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Th1 and Type 1 Cytotoxic T Cells Dominate Responses in T-bet Overexpression Transgenic Mice That Develop Contact Dermatitis

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Contact dermatitis in humans and contact hypersensitivity (CHS) in animal models are delayed-type hypersensitivity reactions mediated by hapten-specific T cells. Recently, it has become clear that both CD4+ Th1 and CD8+ type 1 cytotoxic T (Tc1) cells can act as effectors in CHS reactions. T-bet has been demonstrated to play an important role in Th1 and Tc1 cell differentiation, but little is known about its contribution to CHS. In the present study, we used C57BL/6 mice transgenic (Tg) for T-bet to address this issue. These Tg mice, which overexpressed T-bet in their T lymphocytes, developed dermatitis characterized by swollen, flaky, and scaly skin in regions without body hair. Skin histology showed epidermal hyperkeratosis, neutrophil, and lymphocyte infiltration similar to that seen in contact dermatitis. T-bet overexpression in Tg mice led to elevated Th1 Ig (IgG2a) and decreased Th2 Ig (IgG1) production. Intracellular cytokine analyses demonstrated that IFN-γ was increased in both Th1 and Tc1 cells. Furthermore, Tg mice had hypersensitive responses to 2,4-dinitrofluorobenzene, which is used for CHS induction. These results suggest that the level of expression of T-bet might play an important role in the development of contact dermatitis and that these Tg mice should be a useful model for contact dermatitis.


The Th1/Th2 paradigm proposed by Mosmann et al. (1) holds that CD4+ T cells can be subdivided into two categories, namely Th1 and Th2 (2). These two polarized subsets can be identified on the basis of the cytokines they secrete (3). Th1 cells produce IL-2 and IFN-γ, whereas Th2 cells produce IL-4, IL-5, IL-6, IL-10, and IL-13. More recently, a similar heterogeneity among CD8+ T cytotoxic (Tc)4 cells has also been recognized with the identification of Tc1 and Tc2 subpopulations (4, 5). IFN-γ is also one of the main cytokines produced by differentiated CD8+ effector T cells and has been shown to have a fundamental role in CD8+ T cell-mediated immunity (6). Lineage commitment of CD4+ and CD8+ T cells is transcriptionally regulated, often by the same factors that mediate T cell effector function.

T-bet is known as a Th1 lineage commitment transcription factor as a result of its transactivation of the Th1 cytokine IFN-γ (7). Recently, T-bet has also been shown to regulate cytolytic effector mechanisms of CD8+ T cells (8). T-bet expression is rapidly induced in CD8+ T cells by signaling through the TCR and the IFN-γR, and it functions downstream of STAT1 (6, 9, 10). In the context of Ag-specific activation, T-bet is required for the differentiation of naive CD8+ T cells into effector CTLs.

Contact dermatitis is one of the most common skin diseases (11). Knowledge of the pathophysiology of contact dermatitis is derived chiefly from animal models in which the inflammation induced by hapten painting of the skin is referred to as contact hypersensitivity (CHS) (12). Contact dermatitis and CHS are delayed-type hypersensitivity reactions that are mediated by hapten-specific T cells (12). Skin sensitization resulting in contact dermatitis and CHS is dependent on the initiation of specific T lymphocyte responses (11, 13). Until recently it was believed that the most important cells in these responses were CD4+ T lymphocytes. IL-2 and IFN-γ produced by Th1 cells are thought to play a preeminent role in the evolution of CHS (14, 15). Some investigations in mice found CHS to be associated with CD4+ T lymphocyte function and to be compromised when such cells were deleted (15, 16). However, there is growing evidence that in many instances the predominant effector cell in CHS may be a CD8+ T lymphocyte (13, 17, 18). Wang et al. (17) clearly demonstrated that the deletion of CD8+ Tc1 cells had a more significant suppressive effect than the deletion of CD4+ Th1 cells in CHS responses to 2,4-dinitrofluorobenzene (DNFB). According to these results, both CD4+ Th1 and CD8+ Tc1 cells are key players in CHS.

