ABSTRACT  Anti-2,4-dinitrophenyl (DNP) IgE producing hybridoma B 53 when injected subcutaneously is established equally well in syngeneic BALB/c (heavy-chain allotype a) and congenic CB20 (heavy-chain allotype b) mice. However, secretion of anti-DNP IgE monoclonal antibody is greatly suppressed in CB20 mice. B 53 cells taken from the subcutaneous tumors of CB20 mice produce anti-DNP IgE in vivo in BALB/c mice and in vitro. No difference was observed in IgE production between these cells and the controls taken from BALB/c mice. The suppression of IgE production was due to T cells and/or their product(s) of CB20 mice.

When an appropriate number of the monoclonal anti-dinitrophenyl (DNP) IgE producing B 53 hybridoma cells are injected subcutaneously (s.c.) into syngeneic BALB/c mice, the tumor produced by these cells after a certain period of growth is frequently rejected. During its growth, the tumor secretes into the circulation of the host a large amount of anti-DNP IgE monoclonal antibody (1, 2). Hybridoma B 53 was constructed by fusion of spleen cells from BALB/c mice immunized with DNP keyhole limpet hemocyanin and a nonproducing BALB/c myeloma P3X63Ag8-653 (3). Both cells are from BALB/c mice, and the allotype of the monoclonal anti-DNP IgE is a (4).

We have found that when B 53 hybridoma cells were injected s.c. into allogeneic mice (C57BL/6), the tumor generally did not grow (unpublished observations). However, when CB20 mice were injected with B 53 cells s.c., tumor growth was regularly observed. CB20 is a congenic inbred partner of the BALB/c strain and differs from the BALB/c strain by its chromosome 12, at least in the segment where the clusters of the heavy-chain genes are located, as the heavy chains of BALB/c are of allotype a and those of CB20 are of allotype b. Although the tumor produced by B 53 cells regularly grows in CB20 mice, and often the mice are killed by the expanding tumor, generally only a small amount or no anti-DNP IgE monoclonal antibody is secreted by these tumors, a striking difference with BALB/c mice, in which the titer of anti-DNP IgE antibody correlated very well with the size of the tumor.

In many CB20 mice, s.c. injected B 53 cells produced growing tumors, but the circulating anti-DNP IgE was very low as: (i) no passive cutaneous anaphylaxias (PCA) could be obtained even with a 1:100 dilution of these sera (PCA, <100), and (ii) by ELISA, anti-DNP IgE could not be detected. These mice were designated CB20(T) mice. This report in this study the results of experiments undertaken to examine whether the absence of secretion of IgE was the result of the appearance of a variant (a nonsecreting B 53 cell) or due to other causes.
monospecific anti-mouse IgE agglutinated the IgE-coated cells at low dilution (1:100). However, when dilutions 1:1000 were used, no agglutination was observed. The cells were lysed with this antiserum in the presence of guinea pig complement even at a dilution of 1:32,000 of the antiserum. These preliminary controls showed that the cells coated with this anti-DNP IgE 7a could be agglutinated, and in the presence of guinea pig complement they lysed with an antiserum directed against this IgE antibody. These cells were used to check the presence of antibody against allotype 7a in the sera of CB20(T) mice.

s.c. Injection of B 53 Cells. Four types of experiments were done using B 53 cells in s.c. injection.

In the first type of experiments, 5 × 10⁶ B 53 cells were injected s.c. into CB20 or BALB/c mice. Tumor growth and serum anti-DNP IgE titer were monitored for 4 weeks.

In the second type of experiments, 10⁴ single-cell suspensions from the tumors of CB20(T) or BALB/c(T) mice were injected s.c. into BALB/c recipients, and tumor growth and anti-DNP IgE titers in the sera of the recipients were monitored for 4 weeks.

