Involvement of Epitope Mimicry in Potentiation But Not Initiation of Autoimmune Disease

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We have examined whether the peptide (368–381) from the murine adenovirus type 1 E1B sequence, exhibiting a high degree of homology with the known pathogenic thyroglobulin (Tg) T cell epitope (2695–2706), can induce experimental autoimmune thyroiditis (EAT) in SJL/J mice. The viral peptide was a poor immunogen at the T or B cell level and did not elicit EAT either directly or by adoptive transfer assays. Surprisingly, however, the viral peptide was highly antigenic in vitro, activating a Tg2695–2706-specific T cell clone and reacting with serum IgG from mice primed with the Tg homologue. The viral peptide also induced strong recall responses in Tg2695–2706-primed lymph node cells, and subsequent adoptive transfer of these cells into naive mice led to development of highly significant EAT. These data demonstrate that nonimmunogenic viral peptides can act as agonists for preactivated autoreactive T cells and suggest that epitope mimicry may at times play a potentiating rather than a precipitating role in the pathogenesis of autoimmune disease. The Journal of Immunology, 1999, 162: 5888–5893.

H ashimoto’s thyroiditis is a T cell-mediated autoimmune disease whose etiology remains unknown (1). Microbial infection has been associated with Hashimoto’s thyroiditis or other forms of thyroiditis (2), but the supporting evidence, obtained mostly from serological studies, has not established a cause-effect relationship with viral, retroviral, or bacterial agents (2–5). Viral infection has been more directly linked to the triggering of thyroid disease in animal model studies. Infection of mice with reovirus type 1 has led to infiltration of the thyroid by inflammatory cells and production of autoantibodies against thyroglobulin (Tg) and thyroid peroxidase (6). The lymphocytic choriomeningitis virus has been shown to persist in the thyroids of mice neonatally infected with the virus and to cause a reduction in the levels of Tg mRNA and circulating thyroid hormones (7). In addition, infection of chicken embryos with avian leukosis virus results in hypothyroidism within 3 wk of hatching and the formation of an extensive lymphocytic infiltrate in the thyroids of infected chickens (8). Lastly, rats maintained under pathogen-free conditions are resistant to the induction of experimental autoimmune thyroiditis (EAT) by thymectomy and irradiation (9). Oral administration of intestinal contents from conventionally reared rats significantly enhances their susceptibility to EAT, suggesting that presensitization to the gut flora plays a role in the development of disease.

During an infection, autoreactive T cells may be triggered nonspecifically by microbial superantigens (10) or specifically by self epitopes secondarily released from infected tissue damaged by an immune response to the invading pathogen (11). Alternatively, autoreactive T cells may be activated by molecular mimicry (12) if they cross-react with antigenic determinants derived from microbial proteins. The latter concept has been particularly difficult to test in human or experimental autoimmune thyroid disease because the majority of pathogenic T cell epitopes on thyroid autoantigens remain unknown. To date, five EAT-inducing, T cell determinant sites have been mapped on Tg, and all have been characterized as nondominant (13). One of them is the 18-mer Tg peptide (2695–2713) that causes EAT in SJL (H-2d) (SJL) mice (14). The pathogenicity of this peptide is most likely attributed to the Aβ-restricted, 12-mer T cell epitope (2695–2706) (15), a site that is shared between mouse and rat Tg (16, 17). In this study we have sought to identify sequences of microbial origin exhibiting high homology to Tg2695–2713 with a view to examining whether such sequences could also precipitate EAT.

Materials and Methods

Animals and Ags

Female SJL/J mice were purchased from The Jackson Laboratories (Bar Harbor, ME) and were used for immunizations at 6–10 wk of age. All peptides in this study were synthesized and purified commercially (Alberta Peptide Institute, Edmonton, Canada). The 10-mer E1B peptide SFVSSYIQTL was synthesized by Synpep (Dublin, CA). All peptides carried an acetyl and an amide group at their N- or C-terminal, respectively, and their purity was assessed by HPLC and mass spectroscopic analysis.

Culture medium and cell lines

All assays were performed in DMEM (Life Technologies, Burlington, Canada) supplemented with 10% FBS (Bioproducts for Science, Indianapolis, IN), 20 mM HEPES buffer, 2 mM l-glutamine, 100 U/ml penicillin, 100 μg/ml streptomycin (all from Life Technologies), and 5 × 10–5 M 2-ME (Sigma, St. Louis, MO). The B cell lymphoma LS102.9, used as APC (18), and the IL-2-dependent CTLL-2 line (19) were purchased from American Type Culture Collection (Manassas, VA). The T cell hybridoma clone 6E10 specific for Tg2695–2713 was generated as previously described (14). 6E10 activation was monitored by IL-2 release in the culture supernatant, as measured by the proliferation of CTLL-2 line using [3H]thymidine (DuPont Canada, Mississauga, Canada) (15).