Although T-bet plays an important role in Th1 and Tc1 cell induction, little is known about its contribution to CHS. In the present study we used T-bet overexpression in T cell transgenic (Tg) mice to address this issue.
Materials and Methods

Generation of T-bet Tg mice

A 2.5-kb, full-length cDNA encoding the murine T-bet protein was inserted into a VA CD2 transgene cassette containing the upstream gene regulatory region and locus control region of the human CD2 gene. The VA vector has been reported to direct expression of the inserted cDNA in all single-positive mature T lymphocytes of Tg mice, with expression being linearly proportional to the transgene copy number (19). This T-bet construct was injected into BDF1 fertilized eggs to generate Tg mice. T-bet Tg mice were inbred with C57BL/6 mice for four generations. Mice were maintained in specific pathogen-free conditions in a laboratory animal resource center. All experiments were performed according to the Guide for the Care and Use of Laboratory Animals at the University of Tsukuba (Ibaraki, Japan), and the study was approved by the Institutional Review Board of the university.

Southern hybridization analysis of genomic DNA

Southern hybridization was performed by using the Gene Images random prime labeling module system (Amersham Biosciences). High m.w. DNA was prepared from the tail of each mouse, and 15 µg of DNA was digested with ApaI and then subjected to electrophoresis on 1.0% agarose gels. After electrophoresis, the DNA was transferred to a Hybond-N+ membrane. A fluorescence-labeled ApaI/EcoRI fragment (0.5 kb) of the T-bet cDNA was used as a probe. The transgene copy number was determined from the blot with a BAS 1500 Mac image analyzer.

RT-PCR for transgene expression analysis

Total RNA was prepared from the thymus of 10 wk-old Tg mice or their wild-type transgene-negative littermates (WT mice) using TRIzol reagent according to the manufacturer’s instructions (Invitrogen Life Technologies). First-strand cDNA was synthesized at 42°C for 50 min using the SuperScript II RNase H2 reverse-transcriptase kit (Invitrogen Life Technologies), and 1 µl of this 20 µl reaction mixture was used for the PCR. Amplified products were analyzed on 2% agarose gels. PCR primer sequences were as follows: T-bet, 5'-CGGTACCAGAGCGGCAAGT-3' and 5'-AGCCCCCTTGTGTTGGTGC-3'; GATA-3, 5'-CCCCTTCATTGACCTCAACTACATGG-3' and 5'-GGTGACCATTCTCGCCGCCCAACAG-3'; GAPDH, 5'-CCCCTTCCATGACCTCAACTACATGG-3' and 5'-GCCGTCTTCACCACCCTTGTAGTGC-3'.

Western blot analysis

Thymocyte nuclear extracts were prepared from 10 wk-old Tg mice or WT. The extracts were size-fractionated on a 10% SDS-polyacrylamide gel transferred to a polyvinylidene difluoride membrane (FluoroTrans), and Western blot analysis was performed with cross-linked anti-CD3e (1 µg/ml) and anti-CD28 (10 µg/ml) plus IL-2 (10 ng/ml) in a total volume of 2 ml in 24-well plates. In addition, some cultures received cytokines (10 ng/ml IL-4 or 10 ng/ml IL-12) or mAb to block endogenous cytokines (10 µg/ml anti-IL-4 or 10 µg/ml anti-IL-12). T cells were expanded and maintained under constant culture conditions for 1 wk.

Flow cytometric analysis of intracellular IL-5 and IFN-γ synthesis

Cells were resuspended at 105 to 106 cells/ml and stimulated with PMA (50 ng/ml) plus ionomycin (500 ng/ml). Two hours before cell harvesting, brefeldin A was added at 10 µg/ml using a stock solution of 1 mg/ml in ethanol (100%). Cells were harvested, washed, and resuspended in PBS with brefeldin A before the addition of an equal volume of 4% formaldehyde fixative (final concentration, 2%). After fixation for 20 min at room temperature, cells were stained for cytokines. For intracellular staining, all reagents and washes contained 1% BSA and 0.5% saponin (Sigma-Aldrich), and all incubations were performed at room temperature. Cells were washed and preincubated for 10 min in PBS/BSA/saponin and then incubated with aliphycocyanin-conjugated anti-mouse IL-5 (5 µg/ml) and anti-mouse IFN-γ (5 µg/ml) or isotype-matched control Abs (10 µg/ml) for 30 min. After 20 min, cells were washed twice with PBS/BSA/saponin and then washed with PBS/BSA without saponin to allow membrane permeabilization. Samples were analyzed with a FACScalibur flow cytometer (BD Biosciences). Results were analyzed by using CellQuest software.

