Macrophage Functions in Beige (Chédiak-Higashi Syndrome) Mice

Keith H. Mahoney, Stephen S. Morse, and Page S. Morahan

ABSTRACT

Beige (C57BL/6J-bg/bg) mice are the murine counterpart of the Chédiak-Higashi syndrome, exhibiting abnormal lysosomes in phagocytes. These mice, however, responded normally to Corynebacterium parvum killed bacterial vaccine with splenomegaly and an increase in peritoneal macrophages. The C. parvum-elicited macrophages showed normal immunoglobulin G Fc- and C3b-mediated rosettes and phagocytosis. The antitumor action of the macrophages was assessed against the Lewis lung carcinoma, a tumor that is sensitive to inhibition by activated macrophages both in vitro and in vivo. The elicited macrophages from beige mice showed delays in vitro in cytostatic and cytotoxic activity against the tumor cells, as compared with C57BL/6J-+/+ control mice. The early delays in activity disappeared after 12 to 24 hr, when antitumor activity was similar to that exhibited by C. parvum-elicited macrophages of the C57BL/6J-+/+ mice. These delays in antitumor activity of beige mouse macrophages may be analogous to the delays observed in the bactericidal activity of beige mouse granulocytes. The ultimate antitumor activity, however, was comparable in beige and +/+ C. parvum-elicited macrophages. Moreover, the resistance of mice in vivo to the Lewis lung tumor was not markedly impaired. The growth of the primary tumors and the mean times to death of the tumor-bearing animals of both strains were similar.

INTRODUCTION

CHS4 is a rare genetic disorder characterized by giant granules in most granule-containing cells, especially phagocytic cells (4). Several animal homologs of the disorder have also been detected, including the bg/bg (beige) mouse, the Aleutian mink, cattle, cats, and a killer whale (29). The major clinical manifestation is an increased susceptibility to pyogenic bacterial infections (4, 11, 21), which in many cases is followed by an accelerated phase characterized by a lymphoma-like proliferative disorder. The susceptibility to bacterial infections has been ascribed to a defect in the bactericidal activity of PMN granules and defective chemotaxis in vitro (13, 36). Both macrophages and NK cells are involved in resistance to tumors. The present studies were designed to assess the antitumor functions of macrophages of the beige mouse against the Lewis lung carcinoma. Our previous studies have shown that this tumor is sensitive to the antitumor effects of activated macrophages both in vitro and in vivo (24, 25, 33). Our results indicate that activated macrophages of the beige mouse exhibit delayed antitumor activity that may be similar to the delays in bactericidal activity expressed by beige mouse granulocytes. However, the ultimate antitumor activity of macrophages in vitro and resistance of mice to tumor growth in vivo were similar in the beige and the +/+ mouse genotypes.

MATERIALS AND METHODS

Mice. Sibling mice of the C57BL/6J-bg/bg beige genotype (6) and cosogenic control C57BL/6J-+/+ mice were obtained from The Jackson Laboratory (Bar Harbor, Maine), and C57BL/6N normal and beige mice were from NIH (Bethesda, Md.; courtesy of Dr. Carl T. Hansen). Mice from each source were bred separately in cross-intercross fashion. Age- and sex-matched mice weighing an average of 20 g were used in experiments; male or female mice, or mice from different sources, yielded similar results. Only data with Jackson mice are shown.

PEC. Mice were inoculated with C. parvum vaccine (70 mg/kg; courtesy of Dr. Richard Tuttle, Burroughs Wellcome, Research Triangle, N. C.) i.p. 7 days before obtaining PEC. PEC were obtained by peritoneal lavage, washed 3 times, counted, and resuspended in complete growth medium containing 20% fetal calf serum as described previously (24). The proportion of macrophages was determined by using acridine orange to identify cells with typical macrophage lysosomes (17).

Morphological Antitumor Assay. The Lewis lung carcinoma target cells were maintained in complete growth medium; and the morphological antitumor assay, which measures combined cytostasis and cytotoxicity, was performed as described previously (24) using PEC:target cell ratios of 10:1 and 5:1. For C. parvum-activated PEC, this provided effector macrophage:target cell ratios of about 5:1 and 2.5:1.