ELISA and LNC proliferation assays

The presence of peptide-specific IgG in pooled sera was determined by ELISA as previously described (20) using an alkaline phosphatase-conjugated goat anti-mouse IgG (Sigma) as the second Ab. Detection of cytokines in tissue culture supernatants was performed by sandwich ELISA.
The cells were then harvested, and after washing three times, 2–3 g were 90, 140, 50, and 80 pg/ml for IL-2, IFN-γ, IL-4, and IL-10, respectively. Light absorption at 405 nm was measured using a Vmax plate reader (Molecular Devices, Sunnyvale, CA). Peptide-specific LNC proliferative assays were performed as previously reported (21). The stimulation index was defined as counts per minute in the presence of Ag/counts per minute in the absence of Ag.

**Induction and histological assessment of EAT**

For direct induction of EAT, all mice were s.c. challenged with various doses of peptides emulsified in CFA (with Mycobacterium butyricum, Difco, Detroit, MI). Two weeks later, they were boosted with the same peptide in IFA (Difco). EAT was assessed by histological examination of the thyroids 4 wk after the initial challenge. To induce EAT by adoptive transfer, donor mice were primed s.c. at the base of the tail with 50 nmol of peptide in CFA. Ten days after priming, inguinal LNC were harvested and cultured for 72 h in the presence of the appropriate peptide (10 μg/ml). The cells were then harvested, and after washing three times, 2–3 × 10^9 cells were suspended in HBSS and injected i.p. into each syngeneic recipient. Fourteen days later, thyroid glands and sera were collected. Formalin-fixed thyroids were embedded in methacrylate, and approximately 40 sections, 3 μm thick, were obtained at 36-μm intervals from each gland. The sections were stained with hematoxylin and eosin (H&E) and were scored for the presence of mononuclear cell infiltration as follows: 1 = interstitial accumulation of cells between two or three follicles; 2 = one or two foci of cells at least the size of one follicle; 3 = extensive infiltration, 10–40% of the total area; 4 = extensive infiltration, 40–80% of the total area; and 5 = extensive infiltration, >80% of the total area. The highest infiltration index observed per gland was assigned to each mouse.

**Infection with mouse adenovirus type 1**

Four-week-old female SJL/J mice (n = 5 for each dose) were injected i.p. with 10^−3, 10^−5, or 10^−7 PFU of wild-type murine adenovirus type 1 (MAV-1) in a volume of 100 μl. There are at least 1000 particles/PFU (K. Spindler, unpublished observation) and wild-type 50% lethal doses are around 10^−4 PFU (22, 23). Five mice were injected with 100 μl of conditioned DMEM and used as controls. Mice were monitored twice a day for the appearance of neurologic signs associated with MAV-1 infection (24). At 3 wk postinfection, thyroid glands were removed and fixed in formalin. Spleens were removed, and pools of splenic lymphocyte suspensions for proliferation assays were prepared for each group as previously reported (21). Four of the mice receiving 10^−4 PFU and one mouse receiving 10^−3 PFU presented with severe paralysis between 11 and 14 days postinfection, requiring euthanasia. Spleens, thyroids, and blood were obtained immediately postmortem and processed as described above.

**Results**

We sought to identify from the SWISS-PROT databank sequences of microbial origin exhibiting high homology to the 18-mer Tg peptide (2695–2713) that induces EAT in SJL mice (14). Five sequences scored >30% homology with Tg2695–2713 with various degrees of overlap (Table I). The highest homology (75%) was observed with an octamer peptide from DNA-directed RNA polymerase (25). Viral peptides from the adenoviral E1B protein (26) and the retroviral pol protein (27) exhibited 64.3 and 55.6% homologies, respectively. Lastly, a 12-mer peptide from the acetyl cholinesterase precursor (28) and a 13-mer peptide from an Escherichia coli heat shock protein (29) exhibited 41.7 and 30.8% homologies, respectively. Among these five sequences, the longest (14 aa) overlap was found between Tg2695–2706 and the MAV-1 E1B protein (aa 368–381; Fig. 1). Nine of the 14 overlapping aa were identical (64.2%), whereas conservative substitutions were observed in four other aa positions (28.5%). The coordinates of this high homology site almost coincide with those of the 12-mer Tg2695–2706 peptide that causes EAT in SJL mice and encompasses an α-restricted T cell epitope (15). This observation and a reported association of adenoviral infection with subacute thyroiditis (5) encouraged us to further examine whether the synthetic 14-mer E1B368–381 peptide exhibited immunopathogenic properties.

