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## THE EFFECT OF METHIMAZOLE, IODINE AND SPLENOCYTES ON THYROID TRANSPLANTS IN BB/WOR RATS<sup>1</sup>

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### Abstract [TOP](#)

**Background.** BB/Wor rats develop spontaneous autoimmune insulin-requiring diabetes mellitus and lymphocytic thyroiditis (LT). Our investigations examined the effect of the thyroid-specific agents, iodine and methimazole (MMI) on thyroid graft survival in BB/Wor rats, compared the intrathyroidal cytokine mRNA expression of endogenous and engrafted thyroids, and ascertained whether unfractionated splenocytes could protect thyroid grafts from lymphocytic infiltration.

**Methods.** In study 1, 0.025% iodine water-treated LT-prone NB line BB/Wor rats were randomized to receive one of the following treatments: (1)  $1.0 \times 10^8$  splenocytes, IV from LT-resistant WA line BB/Wor rats, (2) WA rat thyroid transplants, (3) both, or (4) neither (controls). In study 2, after thyroid transplantation, LT-prone BB/Wor rats were randomized to

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receive (1) WA splenocytes, (2) 0.025% iodine water, (3) 0.05% MMI water or, (4) tap water (controls). The incidence of LT was determined by microscopic inspection after hematoxylin and eosin staining. Lymphocytic infiltrates were characterized by immunohistochemistry. Cytokine mRNA was detected by RT-PCR.

Results. Grafts from MMI-treated rats had a significantly lower incidence of lymphocytic infiltration (MMI: 2/5; Tap: 5/5; I 5/5,  $P < 0.05$ ,  $\chi^2$ ). IL-10 mRNA was expressed in 77% (7/9) endogenous thyroids and 20% (1/5) of the transplanted WA thyroids ( $P < 0.05$ ,  $\chi^2$ ) from iodine-treated rats with LT. There was no difference in IL-12 mRNA expression. Lymphocytic infiltration occurred in 100% of the splenocyte-treated graft recipients. Both endogenous and engrafted thyroids contained CD4 and CD8 T cells with scattered IgG staining.

Conclusion. Target organ-specific interventions that suppress antigen presentation may have an adjunctive role in transplantation tolerance. The differential expression of IL-10 may indicate preferential Th2 lymphocyte activation in the endogenous tissues.

The BB/Wor rat develops spontaneous autoimmune insulin-requiring diabetes mellitus (DM)\* and autoimmune lymphocytic thyroiditis (LT). In this animal model, methimazole (MMI) prevents LT by reducing the presentation of thyroid autoantigens (1, 2). Iodine (I), which enhances production of the thyroid-specific antigen, thyroglobulin (Tg) accelerates LT (1, 3). LT/DM-prone BB/Wor rats rarely develop LT before 90 days of age, but antithyroid antibodies are present by 60 days of age. LT/DM-resistant BB/Wor rats are derived from LT/DM prone rats but do not develop LT or DM unless depleted of autoregulatory T lymphocytes (1).

Autoimmune LT is a common thyroid disease histologically characterized by intrathyroidal infiltration with T and B lymphocytes (4, 5). LT has been associated with intrathyroidal interferon- $\gamma$  (IFN $\gamma$ ), IL-2, IL-10, IL-12, tumor necrosis factor- $\alpha$  (TNF $\alpha$ ), and TGF $\beta$  mRNA expression (6-10). IL-10 mRNA has been a consistent finding in several studies and reportedly inhibits T cell proliferation in response to Tg. It also suppresses cytotoxicity against targets primed with Tg but enhances anti-Tg antibody production (7). Although results from studies of intrathyroidal IL-4 mRNA expression have been variable, the combination of IL-4 and IL-10 markedly inhibit T cell responses to Tg in experimental autoimmune thyroiditis.

Similar to allograft rejection, Th 1 lymphocytes are the major effectors of thyroid destruction in LT and both CD4 and CD8 lymphocytes have been implicated in the pathogenesis of this disorder (4, 5). Unfractionated splenocytes from syngeneic DM/LT-resistant BB/Wor rats prevent DM and LT in DM-prone BB/Wor rats (11). This is undoubtedly due to the adoptive transfer of autoregulatory T cells. Similarly, unfractionated pancreatic-draining lymphatic cells from LT-resistant BB/Wor rats prolong the survival of transplanted pancreatic  $\beta$  cell islets and prevent the recurrence of DM in acutely diabetic BB/Wor rats (12, 13).