The third type of experiment was similar to Winn assays (7) already described with B 53 cells. B 53 cells (10⁵) were injected s.c. into BALB/c mice. Five mice were used per group. The B 53 cells were either suspended in sera from CB20(T) mice or were admixed to spleen cells from CB20(T) mice. As controls, sera and spleen cells from BALB/c(T) mice were used. The number of spleen cells was 10⁷ in each case. The spleen cells were treated before admixture with IS and complement to eliminate possible splenic metastatic B 53 cells. Tumor growth and anti-DNP IgE were monitored for 2 weeks.

The fourth type of experiment differed from the previous one in two respects: (i) sera were not used and (ii) the spleen cells were in addition treated with anti-Thy-1.2 and complement. Here, too, tumor growth and anti-DNP IgE were monitored for 2 weeks.

i.p. Injection of Tumor Cells. Tumor cells (2 × 10⁵) taken from s.c. tumors of CB20(T) or BALB/c(T) mice were injected i.p. into BALB/c recipients. Circulating anti-DNP IgE antibody was monitored for 14 days.

i.v. Injection of Sera or Spleen Cells from CB20(T) Donors. Undiluted sera (0.3 ml) or 2 × 10⁷ spleen cells (pretreated with IS and complement) from CB20(T) or BALB/c(T) donors were injected i.v. into 5 × 10⁴ irradiated BALB/c recipients. Irradiation was done 1 day before i.v. injection with a Gammator irradiator (Gammator Radiation Machinery, Parsippany, NJ). Mice injected with sera received, in addition, 2 × 10⁷ spleen cells i.v. from normal BALB/c mice (as in previous experiments (not shown), we had seen that without reconstitution the mice died in a few weeks). One day after i.v. injection of sera or spleen cells, all mice were injected s.c. with 10⁴ B 53 cells. Anti-DNP IgE determinations in sera were done for 2 weeks.

**Short-Term in Vitro Cultures.** Cells were cultured in complete tissue culture medium [RPMI 1640 supplemented with 2 mM L-glutamine, penicillin G (100 units/ml), streptomycin (50 mg/ml) (all from GIBCO), 50 μM 2-mercaptoethanol (Eastern Organic Chemical, Rochester, NY), 10% fetal calf serum (Dutchland Laboratories, Denver, PA)] at 37°C, 5% CO₂, and 95% air in 6-well flat-bottom plates (Costar 3506, Cambridge, MA) for 2 or 3 days. The volume in which the cells were cultured was 2 ml.

In the first experiments aimed to establish anti-DNP IgE secretion by cells from s.c. tumors produced by B 53 cells from CB20(T) and BALB/c(T) mice, the tumors were excised 4 weeks after s.c. injection of 5 × 10⁶ B 53 cells. Tumor cells (5 × 10⁶) were cultured for 2 days. Anti-DNP IgE antibody in the supernatant was determined by PCA.

In the second experiments, 2 × 10⁶ B 53 cells were cultured for 3 days together with 2 × 10⁴ spleen cells from CB20(T) or BALB/c(T) mice taken 3 weeks after s.c. injection of 5 × 10⁶ B 53 cells to compare eventual suppression by CB20(T) spleen cells on anti-DNP IgE secretion. Spleen cells were treated by IS and complement as described above to eliminate potential splenic metastatic B 53 cells. Anti-DNP IgE antibody in the supernatant was measured by ELISA.

In the third experiment, 2 × 10⁶ B 53 cells were cultured for 3 days in presence of 0.2 ml of sera from CB20(T) or BALB/c(T) mice taken 3 weeks after s.c. injection of 5 × 10⁶ B 53 cells. As an additional control, 0.2 ml of serum from BALB/c(T) mice was incubated for the same period in the absence of B 53 cells in order to establish the baseline anti-DNP IgE concentration. Anti-DNP IgE content in the supernatant was checked by ELISA.