SJL mice were first challenged with various doses of Tg2695–2706 ranging from 0.2–200 nmol to confirm the pathogenicity of this peptide (15). All six mice primed with 200 nmol and three of six mice primed with 20 nmol developed lymphocytic infiltration of the thyroid (Table II). EAT was not induced in mice that received 2 or 0.2 nmol of peptide, perhaps due to the nondominant nature of this epitope (14). In addition, LNC from mice primed with the highest doses of Tg2695–2706 proliferated strongly against this Ag in vitro and secreted significant amounts of IL-2 and IFN-γ in an Ag-specific manner because a similar response was not observed against the control Tg2695–2511 (data not shown). The LNC from mice primed with 200 or 20 nmol of Tg2695–2706 peptide in vivo cross-reacted strongly against the viral E1B368–381 peptide in culture, and this was demonstrable by both proliferative capacity and IL-2 or IFN-γ release (Table II). These data suggested that the viral peptide is clearly antigenic.

Surprisingly, however, SJL mice challenged with E1B368–381 in CFA did not develop EAT regardless of the peptide dose used (Table II). Also, the E1B peptide was weakly immunogenic, eliciting only a marginal proliferative response or IL-2 or IFN-γ release in cultures of LNC from mice that received the highest (200 nmol) dose. The lack of response could not be attributed to quantitative effects of the peptide concentration in vitro. As shown in

![FIGURE 1](https://example.com/fig1.png)

**Table I. Homology comparison of Tg peptide (2695-2713) with sequences in Swiss-Protein data bank**

<table>
<thead>
<tr>
<th>Sequence</th>
<th>Protein</th>
<th>% Homology</th>
<th>Overlap</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSFWSK...</td>
<td>Mouse thyroglobulin</td>
<td>100</td>
<td>18</td>
<td>16</td>
</tr>
<tr>
<td>KITG...</td>
<td>DNA-directed RNA pol</td>
<td>75.0</td>
<td>8</td>
<td>25</td>
</tr>
<tr>
<td>SFYSI...</td>
<td>Mouse adenovirus E1B protein</td>
<td>64.3</td>
<td>14</td>
<td>26</td>
</tr>
<tr>
<td>SFYWAV...</td>
<td>Retrovirus pol protein</td>
<td>55.6</td>
<td>9</td>
<td>27</td>
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<tr>
<td>SFSDWNY...</td>
<td>Acetylcholinesterase precursor</td>
<td>41.7</td>
<td>12</td>
<td>28</td>
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<tr>
<td>SFNQWEG...</td>
<td>Heat shock protein</td>
<td>30.8</td>
<td>13</td>
<td>29</td>
</tr>
</tbody>
</table>

* A total of 26,706 sequences in the database were searched using the FASTA program. Identical amino acids are denoted in bold letters. Conservatively substituted amino acids are underlined.
The presence of 10-mer peptides resulted in in vitro responses ranging from 2,572 for Tg peptide-primed LNC and from 530 to 6,605 for E1B peptide-primed LNC. No group yielded a response against the control peptide Tg 2495-2511. Similar results were obtained in three additional experiments.

E1B368–377 was identified as a viral epitope that could act as an agonist or partial agonist for T cells previously selected to respond to the thyroid-autoantigen. This delineated the 10-mer as a highly immunogenic peptide.

In contrast, within the same molar range in vitro, E1B368–381 could not induce proliferation of LNC from SJL mice previously primed with the viral peptide itself (Fig. 2B). These results attributed the lack of the in vitro response to the absence of efficient priming in vivo and confirmed that the viral epitope is an extremely weak immunogen.

To confirm cross-recognition of peptides at the clonal T cell level, we used the A'-restricted CD4+ T cell hybrid clone 6E10, which secretes IL-2 upon specific activation with Tg 2695–2706 (15). A'-expressing, L512.9 cells pulsed with the 12-mer Tg epitope or the 10-mer E1B 368–377 stimulated 6E10 for maximal IL-2 release, although the viral peptide was effective at an 8- to 10-fold higher molar concentration (Fig. 3). This delineated the 10-mer E1B 368–377 as a viral epitope that can act as an agonist or partial agonist for T cells previously selected to respond to the thyroid-autoantigen.

Evidence for lack of immunogenicity of E1B368–381 was also provided at the serological level. Following s.c. challenge with Tg 2695–2706 and cross-boosted in vitro with E1B 368–377 presented by splenocytes from SJL mice, adoptive transfer into naive hosts induced EAT and alterations in their thyroids (Fig. 5). Spleen cells from such mice also failed to proliferate specifically to E1B 368–381 or Tg 2695–2713 in vitro (data not shown).