Tissue-specific cytotoxic T cells have been implicated in both allograft rejection and autoimmune disease (14-16). Organ-specific interventions to prevent immunologically mediated damage could alleviate requirements for global immunosuppression after solid organ transplantation and prevent autoimmune disease. Our investigations examined the effect of the thyroid-specific agents, iodine (I) and MMI on thyroid graft survival in BB/Wor rats. In addition, endogenous and engrafted thyroids were compared for intrathyroidal cytokine mRNA expression and incidence of lymphocytic infiltration.

## MATERIALS AND METHODS TOP

*Animals.* Fifty- to 60-day-old male and female LT-prone NB line and LT-resistant WA line BB/Wor rats were obtained from University of Massachusetts Medical Center (Worcester, MA). Fisher rats were obtained from Harlan Sprague Dawley (Indianapolis, IN). Institutional Animal Care Committee approval was obtained for all experiments. The animals were maintained on standard rat food and water ad libitum.

*Treatment protocols.* In study 1, NB line BB/Wor rats were divided into controls and three treatment groups. The splenocytes, only group received  $1.0 \times 10^8$  splenocytes from LT-resistant WA line BB/Wor rats by tail vein infusion. The

transplantation (Tx), only group were transplanted with WA thyroids under the renal capsule as previously described (17). The Tx+splenocytes group received combined thyroid transplantation and splenocyte infusion. Forty-eight hr after treatment, the animals were administered 0.025% I water ad libitum to optimize the development of LT (2). Control animals received 0.025% I water, only. All grafts and splenocyte transfusions were sex-matched. Syngeneity was verified by skin grafting. The animals were euthanized 5 weeks after treatment at ~95 days of age. A study to examine the kinetics of lymphocytic infiltration showed that both WA and Fisher thyroid grafts developed lymphocytic infiltration within 2 weeks after transplantation into LT-prone rats. Therefore, in subsequent studies designed to determine whether I or MMI affected the incidence of lymphocytic infiltration in thyroid grafts, the animals were euthanized 2 weeks after transplantation at ~74 days of age. In this study, all of the NB line rats were transplanted with WA line rat thyroids. One group (Tx+splenocytes) received splenocyte infusion and were maintained on tap water. The remaining graft recipients did not receive splenocytes but were maintained on either tap, 0.05% MMI, or 0.025% I water. As controls to determine whether the transplantation procedure itself precipitated graft destruction Fisher rats, which are not LT-prone, were transplanted with Fisher rat thyroids.

*Histology.* Engrafted and endogenous thyroids were frozen, stained with hematoxylin and eosin and blindly evaluated for the presence of LT according to the extent of lymphocytic infiltration per low power field as follows: grade 0= $\leq$ 10%, 1=10 to 20%, 2=30 to 50%, 3=50%, 4= $>$ 50%. A grade of 1 or above was considered positive for LT. The tissues were stained for the presence of CD4, CD8, and IgG by immunohistochemistry. Anti-Tg antibodies were measured by enzyme-linked immunosorbent assay (2).

*RNA extraction and RT-PCR.* Total RNA was extracted from thyroids by the guanidine thiocyanate-phenol and chloroform method with TRIzol (GibcoBRL, Gaithersburg, MD, cat. no. 15596-026) (18). After DNA digestion with deoxyribonuclease I (GibcoBRL, cat. no. 18068-015), 1.0  $\mu$ g of total RNA was converted to cDNA using 0.5  $\mu$ g oligo(dT) (GibcoBRL, cat. no. 18418-012) and Superscript II (Gibco-BRL, cat. no. 18064-014). Engrafted and endogenous thyroids from transplanted rats and nontransplanted controls were analyzed for the presence of the following rat mRNAs:  $\beta$ -actin (457 bp) (Biosource, Camarillo, CA, int. cat. no. GRL1001), IL-10 (376 bp) (Biosource, cat. no. GRC0101), IL-4 (177 bp) (Biosource, cat. no. GRC0041), IL-12(p35) (308 bp) (Biosource, cat. no. GRC0121), T cell receptor- $\beta$  (TCR $\beta$ ) (485 bp): 5'CTGAAAACGGTGACTCCACCCAAGG, 3'GCACCAGGGCACTGACTAGCACAGC (6), IFN $\gamma$  (442 bp): 5'GCTCTGCCTCATGGCCCTCTCTGGC, 3'GCACCGACTCCTTTTCCGCTTCCTT (6), IL-2 (351 bp): 5'GCGCACCCACTTCAAGCCCT, 3'CCACCACAGTTGCTGGCTCA (19). The PCR reaction mixture contained 0.5 mM of each deoxynucleotide triphosphate, 1.0  $\mu$ M 5' and 3' primer, and 1.25 U Taq DNA polymerase (Perkin Elmer, Norwalk, CT, cat. no. G1313) in a total volume of 50  $\mu$ l with PCR buffer. Samples were overlaid with mineral oil and amplified in a thermocycler (Perkin Elmer). The denaturation cycle was set at 94°C for 3 min followed by 35 cycles at 94°C for 30 sec, 60°C for 45 sec, and 72°C for 45 sec, with a final extension step at 72°C. The amplification products were electrophoresed on a 2% agarose gel and detected by ethidium bromide staining.  $\beta$ -actin positive controls were run with each reaction. Negative controls consisted of primer without sample.