The suppression of anti-DNP IgE secretion was calculated by the formula:

\[
\text{% suppression} = \frac{\text{control (mg/ml) - experimental (mg/ml)}}{\text{control (mg/ml)}} \times 100.
\]

**RESULTS**

**s.c. Injection of B 53 Cells into CB20 or BALB/c Mice.** The results are summarized in Table 1. In BALB/c mice, tumor size and circulating anti-DNP IgE titer correlated well. It should be noted that in BALB/c mice at least 5 of 10 had considerably lower anti-DNP IgE titer and smaller tumors at 4 weeks than at 3 weeks. This rejection of B 53 cells in BALB/c mice has already been described (2). In CB20 mice, only one mouse had a smaller tumor at 4 weeks than at 3 weeks. As previously observed, BALB/c mice with large tumors had high levels of circulating anti-DNP IgE (2). In CB20 mice, in spite of large tumors, 5 of 10 mice had low levels of circulating anti-DNP IgE, and in 3 of them the titer was 0-5 ppm.

<table>
<thead>
<tr>
<th></th>
<th>3 weeks</th>
<th>4 weeks</th>
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<tbody>
<tr>
<td></td>
<td>PCA</td>
<td>TS</td>
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<tr>
<td>BALB/c</td>
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<td></td>
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<tr>
<td>1600</td>
<td>++</td>
<td>100</td>
</tr>
<tr>
<td>6400</td>
<td>+++</td>
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<td>+</td>
<td>12,800</td>
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<tr>
<td>400</td>
<td>++</td>
<td>400</td>
</tr>
</tbody>
</table>

TS, tumor size; –, no tumor; ±, 0–5 mm; ±, 5–15 mm; ++, 15–25 mm; +++, 25–35 mm; +++++, >35 mm; ND, not done. Circulating anti-DNP IgE was determined by PCA at various times after s.c. injection.
was <1/100 PCA units at 4 weeks. These determinations were also confirmed by ELISA (not shown). These mice were designated CB20(T), as mentioned above.

**Secretion of Anti-DNP IgE by Tumor Cells from CB20(T) Mice.** Single-cell suspensions were made from excised tumors of CB20(T) (IgE, <1:100 PCA) and BALB/c(T) (IgE, >1:1600 PCA) mice, and the secretion of anti-DNP IgE was investigated by three methods.

Tumor cells (10^6) were injected s.c. into three BALB/c mice. Tumor growth and anti-DNP IgE in the circulating blood were checked for 4 weeks. The results are presented in Table 2.

Tumor cells (2 × 10^6) were cultured i.p. into three BALB/c mice, and anti-DNP IgE in the circulating blood was checked for 14 days. The results are presented in Table 3.

Tumor cells (5 × 10^6) were cultured for 2 days in vitro in duplicate, and anti-DNP IgE was determined in the supernatant. The results are presented in Table 4.

The results of these experiments, presented in Tables 2-4, show that tumor cells from CB20(T) mice secreted anti-DNP IgE in comparable amounts to that secreted by BALB/c(T) tumor cells.

**Suppression of Anti-DNP IgE Secretion from s.c. Injected B 53 Cells by Sera or Spleen Cells from CB20(T) Mice.** Recipient BALB/c mice were injected s.c. with 10^6 B 53 cells admixed to 10^6 spleen cells of CB20(T) mice or suspended in undiluted sera from CB20(T) mice. The results of this Winn-type assay are presented in Table 5. Sera from CB20(T) mice had an inhibitory effect at 1 week on anti-DNP IgE secretion, but at 10 days injection was not appreciable. Spleen cells had an inhibitory effect for 10 days; at 2 weeks, the inhibitory effect was already weak.

Suppression of anti-DNP IgE secretion from s.c. injected B 53 cells by i.v. injection of sera or spleen cells from CB20(T) mice was also investigated. The recipient BALB/c mice were injected i.v. with 0.3 ml of undiluted serum plus 2 × 10^6 normal BALB/c spleen cells for reconstitution or 2 × 10^6 spleen cells from CB20(T) mice, and 1 day later they were injected s.c. with 10^6 B 53 cells. The results are presented in Table 6. Both sera and spleen cells from CB20(T) donors had an inhibitory effect at 1 week, but no inhibition was observed at 2 weeks.

