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Title	Gamma-interferon activates a nuclear protein that binds to the gamma-interferon activation site of the thyroglobulin gene
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68

A CHANGE FROM STIMULATORY TO BLOCKING ANTIBODY ACTIVITY IN GRAVES' DISEASE DURING PREGNANCY

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Remission of Graves' disease (GD) during pregnancy with recrudescence after delivery is commonly observed. However, as pregnancy is associated with type 2 rather than type 1 cytokines production, a decrease in thyroid stimulating antibody activity alone is unlikely to account for the remission during pregnancy. We hypothesized that a change in the antibody characteristics may occur as pregnancy advances. Fifteen women were studied at 1st, 2nd, 3rd trimester of pregnancy and at 4 months postpartum. TSH receptor antibodies were determined using human thyroid cell cultures and lymphocyte subsets were measured by flow cytometry.

Thyroid stimulating antibody (TSAb, determined by cAMP release) decreased from 280% (96-3200) to 130% (35-350, median (range), $P<0.05$) during pregnancy but no significant change was noted with the TSH binding inhibitory antibody (TBII, determined by radioreceptor assay). Thyroid stimulation blocking antibody (TSBAb, inhibition of TSH-stimulated cAMP release) increased from 16 ± 9 % to 43 ± 16%, mean ± SD ($p<0.005$). The increase in TSBAb was observed even amongst those patients who were in clinical remission prior to pregnancy. Overall, a negative correlation was observed between TSBAb activities and fT4 levels during pregnancy ($r = -0.279$, $p<0.05$). Reciprocal changes in the TSAb, TBII and TSBAb levels were observed in the 7 patients who relapsed during the postpartum period. In comparison, the healthy pregnant women ($n = 14$) were all negative for TSAb, TBII and TSBAb throughout pregnancy.

Absolute number of T lymphocytes, T helper cells and NK-cells but not B cells decreased significantly during pregnancy in both healthy women and GD patients. GD patients had significantly more $CD5^+B$ cells at all stages of pregnancy when compared to controls. In conclusion, a change in specificity from stimulatory to blocking antibodies was observed in GD patients during pregnancy and may contribute to the remission of GD during pregnancy.

69

GAMMA-INTERFERON ACTIVATES A NUCLEAR PROTEIN THAT BINDS TO THE GAMMA-INTERFERON ACTIVATION SITE OF THE THYROGLOBULIN GENE

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The release of interferon-gamma (IFNγ) has been demonstrated from the infiltrating T lymphocytes of the thyroid gland from patients with autoimmune thyroid disease (AITD). We had previously shown the IFNγ inhibited thyroglobulin (Tg) gene transcription, and its action was mediated by an increase in intracellular calcium and inositol phosphates. In the present study, we tried to determine the specific site of action of IFNγ on the Tg gene. A 565 bp fragment (position -530 to +34) spanning the transcriptional start site of the human Tg promoter was ligated to the luciferase plasmid and transiently transfected into human thyrocytes. Stimulation with TSH (10 mIU/l) and IFNγ (500 IU/l) resulted in a two-fold increase and 60% reduction in the luciferase activity respectively, as similar to the effect observed with endogenous Tg gene. Deletion studies revealed that the region with strongest suppression by IFNγ lied between 5' -388 to -258. Mobility gel shift experiments and DNA foot-printing experiments demonstrated that the action of IFNγ was mediated through a trans-acting protein which complexed to position -282 to -262 TTGAGCCTGTTCCCTCCAAA. Position -272 to -261 TTCCCTCCAA corresponded to the gamma-interferon activation site (GAS) consenus sequence TTNC $\begin{matrix}C\\T\end{matrix}$ NNNAA. The turnover time of the nuclear protein lasted for only 4 hours although the suppressive effect of IFNγ on Tg gene transcription lasted for 48 hours. The effect of IFNγ was lost when the thyrocytes were co-treated with genistein, a specific tyrosine kinase inhibitor.

The presence of the GAS in the promoter sequence of Tg gene confirms the specific action of IFNγ in thyroid hormone metabolism. In conclusion, apart from its regulatory role in the T cell development and perpetuation of the immune response in AITD, IFNγ may also play a role in altering cellular function of the thyrocytes by its action on the Tg gene promoter.