*Statistical analysis.* The incidence of lymphocytic infiltration between treatment groups was compared by  $\chi^2$ . Antithyroglobulin antibody levels were compared by one-way analysis of variance with Bonferroni correction.

## RESULTS TOP

Thyroid grafts from MMI-treated rats had a lower incidence of lymphocytic infiltration compared to both tap water and iodine-treated animals ( $P<0.05$ ,  $\chi^2$ ) (Table 1). As expected MMI, was associated with hypothyroidism as evidenced by elevated thyroid stimulating hormone (TSH) levels and hyperplasia in the engrafted and endogenous thyroids (Figs. 1 and 2). In contrast, lymphocytic infiltrates were present in 100% of the engrafted thyroids regardless of splenocyte therapy. It is unlikely this outcome was due to iodine because comparable results were obtained when the animals received tap water (Table 1). The failure of the transplantation procedure itself to precipitate lymphocytic infiltration was verified by the observation that Fisher rats transplanted with Fisher thyroids did not develop lymphocytic infiltration. Splenocyte infusion also did not reduce the incidence of LT in endogenous NB rat thyroids (Table 2).

Table 1. The effect of treatment on thyroid grafts

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Figure 1. A, Hematoxylin and eosin stain of a thyroid graft from an MMI-treated rat 2 weeks after thyroid transplantation (40x). B, The endogenous thyroid from the same rat. Note the follicular hyperplasia (16x).

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Figure 2. A, Hematoxylin and eosin stain of a thyroid graft from a tap water-treated rat 2 weeks after thyroid transplantation (40x). Note the extensive lymphocytic infiltration B, The endogenous thyroid from the same rat (16x).

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Table 2. The effect of treatment on LT in endogenous thyroids

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To compare the cytokine profile of intrathyroidal lymphocytic infiltrates in endogenous and engrafted thyroids, infiltrate positive samples from iodine-treated rats that had not received splenocyte infusions were examined from both studies. mRNA was extracted from the endogenous thyroids of three nontransplanted animals and seven transplanted rats with their respective thyroid grafts. These samples were analyzed for TCR $\beta$ , IL-2, IL-4, IL-12, and IFN $\gamma$  mRNA by RT-PCR. TCR $\beta$  mRNA was detected in 9 of 10 endogenous thyroids and 5 of 7 grafts. Of the TCR $\beta$  positive samples, 77% (7 of 9) endogenous thyroids and 20% (1 of 5) of the grafts expressed IL-10 mRNA ( $P < 0.05$ ,  $\chi^2$ ). IL-12 mRNA expression was similar in both, 55% (5/9) of the endogenous thyroids versus 60% (3/5) of the grafts. IL-4, IL-2, and IFN $\gamma$  mRNA were not detected in any of the samples examined.

Endogenous and engrafted thyroids were immunohistochemically similar, containing CD4 and CD8 T lymphocytes as well as IgG $^+$  cells (Figs. 3 and 4). In study 1, anti-Tg levels in the Tx+splenocyte group, which had a 33% incidence of LT in the endogenous thyroids, were higher than controls in which LT occurred in 100% ( $P < 0.05$ , analysis of variation with Bonferroni correction) (Table 2).

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Figure 3. Immunohistochemical staining of the thyroid from a non-transplanted NB line BB/Wor rat after 5 weeks of 0.025% iodine water (40x magnification). A, Hematoxylin and eosin, stain. B, Horseradish peroxidase (HRP) anti-Ig G. C, HRP anti-CD4. D, HRP anti-CD8.

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Figure 4. Immunohistochemical staining of thyroids from a transplanted NB line BB/Wor rat after 5 weeks of 0.025% iodine water (40x magnification). A-C, The endogenous thyroid. D-F, The WA BB/Wor rat thyroid graft beneath the NB line rat renal capsule (40x magnification). A and D, HRP anti-Ig G. B and E, HRP anti-CD4. C and F, HRP anti-CD8.