Peptides that do not directly induce proliferative LNC responses or thyroid pathology are nevertheless known to mediate EAT by adoptive transfer into naive hosts of peptide-specific LNC (13). This protocol usually leads to consistent EAT induction and a more severe lymphocytic infiltration of the thyroid than direct challenge of mice with peptide in adjuvant. To test whether E1B368–377 falls in this category, LNC from SJL mice primed with this peptide were boosted in vitro with the same Ag and were subsequently i.p. transferred into naive animals. Fourteen days later, histological examination showed only focal lymphocytic infiltration in the thyroid in one of seven recipients (Table III, group 1). In contrast, five of six animals that received LNC primed with Tg 2695–2706 and cross-boosted in vitro with E1B368–377 presented with significant thyroid lesions (group 2). This is similar to the frequency (six of six SJL mice) and severity (infiltration index, 3–4) of EAT observed in previous studies in which LNC primed and boosted with Tg 2695–2706 were adoptively transferred to naive SJL mice (15). LNC that were stimulated in vitro with the control 9-mer pathogenic peptide Tg 2496–2704 that binds to A' (30) (group 3) or cultured in medium alone (group 4) did not transfer EAT in any of the mice tested. These data confirmed that despite its lack of immunogenicity, E1B368–377 acts as an agonist or partial agonist for T cells previously selected to respond to the thyroid-autoantigen.

**FIGURE 2.** Proliferative in vitro responses to the indicated peptides of pooled LNC from SJL mice (two mice per group) s.c. primed 10 days earlier with 50 nmol of either Tg 2695–2706 (A) or E1B368–381 (B) peptide. Background counts per minute were 1257 for A and 1896 for B. The Tg 2701–2713 epitope was used as a control. Similar results were obtained in three additional experiments.

<table>
<thead>
<tr>
<th>Peptide In Vivo</th>
<th>Dose (nmol)</th>
<th>Mice with EAT*</th>
<th>Infiltration Index (± SD)</th>
<th>Cytokine (pg/ml)</th>
</tr>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>In vitro response against Tg 2695–2706</td>
</tr>
<tr>
<td>Tg 2695–2706</td>
<td>200</td>
<td>6/6</td>
<td>2.7 ± 0.5</td>
<td>S.I. IL-2 IFN-γ</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>3/6</td>
<td>1.3 ± 0.5</td>
<td>15.9 7410 5760</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>0/6</td>
<td>0.0 ± 0.0</td>
<td>6.3 3430 2614</td>
</tr>
<tr>
<td></td>
<td>0.2</td>
<td>0/6</td>
<td>0.0 ± 0.0</td>
<td>2.3 320 260</td>
</tr>
<tr>
<td>E1B368–381</td>
<td>200</td>
<td>0/6</td>
<td>0.0 ± 0.0</td>
<td>1.4 &lt;90 &lt;140</td>
</tr>
<tr>
<td></td>
<td>20</td>
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<td>1.8 &lt;90 &lt;140</td>
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<tr>
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<tr>
<td></td>
<td>0.2</td>
<td>0/6</td>
<td>0.0 ± 0.0</td>
<td>1.5 &lt;90 &lt;140</td>
</tr>
</tbody>
</table>

* SJL/J mice were primed with the indicated dose of peptide in CFA, and 2 wk later they were boosted with the same dose of peptide in IFA. EAT was assessed 4 wk after the initial challenge.

* In all cultures, IL-4 and IL-10 were undetected over the ELISA sensitivity limit of 50 and 80 pg/ml, respectively.

* SJL mice (two mice per group) were primed with the indicated dose of peptide in CFA, and 10 days later their inguinal LNC were allowed to proliferate for 96 h in the presence of 10 µM of Tg 2695–2706 or E1B368–381. Stimulation index (S.I.) denotes (cpm in the presence of Ag/cpm in the absence of Ag). Background cpm ranged from 866 to 2,572 for Tg peptide-primed LNC and from 530 to 6,605 for E1B peptide-primed LNC. No group yielded an in vitro response against the control peptide Tg 2695–2713. Similar results were obtained in two other experiments.