Induction of CHS

Induction of CHS was conducted using the methods described previously (21). Briefly, mice were sensitized to DNFB by painting the shaved abdomen with 50 µl of 5% DNFB in acetone/olive oil (4:1) and each footpad with 5 µl of the mixture on days 0 and 1. On day 5, mice were challenged with 20 µl of 0.3% DNFB on each side of the left ear. As a control, the right ear was painted with an identical amount of vehicle. The ear thickness was measured at 12, 24, 48, and 72 h after challenge at three locations. The ear swelling was calculated as (T - T0) right ear) - (T - T0) left ear), where T0 and T represent the values of ear thickness before and after the challenge, respectively.

Results

Generation of Tg mouse lines overexpressing T-bet in T cells

To generate Tg mouse lines expressing high levels of T-bet specifically in T cells, the mouse T-bet cDNA was inserted into the VA vector (Fig. 1A). Genomic Southern blotting analysis was performed to confirm the integrity and copy number for each Tg mouse line. The length of the ApoI fragment containing the T-bet transgene was 1.2 kb, whereas the corresponding fragment for the endogenous T-bet gene was 4.0 kb (Fig. 1A). The transgene was detected in mice of Tg lines 710, 725, and 731 (Fig. 1B). In densitometric analyses, line 710 seemed to contain more than 12 copies of the transgene, whereas lines 725 and 731 contained approximately 12 and 8 copies, respectively. However, line 710 could not transmit the genes to the next generation, but the transgenes in both line 725 and line 731 were stably transmitted to progeny.
Overexpression of T-bet in Tg mice

To confirm expression of the transgene, RT-PCR and immunoblot analyses were performed to monitor T-bet mRNA and protein levels in thymocytes from the two Tg lines (Fig. 2, A and B). Overexpression of T-bet mRNA and protein was detected in all Tg mice tested. The amount of T-bet protein in Tg line 725 cells was slightly higher than the amount in Tg line 731, indicating that the expression level of the protein was copy number dependent. The T-bet protein was not detected in WT mice in this analysis.

Higher ratio between IgG2a and IgG1 in T-bet Tg mice

To determine cytokine levels we first analyzed serum by the ELISA method, but all samples were below the level of detection (data not shown). Because Th1/Th2 cytokines contribute to control of Ig subtype production, we next analyzed serum IgG1 and IgG2a. Th1 cells support macrophage activation, delayed-type hypersensitivity responses, and Ig isotype switching to IgG2a. In contrast, Th2 cells provide efficient help for B cell activation and class switching to IgG1 (22, 23). To confirm the Th1-dominant response in T-bet Tg mice, serum IgG levels were measured by ELISA (Table I). Tg line 731 mice had serum total IgG levels similar to those of WT mice (Tg line 731, 394.0 ± 37.6 mg/dl; WT, 340.3 ± 18.7 mg/dl), but Tg line 725 levels were significantly higher than those of WT mice (547.4 ± 108.9 mg/dl). Serum IgG1 levels of Tg mice (Tg line 731, 79.4 ± 7.4 mg/dl) tended to be lower than those of WT mice (174.0 ± 33.7 mg/dl) but, in contrast, IgG2a levels were higher (Tg line 725, 253.1 ± 77.9 mg/dl; WT, 90.7 ± 12.6 mg/dl). To confirm the promotion of the IgG2a class switch and repression of IgG1 Tg mice, IgG2a/IgG1 ratios were calculated. These were found to be significantly higher in Tg mice (Tg line 725, 2.93 ± 0.95; Tg line 731, 1.22 ± 0.13) than in WT mice (0.62 ± 0.08) (*p < 0.01).