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## DISCUSSION TOP

The significance of target organ-specific intervention is supported by this study's observation that the antithyroid agent MM reduced the incidence of lymphocytic infiltration in thyroid grafts. The immunosuppressive nature of MMI remains controversial, but it is generally accepted that MMI ameliorates autoimmune thyroid disease by preventing the synthesis of a major thyroid-specific autoantigen, Tg (20-22). It is unlikely that MMI-induced hypothyroidism was responsible for MMI's ameliorative effect because we have previously reported that hypothyroidism may actually potentiate LT in this animal

model (23). Although it is possible that MMI only delayed graft destruction, we have observed that MMI provides longterm protection against LT (2). Suppression of graft specific antigenic stimulation could provide a helpful adjunct to induction therapy. The ability of MMI to suppress or delay lymphocytic infiltration in engrafted WA thyroids implicates organ-specific antigenic stimulation in the immunological destruction of these grafts. It does not establish whether lymphocytic infiltration was due to rejection or recurrent autoimmunity. However, the fact that NB and WA line rats are syngeneic makes rejection less likely (1).

This study also found that IL-10 mRNA expression was more frequent in endogenous thyroids than thyroid grafts that had severe grade 4 lymphocytic infiltration. IL-10 is a Th2 cytokine that induces antibody production but suppresses cytotoxicity (7). The administration of IL-10 and IL-4 prevents recurrent insulinitis and DM in islet-transplanted NOD mice and IL-10 mRNA expression correlates with graft survival (24, 25). Although Th1 lymphocytes can also provide B cell help, the presence of IL-10 mRNA in glands with LT may reflect protective Th2 activity within the thyroid that is also the site of anti-Tg antibody production (4, 5). Anti-Tg antibodies often fail to correlate with histological LT. Therefore, elevated anti-Tg levels in the combined splenocyte and transplantation treatment group, which had a lower incidence of LT, may actually indicate defensive Th2 responses. Our detection of intrathyroidal IL-10 and IL-12 mRNA concurs with semiquantitative RT-PCR data from Zipris et al. (6) showing that inflamed thyroids from RT6-depleted DR (WA) BB rats expressed strong signals for IFN $\gamma$  and IL-12 mRNA but low levels of IL-2, IL-4, and IL-10 (6). However, the absence of IFN $\gamma$  and IL-2 in thyroids from the LT/DM-prone NB line BB/Wor rats used in our study suggests that there may be differences between the lymphocytic infiltrates involved in spontaneously occurring LT and the infiltrates involved in RT6 depletion-induced LT in LT-resistant WA line BB/Wor rats.

In contrast to the results of previous studies, splenocytes from LT/DM-resistant BB/Wor rats did not prevent LT or protect WA thyroid grafts. Burnstein et al. (11) reported that DM-prone BB/Wor rats were protected from LT and DM if WA splenocytes were infused by 45 days of age. In our study, the animals were ~60 days of age at the time of splenocyte infusion. This may explain the lack of tolerance induction. In a previous study, peripancreatic lymph node cells protected pancreatic  $\beta$  cell islet transplants from immunological destruction in acutely diabetic LT-prone BB/Wor rats (12) and subsequent studies have shown that graft tolerance was accompanied by host chimerism with donor-specific RT6<sup>+</sup> T cells (13, 25). However, in addition to lymphocytes, unfractionated lymphatic tissue also contains antigen presenting cells (APCs) which are important for antigen presentation and costimulation (27, 28). Organ-draining APCs may be more effective at tissue-specific antigen presentation than splenocyte-derived APCs (29-31). Three studies have illustrated the pivotal role of APCs in tolerance and autoimmunity in BB/Wor rats. In a study by Woehrlé et al. (32), removal of passenger APCs from pancreatic islets prolonged the survival of major histocompatibility complex-(MHC) incompatible grafts but not MHC-compatible ones. Similarly, Bartlett et al. (17) demonstrated that culturing thyroid fragments before transplantation prolonged allograft survival but promoted destruction of MHC-compatible thyroid grafts. Finally, Delemarre et al. (33) have reported that thyroid-draining cervical node dendritic cells from LT-resistant BB/Wor rats delayed the onset of LT in LT-prone BB/Wor rats. Together, these data imply that MHC-incompatible APCs are immunogenic, but MHC-compatible APCs may be tolerogenic and important in the prevention of recurrent autoimmune disease in engrafted tissue. Thyroid draining cervical lymphatic tissue might have been more effective than splenocytes at preventing lymphocytic infiltration in thyroid grafts. Therefore, both the source of lymphatic tissue and timing of infusion may explain why splenocytes did not prevent LT or thyroid graft destruction in our study.

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\* Abbreviations: DM, diabetes mellitus; APC, antigen-presenting cells; I, iodine; INF, interferon; LT, lymphocytic thyroiditis; MHC, major histocompatibility complex; MMI, methimazole; PCR, polymerase chain reaction; TCR, T cell receptor; Tg, thyroglobulin; TNF, tumor necrosis factor; Tx, transplantation. [\[Context Link\]](#)

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