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**Table II. Immunopathogenic properties of Tg and adenoviral E1B T-cell epitopes**

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<tr>
<td></td>
<td>20</td>
<td>3/6</td>
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<td>15.9 7410 5760</td>
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<td></td>
<td>2</td>
<td>0/6</td>
<td>0.0 ± 0.0</td>
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<td></td>
<td>0.2</td>
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**FIGURE 2.** Proliferative in vitro responses to the indicated peptides of pooled LNC from SJL mice (two mice per group) s.c. primed 10 days earlier with 50 nmol of either Tg 2695–2706 (A) or E1B368–381 (B) peptide. Background counts per minute were 1257 for A and 1896 for B. The Tg 2701–2713 epitope was used as a control. Similar results were obtained in three additional experiments.
E1B368–377 may be pathogenic in a strain other than SJL, but it is activated autoreactive T cells. The present data cannot exclude that and their detection would be possible only through the use of pre-importance only during the effector phase of the immune response, nonimmunogenic nature, such epitopes would assume biological nevertheless potentiate and expand pathogenic T cells. Due to their going EAT, potentiation of disease via molecular mimicry is a remains to be seen whether MAV-1 infection can exacerbate on-homologous to thyroiditogenic determinants on self Tg. While it does not induce EAT but can harbor potentially harmful epitopes results document an alternative scenario in pathogenesis; MAV-1 precipitate autoimmune disease following viral infection. Our re-

plausible hypothesis and in accord with epidemiological studies proposing infection as a necessary cofactor in the induction of autoimmune (2). The nondominant nature of Tg2695–2713, which can be occasionally generated by processing of self Tg in vivo but not in vitro (14), is not incompatible with the above hypothesis. A variety of mechanisms may generate the Tg peptide to trigger EAT, such as increased uptake or modified processing of self Tg (38). Alternatively, Tg peptide-reactive T cells may arise following intramolecular spreading during the course of an autoimmune response and further expand into effector cells via molecular mimicry with foreign peptides. Epitope spreading may even be facilitated during an infection, as has been recently shown for Theiler’s murine encephalomyelitis virus (11).

Our data are in agreement with the differential recognition of peptide analogues observed in naive vs activated CD4+ T cells responding to the encephalitiogenic: 139–151 peptide of the proteolipid protein (PLP) (39). Those observations as well as the present findings can be explained on the basis that naive Tg peptide-specific CD4+ T cells have more stringent Ag and costimulatory requirements than memory T cells of the same specificity (40–42). Up-regulation of adhesion/costimulatory molecules on the surface of preactivated, self-reactive T cells may compensate for decreased TCR affinity for altered peptides of microbial origin encountered during the course of infection. However, degeneracy of T cell recognition is limited, since we have previously shown that the human homologue of Tg2695–2706, carrying only two amino acid substitutions, Q2703S and T2704S, is not recognized by T cells and exhibits contrasting immunopathogenic properties (15). These residues may be required for TCR contact or for binding to Aα molecules. Such a view is supported by the present study, because E1B368–377 is identical with Tg2695–2706 at eight aa positions, including Q2703 and T2704.

Our results are also in agreement with the recent findings of Carrizosa et al. (43), who demonstrated that viral homologue peptides of PLP139–151 cannot directly induce EAE but they can be recognized by T cells previously activated with the self PLP epitope. However, in contrast to our data the viral peptides in that study were immunogenic, i.e., they elicited cross-reactive T cells that required expansion by the self Ag to induce disease. Although the reasons for such discrepancies between studies are not clear, the emerging experimental evidence supports the existence of microbial epitopes that cross-react with self peptides but cannot precipitate autoimmune disease. These molecular mimics may even be extremely weak immunogens as shown here, but they nevertheless can clearly play an important pathogenic role promoting the differentiation of partially activated autoreactive T cells into the effector stage. Expansion of autoreactive T cells by self Ag
before or during the infection stage may be an important predisposing factor that could at least in part explain the lack of a cause-effect relationship between infection and autoimmune disease at the population level.

This is the first report in the field of mouse EAT demonstrating induction of thyroid pathology due to molecular mimicry of a mouse Tg epitope with a viral peptide. It is unknown whether other sequences with significant homology with mouse MTG2695-2706 (Table I) can be cross-reactive and/or thyroiditogenic. Of particular interest is the homology with acetylcholinesterase, since patients with myasthenia gravis or Graves’ disease have cross-reactive Abs to Tg and acetylcholinesterase (44). Amino acid sequence homologies between adenoviral proteins and human thyroid peroxidase, another major thyroid autoantigen, have also been reported by Dyrb erg (45), but the homologous viral peptides have not been examined for immunopathogenicity. Knowledge of thyroiditogenic sites will facilitate screening for peptide molecular mimics from various pathogens. It remains to be seen whether such peptides will tend to precipitate EAT in naive animals or amplify the thyroiditogenic cascade in susceptible mice with pre-existing autoreactive immune responses.

Acknowledgments

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References


