**Summary**

**Context:** Hyperthyroidism in Graves' disease (GD) is caused by thyroid-stimulating autoantibodies to the TSH receptor (TSHR), whereas hypothyroidism in Hashimoto's thyroiditis (HT) is associated with thyroid peroxidase and thyroglobulin autoantibodies. In some patients with GD, thyroiditis becomes sufficiently extensive to cure the hyperthyroidism with resultant hypothyroidism. Factors determining the balance between these two diseases, the commonest organ-specific autoimmune diseases affecting humans, are unknown.

**Methodology:** Serendipitous findings in transgenic BALB/c mice, with the human TSHR A-subunit targeted to the thyroid, shed light on this relationship. Of 3 transgenic lines, 2 expressed high levels and 1 expressed low intrathyroidal A-subunit levels (Hi- and Lo-transgenics, respectively). Transgenics and wild-type littermates were depleted of T regulatory cells (Treg) using antibodies to CD25 (CD4(+) T cells) or CD122 (CD8(+) T cells) before TSHR-adenovirus immunization.

**Results:** Regardless of Treg depletion, high-expressor transgenics remained tolerant to A-subunit-adenovirus immunization (no TSHR antibodies and no hyperthyroidism). Tolerance was broken in low-transgenics, although TSHR antibody levels were lower than in wild-type littermates and no mice became hyperthyroid. Treg depletion before immunization did not significantly alter the TSHR antibody response. However, Treg depletion (particularly CD25) induced thyroid lymphocytic infiltrates in Lo-transgenics with transient or permanent hypothyroidism (low T4, elevated TSH). Neither thyroid lymphocytic infiltration nor hypothyroidism developed in similarly treated wild-type littermates. Remarkably, lymphocytic infiltration was associated with intermolecular spreading of the TSHR antibody response to other self thyroid antigens, murine thyroid peroxidase and thyroglobulin.

**Conclusion:** These data suggest a role for Treg in the natural progression of hyperthyroid Graves' disease to Hashimoto's thyroiditis and hypothyroidism in humans.

**Comment**

Graves’ disease (GD) is caused by antibodies that activate the TSH receptor (TSHR). Other autoantibodies (Tg-Ab, TPO-Ab) are also frequently found in GD patients. These antibodies are the classical markers of Hashimoto’s thyroiditis (HT), a condition leading to progressive fibrosis of the gland and hypothyroidism. Patients with GD who have been cured from active disease by antithyroid drug treatment often present (in their long term evolution) a lymphocytic thyroiditis resembling HT, and they develop hypothyroidism. The relationship between GD & HT has been debated for decades, and it is presently considered that both clinical entities are not separate diseases but represent the two opposite ends of the same ‘rope’. Thyroid stimulating antibodies arise from breakdown in self-tolerance to the TSHR, a
G-protein-coupled receptor expressed at the basal membrane of thyrocytes. The autoantigen that drives the autoimmune response in GD is presently believed not to be the full-length receptor but the A-subunit, a component of the receptor ectodomain that is shed into the milieu after receptor cleavage.

The authors have generated transgenic mice with the human A-subunit of TSHR targeted to the thyroid gland. When the transgenic animals were crossed with a strain of mice (BALB/c) susceptible to immunization with adenovirus expressing the TSHR (either full-length or the A-subunit), the transgenics failed to develop T cell responses after low-dose A-subunit immunization. This implies that immune tolerance took place, which could be due to the regulatory T cells (Treg) that control autoreactive T cells in the periphery.

In present study, the authors used A-subunit transgenic animals to probe the hypothesis that the levels of expression of the A-subunit transgene and Treg depletion (using monoclonal anti-CD25 or anti-CD122 antibodies before immunization) influence immune responses to adenovirus immunization with the TSHR.

They show that Treg is a major factor in intermolecular spreading of the immune response from the TSH receptor to TPO and Tg as well as in the shift from hyperthyroidism to full-blown HT with massive lymphocytic infiltration and hypothyroidism.

In summary, present studies provide novel insight into the enigmatic balance between hyperfunction and thyroid destruction in Graves’ disease.

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See Figures below

**Figure B (upper left graph):** the wild-type littermates show a robust TBI response after immunization. **Figure C (upper right graph):** high expressor transgenic mice remain immunotolerant even after Treg depletion. **Figure D (lower left graph):** in low expressor transgenic mice, Treg depletion did not alter the TSH receptor antibody response.