Increased synthesis of IFN-γ in T-bet Tg mice

From the above data, Tg line 725 mice had greater overexpression of T-bet than Tg line 731 mice and were therefore used in the following studies. To confirm the observed differences in

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**Table I. Serum immunoglobulins for 30-week-old mice**

<table>
<thead>
<tr>
<th>Measurement</th>
<th>WT (n = 12)</th>
<th>Tg Line 725 (n = 8)</th>
<th>Tg Line 731 (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG (mg/dl)</td>
<td>340.3 ± 18.7</td>
<td>547.4 ± 108.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>394.0 ± 37.6</td>
</tr>
<tr>
<td>IgG1 (mg/dl)</td>
<td>174.0 ± 33.7</td>
<td>174.9 ± 89.0</td>
<td>79.4 ± 7.4&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>IgG2a (mg/dl)</td>
<td>90.7 ± 12.6</td>
<td>253.1 ± 77.9&lt;sup&gt;b&lt;/sup&gt;</td>
<td>97.1 ± 13.4</td>
</tr>
<tr>
<td>IgG2a/IgG1 ratio</td>
<td>0.62 ± 0.08</td>
<td>2.93 ± 0.95&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.22 ± 0.13</td>
</tr>
</tbody>
</table>

<sup>a</sup> Data are expressed as mean ± SEM.
<sup>b</sup> p < 0.05 versus WT.
<sup>c</sup> p < 0.01 versus WT.
cytokine production at the single-cell level, we studied their intracellular synthesis by flow cytometry. CD4+/CD8+ T cells from WT and Tg line 725 mice were cultured in the presence of medium alone, anti-IL-4 plus IL-12 (Th1 differentiation conditions), or anti-IL-12 plus IL-4 (Th2 differentiation conditions) and analyzed by flow cytometry for intracellular synthesis of IFN-γ and IL-5. The frequencies of IFN-γ-producing cells are shown on the x-axis and those of IL-5-producing cells on the y-axis. Intracellular synthesis of IFN-γ in Tg line 725 mice was increased under all conditions. B, CD8+ T cells from WT and Tg line 725 mice were cultured in the presence of medium alone and analyzed by flow cytometry for intracellular synthesis of IFN-γ and IL-5. Results are representative of three independent experiments.

FIGURE 3. Intracellular cytokine analysis of CD4+ (A) and CD8+ (B) T cells from each group. A, CD4+ T cells from WT and Tg line 725 mice were cultured in the presence of medium alone, anti-IL-4 plus IL-12 (Th1 differentiation conditions), or anti-IL-12 plus IL-4 (Th2 differentiation conditions) and analyzed by flow cytometry for intracellular synthesis of IFN-γ and IL-5. The frequencies of IFN-γ-producing cells are shown on the x-axis and those of IL-5-producing cells on the y-axis. Intracellular synthesis of IFN-γ in Tg line 725 mice was increased under all conditions. B, CD8+ T cells from WT and Tg line 725 mice were cultured in the presence of medium alone and analyzed by flow cytometry for intracellular synthesis of IFN-γ and IL-5. Results are representative of three independent experiments.

FIGURE 4. GATA-3 mRNA expression analysis by RT-PCR in intracellular cytokine production experiment. P, Prestimulation; M, medium-alone condition; Th1, Th1 differentiation conditions; Th2, Th2 differentiation conditions; N, PCR without template as negative control.
analyses were also done. IL-4 production in cells from Tg and WT mice was similar and the percentage of positive cells was very low under all conditions (data not shown). These results demonstrate that T cells from T-bet Tg mice have a dominant Th1 differentiation pattern and suggest that overexpression of T-bet prevents Th2 differentiation. CD8⁺ T cells from Tg mice also had higher levels of IFN-γ than WT mice in neutral condition, but not so markedly as that of CD4⁺ T cells from Tg mice (Fig. 3B). We also determined the GATA-3 mRNA expression in the intracellular cytokine production analyses (Fig. 4). GATA-3 mRNA expression in Tg mice showed lower levels than those of wild mice, especially in a Th1 condition.