In both types of experiments, the controls were sera or spleen cells from BALB/c(T) mice. As these mice had high levels of circulating anti-DNP IgE antibody titer, it was necessary to determine whether sera from these mice could have any effect on the determination of anti-DNP IgE antibody. As expected, because of the very short halflife of circulating IgE in the mouse [5-12 hr (8, 9)], no circulating anti-DNP IgE could be demonstrated in BALB/c mice injected 1 week before with sera from BALB/c(T) mice (data not shown).

**Effect of Anti-Thy-1.2 Treatment in the Activity of CB20(T) Cells.** The results are presented in Table 7. Anti-Thy-1.2 and complement completely destroyed all inhibitory activity.

**Passive Hemagglutination and Passive Lysis of Sheep Erythrocytes Coupled to DNP and Coated with IgE 7a.** Neither hemagglutination nor passive lysis was observed in any of the dilutions of sera from CB20(T) mice. The lowest dilution for hemagglutination was 1:2,000, and for passive lysis it was 1:500. The highest dilution was 1:6,400 for both tests.

As described in Materials and Methods, the spleen cells were treated with IS and complement to eliminate potential splenic metastatic B 53 cells. Anti-DNP IgE (2.548 μg) was secreted in the cultures by B 53 cells when the spleen cells present were from BALB/c(T) mice, but only 1.118 μg was secreted when the spleen cells present were from CB20(T) mice. The suppression, therefore, was 56.1%. When B 53 cells were cultured with normal BALB/c spleen cells, the suppression was 0.8%.

<table>
<thead>
<tr>
<th>2 weeks</th>
<th>3 weeks</th>
<th>4 weeks</th>
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<tbody>
<tr>
<td>PCA</td>
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<td>PCA</td>
</tr>
<tr>
<td>6400</td>
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<td>25,600</td>
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<tr>
<td>1600</td>
<td>++</td>
<td>12,800</td>
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<tr>
<td>1600</td>
<td>++</td>
<td>12,800</td>
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</table>

TS, tumor size (indicated as described in Table 1).

<table>
<thead>
<tr>
<th>Experiment 1</th>
<th>Experiment 2</th>
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<tbody>
<tr>
<td>CB20(T)</td>
<td>BALB/c</td>
</tr>
<tr>
<td>640</td>
<td>640</td>
</tr>
<tr>
<td>640</td>
<td>320</td>
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For PCA and TS, see Table 1. B 53 cells and sera or spleen cells were mixed and injected s.c. into BALB/c mice.

<table>
<thead>
<tr>
<th>7 days</th>
<th>10 days</th>
<th>14 days</th>
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<tbody>
<tr>
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<td>±</td>
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<tr>
<td>20</td>
<td>800</td>
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<td>53 cells and BALB/c(T) sera</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>800</td>
<td>+</td>
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<tr>
<td>200</td>
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<tr>
<td>200</td>
<td>800</td>
<td>+</td>
</tr>
<tr>
<td>B 53 cells and BALB/c(T) spleen cells</td>
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For PCA and TS, see Table 1. B 53 cells and sera or spleen cells were mixed and injected s.c. into BALB/c mice.
immunology: maekawa et al.

Table 6. Suppression of anti-DNP IgE secretion from s.c. injected B 53 cells by i.v. injected sera or spleen cells from CB20(T) mice

