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THYROID LOCAL EXPRESSION OF INTERLEUKIN-4 PROMOTES AUTOIMMUNE THYROIDITIS IN SUSCEPTIBLE NOD.H2H4 MICE AND ATTENUATES GRAVES'S HYPERTHYROIDISM IN HTSHR IMMUNIZED MICE

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Introduction: Interleukine-4 (IL-4), a T-helper type 2 cytokine (Th2), is implicated in the pathogenesis of autoimmune thyroid diseases (AITD). However, its implication remains controversial in the development of Graves' disease (GD) and Hashimoto's thyroiditis (HT). We have generated a new transgenic mouse model overexpressing IL-4 in the thyroid (Thyr-IL-4). RNA profiling of Thyr-IL-4 thyroids revealed a modulation of the expression of genes involved in inflammation.

Methods: We explored the impact of a thyroidal overexpression of IL-4 in AITD pathogenesis in two experimental mouse models: 1. GD: Female F1 BALB/c-C57BL6-Thyr-IL-4 hybrid mice immunized with adenovirus expressing the A-subunit of the human TSH receptor (Ad-TSHR) or the β-galactosidase (Ad-Con). 2. HT: Spontaneous autoimmune thyroiditis NOD.H2^{h4}-Thyr-IL-4 mice treated with 0.05% NaI. Total T4, anti-hTSHr (TRAb) and anti-mouse thyroglobulin (mTGAb) antibodies were measured in the sera by ELISA. Thyroid stimulating antibodies (TSAbs) and TSH blocking antibodies (TBAbs) were evaluated using hTSHr-expressing CHO cells, by measurements of the total cAMP content. Moreover, we explored the thyroid histology and the immune cell infiltration by immunostaining.

Results: All F1 WT and Thyr-IL-4 female mice showed detectable nonpathogenic TRAbs in their serum, confirming the immunization protocol efficacy. However, the number of hyperthyroid mice (47% vs 87%) and the level of total T4 were significantly decreased in Thyr-IL-4 mice compared to WT animals. This was correlated with the lower number of transgenic mice presenting pathogenic TSAbs (53% vs 94%). No difference was observed in the TBAbs, and all hyperthyroid animals presented a goiter, increased NIS expression and histological alterations compatible with a hyperstimulated gland. Moreover, Ad-Con transgenic animals showed significantly more CD45^{+} leucocyte infiltration compared to WT mice, which was exacerbated after Ad-TSHR immunizations.

After 16 weeks of NaI treatment, circulating mTGAbs were significantly higher in NOD.H2^{h4}-Thyr-IL-4 mice compared to WT animals. NOD.H2^{h4}-Thyr-IL-4 developed intense lymphocytic infiltration composed of CD4^{+}, CD8^{+} and B220^{+} cells compared to WT NOD.H2^{h4} littermates. Moreover, the relative mRNA expression of IFNγ, IL-10 and IL-13 was also significantly increased in transgenic animals.

Conclusions: We have shown that thyroid expression of IL-4 had contrasting effects in the development of the two classical AITDs. In our Graves' murine model, Thyr-IL-4 animals presented attenuated thyrotoxicosis and TSAb incidence, whereas transgenic NOD.H2^{h4} mice developed a more severe Hashimoto's thyroiditis.