FIGURE 5. Tg mice develop dermatitis. In severe cases, individual Tg mice lost hair all over the body (A). In mild cases, the surface of the face, ear, foot, and tail showed redness and scaling (B and C).

FIGURE 6. Histological appearance of the ear skin. A and B, In the histological analysis of ear skin, hyperkeratosis, acanthosis, broadening of the papillae, and infiltration of neutrophils lymphocytes, and melanophages are seen. C and D, At higher magnification of the squares from A and B, infiltration of mononuclear cells and neutrophils is observed. (H&E staining; magnification: ×100 (A), ×100 (B), ×200 (C), and ×400 (D).
Development of contact dermatitis in T-bet Tg mice

During the initial analysis of the Tg cohorts we found that they developed dermatitis. At \( \sim 10 \) wk of age, \( \sim 28\% \) of Tg line 725 (12 of 43) and 5% of Tg line 731 (3 of 61) mice spontaneously developed dermatitis characterized by swollen, flaky, and scaly skin in regions lacking body hair (e.g., tail or ears), which in some individuals progressed all over the body, together with alopecia (Fig. 5). Histological examination of the affected skin showed epithelial hyperkeratosis and neutrophil and lymphocyte infiltration similar to what is seen in contact dermatitis in humans (Fig. 6). To prove that the skin lesion was contact dermatitis although the Ag was not determined, we performed cell transfer experiment. We transferred total spleen cells from T-bet to WT mice and found that dermatitis was induced in 70% (7 of 10 mice) within one month. However, dermatitis was not observed after the transfer of separated CD4\(^+\) or CD8\(^+\) cells alone.

**Augmentation of CHS reactions in Tg mice**

To determine the role of T-bet overexpression in T cell subpopulations in CHS responses, 6-wk-old WT and Tg (Tg line 725) mice, which did not develop dermatitis, were sensitized with DNB as described in Materials and Methods. Ear swelling responses to DNB were significantly increased in Tg mice compared with WT mice (Fig. 7). The CHS response was significantly higher at 24 and 48 h after challenge. Histological analysis of hapten-treated WT and Tg ears showed characteristic features of CHS including dermal edema, mononuclear cell infiltration, and vascular enlargement (Fig. 8B). These histological changes were dramatically enhanced in hapten-treated Tg mouse ears (Fig. 8B).

**Both CD4\(^+\) and CD8\(^+\) T cell lymph node cells (LNCs) produce significant amounts of IFN-\( \gamma \) in T-bet Tg mice**

To determine IFN-\( \gamma \) production in skin-draining lymph nodes of Tg and WT mice, DNB-primed LNCs were cultured under condition with medium alone. A significant increase of IFN-\( \gamma \)-producing cells was found among both CD4\(^+\) and CD8\(^+\) LNCs from DNB-stimulated Tg mice (Fig. 9). In Tg mice, IFN-\( \gamma \)-producing cells were increased in CD4\(^+\) LNCs even without DNB stimulation. After stimulation, IFN-\( \gamma \)-producing cells increased further (Fig. 9A). Regarding CD8\(^+\) LNCs, WT and Tg mice had the similar levels of IFN-\( \gamma \)-producing cells, but after DNB stimulation the increase of IFN-\( \gamma \)-producing cells was greater in Tg mice (Fig. 9B). IL-10 production was also analyzed as a marker cytokine of...
serum cytokines were below the level of detection, we analyzed T-bet Tg mice showed Th1-dominant Ig production in vivo and (7). In this study, we generated T-bet-overexpressing mice char-

Intracellular cytokine analyses showed that T-bet-overexpressing mice were found (data not shown). These results suggest that Tg mice had a Th1-dominant background but also a potential Tc1-dominant background.