<table>
<thead>
<tr>
<th>1 week</th>
<th>2 weeks</th>
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<tbody>
<tr>
<td>IgE TS</td>
<td>IgE TS</td>
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<tr>
<td>BALB/c(T) sera</td>
<td>BALB/c(T) sera</td>
</tr>
<tr>
<td>200 - -</td>
<td>3200 ++</td>
</tr>
<tr>
<td>50 - -</td>
<td>3200 ++</td>
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<tr>
<td>100 - -</td>
<td>1600 ++</td>
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<tr>
<td>50 - -</td>
<td>1600 ++</td>
</tr>
<tr>
<td>200 - -</td>
<td>1600 ++</td>
</tr>
<tr>
<td>CB20(T) sera</td>
<td>CB20(T) sera</td>
</tr>
<tr>
<td>&lt;20 - -</td>
<td>3200 ++</td>
</tr>
<tr>
<td>&lt;20 - -</td>
<td>1600 ++</td>
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<tr>
<td>&lt;20 - -</td>
<td>1600 ++</td>
</tr>
<tr>
<td>&lt;20 - -</td>
<td>3200 ++</td>
</tr>
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Table 7. Effect of anti-Thy-1.2 treatment of CB20(T) spleen cells in Winn-type assays

<table>
<thead>
<tr>
<th>7 days</th>
<th>10 days</th>
<th>14 days</th>
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<tbody>
<tr>
<td>IgE TS</td>
<td>IgE TS</td>
<td>IgE TS</td>
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<tr>
<td>800 ±</td>
<td>6400 ++</td>
<td>12,800 ++</td>
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<td>6400 ++</td>
<td>12,800 ++</td>
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<td>1600 +</td>
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<td>1600 ±</td>
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<td>12,800 ++</td>
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<tr>
<td>B 53 and CB20(T) Thy-1- spleen cells</td>
<td>B 53 and CB20(T) Thy-1- spleen cells</td>
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<tr>
<td>800 +</td>
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<td>12,800 ++</td>
</tr>
<tr>
<td>1600 +</td>
<td>6400 ++</td>
<td>12,800 ++</td>
</tr>
</tbody>
</table>

Table 8. Short term in vitro culture of B 53 cells together with sera or spleen cells from CB20(T) mice

<table>
<thead>
<tr>
<th>Anti-DNP IgE,</th>
<th>% suppression</th>
</tr>
</thead>
<tbody>
<tr>
<td>µg/ml</td>
<td></td>
</tr>
<tr>
<td>B 53 and BALB/c(T) spleen cells</td>
<td>2.548</td>
</tr>
<tr>
<td>B 53 and CB20(T) spleen cells</td>
<td>1.118</td>
</tr>
<tr>
<td>B 53 and BALB/c(T) sera (I)</td>
<td>49.992</td>
</tr>
<tr>
<td>BALB/c(T) sera alone (II)</td>
<td>33.120</td>
</tr>
<tr>
<td>I</td>
<td>II</td>
</tr>
<tr>
<td>16.872</td>
<td>66.7</td>
</tr>
<tr>
<td>B 53 and CB20(T) sera</td>
<td>5.625</td>
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</table>

Anti-DNP IgE in supernatants of cultures was determined by ELISA after 3 days of culture. Results represent mean of duplicate determinations.

Discussion

In BALB/c mice, tumor size and the anti-DNP IgE secretion correlated well. However, in some CB20 mice, this correlation was not observed because, in spite of large tumors, the IgE secretion was very low. These mice were designated CB20(T). BALB/c control mice in which there was abundant circulating anti-DNP IgE were designated BALB/c(T). The striking observation was that the tumors from CB20(T) mice begin to secrete anti-DNP IgE antibody as soon as they were taken out from the "milieu" of CB20(T) mice. There was no difference with respect to anti-DNP IgE production from tumor cells taken from CB20(T) mice or from BALB/c(T) mice. This was observed in vivo, when the cells were injected s.c. or i.p. into BALB/c mice, or when they were cultured in vitro in short term cultures (Tables 2–4).

The principal finding can be summarized as follows: anti-DNP IgE secretion of hybridoma B 53, which constitutively secretes anti-DNP IgE (allotype 7a), was compared in BALB/c (heavy-chain allotype a) and CB20 (heavy-chain allotype b), and it was found that in CB20 mice the secretion of the anti-DNP IgE was inhibited. One obvious conclusion is that 7a suppression in a heavy-chain allotype b recipient.

