develop risk stratification algorithms, and guidelines for follow-up and therapy, as well as to evaluate the usefulness of T4 therapy in patients starting IFN $\alpha$  therapy.

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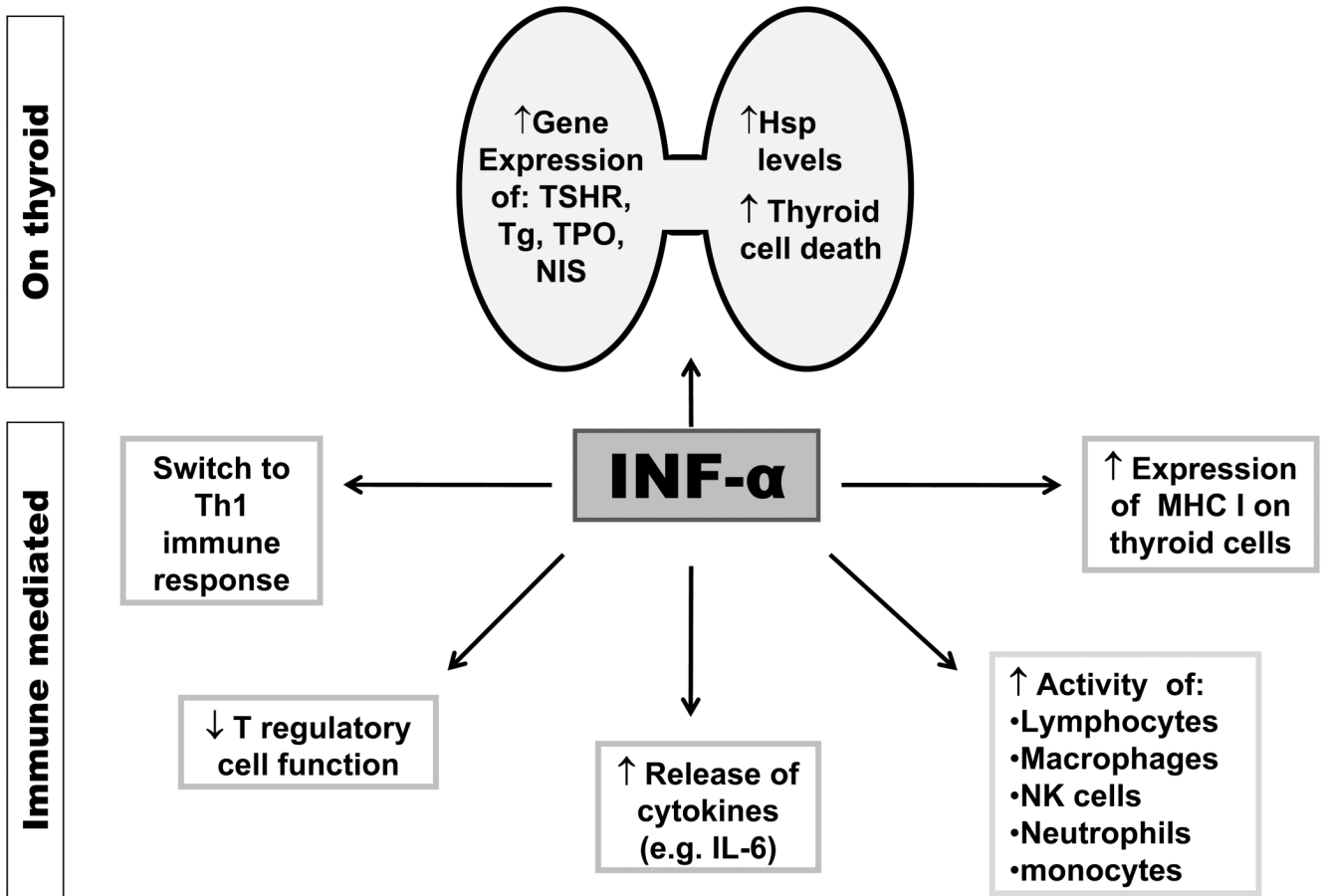


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**Figure 1.**

Postulated mechanism for the development of IIT. Both autoimmune and non-autoimmune effects of  $IFN\alpha$  are involved. Immune effects of  $IFN\alpha$  include activation of immune cells, switching the immune response to Th1 pathways, downregulation of Treg cells, and induction of cytokine release and MHC I expression. Direct thyroid toxic effects include upregulation of thyroid-specific proteins (TSHR, Tg, TPO, NIS) expression, as well as induction of heat shock proteins (Hsp) expression, and thyroid cell death. The combination of direct thyroid toxicity and immune stimulation can cause release of thyroid auto-antigens and their presentation to resident T-cells. This will initiate an autoimmune response by a bystander mechanism.