FIGURE 9. The number of IFN-γ-producing cells among CD4+ and CD8+ T cells was increased in CHS-sensitized Tg LNCs. LNCs from 72 h DNFB-sensitized or non-sensitized WT and Tg mice were cultured in me-

Discussion
T-bet is known as a master regulator of Th1 development. It in-

Contact allergens such as DNFB, oxazolone, and 2,4-dinitro-

serological Ig findings are therefore consistent with data from CD4+ T cell intracellular cytokine assays, emphasizing that these do indeed reflect the Th1/Th2 balance in vivo. T-bet has also been shown to regulate cytolytic effector mechanisms of CD8+ T cells (8). Its expression is rapidly induced in CD8+ T cells by signaling through the TCR and the IFN-γR, and it functions downstream of STAT1 (6, 9, 10). In the context of Ag-specific activation, T-bet is required for the differentiation of naive CD8+ T cells into effector CTLs. In the present study, Tg mice also had a higher fraction of IFN-γ-producing CD8+ T cells according to intracellular cytokine assays, but not as markedly as CD4+ T cells. However, Tg mice showed higher response for IFN-γ-producing CD8+ T cells in the CHS response. From the above results, we speculated that Tg mice not only had a Th1-dominant background but also a potential Tc1-dominant background.

In this study, spontaneous skin inflammation was observed in Tg mice, first occurring in regions lacking body hair such as the tail or ears, where the skin is easily in contact with external agents. Histological examination of affected skin showed epidermal hyper-

Materials and Methods

Materials and Methods

The higher IgG2a/IgG1 ratio present in the sera of Tg mice sug-

It is known that Th1 activity greatly contributes to the development of dermatitis (25, 26). It is shown here that a Th1-

was found (data not shown).

Intracellular cytokines and found that CD4+ T cells from Tg mice produced higher levels of IFN-γ than WT mice under neutral, Th1-

Parakeratosis. The possible importance of several cytokines such as IL-2 (27), IL-6 (28), and IL-7 (29) in the development of contact dermatitis has also been investigated using Tg mouse models (30). In this study we used Tg mice overexpressing the T cell differentiation transcription factor T-bet, but not cytokine transgenes, to address contact dermatitis for the first time. The results from this study suggested that transcriptional regulation of T-bet might play an important role in contact dermatitis.

Tg mice not only had a Th1-dominant background but also a potential Tc1-dominant background.

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Serum cytokines were below the level of detection, we analyzed T-bet Tg mice showed Th1-dominant Ig production in vivo and (7). In this study, we generated T-bet-overexpressing mice char-

Intracellular cytokine analyses showed that T-bet-overexpressing mice were detected in DNFB-sensitized Tg CD4+ (A) and CD8+ (B) T cells. Results are representative of three independent experiments.

Th2 or Tc2. However, no significant differences between Tg and WT mice were found (data not shown).

Intracellular cytokines and found that CD4+ T cells from Tg mice produced higher levels of IFN-γ than WT mice under neutral, Th1-

or Th2-promoting conditions. In contrast, IL-5 production in CD4+ T cells from Tg mice was lower than that in CD4+ T cells from WT mice under neutral or Th2-promoting conditions. The
24 to 48 h in the mouse (12), coinciding closely with our results on 24- and 48-h DNBF hyperresponsiveness.

In contrast to T-bet, GATA-3 is known as a Th2 lineage commitment transcription factor (35, 36). We have previously shown that GATA-3 overexpression in Th1-dominant autoimmune disease can diminish autoimmune nephritis (20, 37), and therefore, that therapy to regulate expression levels of transcriptional factors may be useful to control unbalanced Th1/Th2 activity in many diseases. The results of the present study also suggest that to control Th1 and Tc1 reactions via down-regulation of T-bet expression might be useful for alleviating contact dermatitis.

In conclusion, we have generated Th1- and Tc1-dominant mice that developed spontaneous skin inflammation very similar to contact dermatitis. These mice should be useful for revealing a link between some immune diseases and Th1/Th2 and Tc1/Tc2 dysbalance and may offer a valuable murine model of contact dermatitis.

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Disclosures

The authors have no financial conflict of interest.

References