To investigate what was the determinant cause of this phenomenon, we injected sera or spleen cells from these mice into BALB/c recipients in which we checked the production of anti-DNP IgE antibody by B 53 cells injected s.c. Care was taken to inject B 53 cells in the same number and from the same pool into control mice to avoid eventual variations, which is always possible in in vivo experiments.

When we used a Winn-type assay, the inhibition of IgE secretion by B 53 cells was strong at 1 week with sera or spleen cells from CB20(T) donors. With sera, inhibition was detected at 10 days, but not at 2 weeks. With spleen cells, it was still detected at 2 weeks (Table 5).

When sera or spleen cells from CB20(T) mice were injected i.v. and B 53 cells were injected s.c., inhibition was manifest at 1 week, but not at 2 weeks (Table 6). The inhibition in these in vivo transfers was not long lasting. However, we did not expect to find the same degree of inhibition with the transfer of 0.3 ml of serum or 2 × 10³ spleen cells from CB20(T) mice as that found in the CB20(T) mice themselves.

When the percentage of inhibitions produced by sera or spleen cells from CB20(T) mice in in vitro cultures was calculated, similar inhibitions were found (67% with sera and 56% with spleen cells).
These data indicated that spleen cells and/or some of their secreted product(s) are potential candidates for the inhibition observed.

Anti-allotype 7a antibody was not found in sera of CB20(T) mice by passive hemagglutination or by passive hemolysis. To investigate which type of cells might be involved, spleen cells from CB20(T) mice were treated with anti-Thy-1.2 and complement. No inhibition of anti-DNP IgE secretion was observed with spleen cells treated by anti-Thy-1.2 and complement (Table 7). It was therefore concluded that this inhibition was caused by T cells and/or the product(s) present in CB20(T) mice.

Allotype suppression in adult mice was described by Bosma and collaborators (12–16). They demonstrated the suppression of IgG2a allotype b (Ig-1b) from cells and tumors secreting Ig-1b molecules in different allotype congenic mice. Tumor growth was also suppressed. The reciprocal suppression—i.e., suppression of Ig-1a in allotype b mice—was much weaker. T cells from allotype a mice immunized against Ig-1b could suppress in adoptive transfer specifically the secretion of Ig-1b in vivo and the T cells after in vitro restimulation were cytotoxic in vitro against hybridoma and plasmacytoma cells secreting Ig-1b. Allotype 4 was never suppressed.

On the other hand, Curling et al. (17) reported an allotype suppression that did not involve the induction of suppressor T cells. They showed that Ig-1b plaque-forming cells were suppressed in irradiated BALB/c mice injected with (BALB/c × CB20)F1 spleen cells together with antigen and monoclonal anti-Ig-1b antibody when, and only when, the isotype of monoclonal antibody was IgG3 or IgG2a (two complement-fixing antibodies).

Our study demonstrates suppression of allotype 7a in allotype congenic heavy-chain allotype b mice. Moreover, the secretion of anti-DNP IgE antibody from a hybridoma constitutively secreting allotype 7a in nonimmunized allotype b mice was suppressed without suppression of tumor growth. The suppression of secretion was mediated by T cells and/or their product(s). In this respect, suppression of immunoglobulin secretion without suppression of tumor growth resembles the idiotypic suppression described by Abbas et al. (18). These authors observed that T cells specific for the idiotype of one of the immunoglobulins secreted by a double-producer hybridoma suppressed only the secretion of the immunoglobulin for which they were specific without suppressing secretion of the other immunoglobulin and without suppressing tumor growth.

In conclusion, a striking difference was observed between the behavior of B 53 cells in BALB/c and CB20 mice. The growth of B 53 cells in these mice was initially comparable. In BALB/c mice, tumor size and anti-DNP IgE secretion correlated very well. In some CB20 mice, this correlation was not observed, as despite large tumors, anti-DNP IgE secretion was very low.

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