Cytotoxicity ([3H]Thymidine Release) Assay. A 25-sq cm flask of Lewis lung cells was preincubated with 30 μCi of carrier-free [3H]thymidine (41 Ci/mmol; Amersham Searle, Arlington Heights, Ill.) for 24 hr, and then trypsinized and resuspended in complete growth medium. The labeled Lewis lung cells (5 × 10⁴) were added to microtiter wells in which macrophages (effector:target ratio, about 5:1) had been adhered for 2 hr and nonadherent cells had been removed by washing. The cultures were incubated at 37°C for 12, 24, or 48 hr, when...
a portion of the supernatant fluid of each well was removed and counted in a liquid scintillation counter.

**Cytostasis ([125I]IdUrd Incorporation) Assay.** PEC (macrophage:target ratio, 5:1) were adhered to microtiter wells for 2 hr, nonadherent cells were removed by washing, and Lewis lung cells (5 x 10⁶) were added. At various times, cells were washed as recommended by Evans and Booth (12), and labeled for 2 hr at 37° with [125I]IdUrd (0.1 µCi/well) containing 10⁻⁶ M 5-fluorodeoxyuridine (New England Nuclear, Boston, Mass.). The plates were then rinsed with warm Hanks’ balanced salt solution, fixed with absolute methanol, dried, sprayed with acrylic lacquer, dried, cut into single wells, and counted in a gamma counter. There was essentially no incorporation of IdUrd in macrophage control wells.

**C3b Rosette and Phagocytosis Assay.** SRBC were washed in Veronal buffer and sensitized with anti-SRBC IgM (Cordis Laboratories, Miami, Fla.) and C5-deficient A/He mouse serum as described previously (3). These EAC were placed in wells of single-well depression slides, coverslips with 2 hr adherent PEC were placed over the depressions, and the slides were inverted and incubated at 37° for 60 min. The slides were then examined microscopically for rosettes. To measure phagocytic activity, the extracellular SRBC were lysed by brief hypotonic shock, fixed in absolute methanol, stained with Giemsa, and evaluated microscopically.

**Lewis Lung Carcinoma Studies In Vivo.** The Lewis lung carcinoma was maintained as a s.c. implant as described previously and trypsinized after about 2 weeks to provide cells for tumor inoculation. Tumor cells (2 x 10⁶ in 0.02 ml) were inoculated into the footpad, and tumor volume was determined.

**Statistics.** Results were compared using the Student 2-tailed t test.

**Ectoenzyme Assays.** Assays for 5’-nucleotidase (9) and alkaline phosphodiesterase I (10) were performed as described previously. The specific activity is expressed as nmol of product per mg protein per min at 37°.

### RESULTS

**Effect of C. parvum In Beige Mice.** The peripheral blood PMN of the beige mouse showed the giant peroxidase-positive granules characteristic of CHS. In addition, the peritoneal macrophages of beige mice showed giant lysosomes visible by acidic orange staining, while the coisogenic +/+ (control) mice did not show these abnormalities.

Treatment of both mouse strains with C. parvum, however, elicited a normal macrophage response (Table 1). Splenomegaly of 3- to 3.5-fold occurred in both strains. Moreover, there was a comparable increase in the total number of peritoneal cells as well as in the proportion of peritoneal macrophages. Changes in the peripheral blood cells were also similar, with C. parvum producing a decrease in the proportion of lymphocytes, with a concomitant increase in the proportion of monocytes (from 12 to 14%, to 23 to 30%) and polymorphonuclear leukocytes (from 13 to 16%, to 31 to 33%) in both mouse strains. Histopathological examination of the spleens from C. parvum-treated mice also showed the expected signs of enlarged germinal centers due to WBC infiltration in both mouse strains. These observations indicated that the beige mouse mononuclear phagocyte system was able to marshal a normal macrophage response after the eliciting stimulus of C. parvum.

The response to the eliciting stimulus of Brewer’s thioglycolate broth was also similar in the 2 mouse strains, with an increase in peritoneal macrophages to 72% in beige and 63% in the +/+ mice.

**Fc and C3b Receptor-mediated Functions.** Despite their morphological abnormalities, macrophages of beige mice were generally normal in expression of receptors and in phagocytic ability. After 2 hr of adherence and removal of nonadherent cells, macrophages were tested for ability to rosette and phagocytize via Fc receptors. Over 98% of the C. parvum-activated beige or +/+ macrophages showed IgG Fc rosetting, and over 75% of these macrophages showed phagocytosis even though they were not completely spread. As has been reported previously for other mouse macrophages (3), none of the macrophages showed Fc receptors for IgM. No differences were observed between beige and +/+ cells in density of cells adhered.

One indication of macrophage activation is the ability of activated macrophages to phagocytose via the C3b receptor. While both resident and activated macrophages rosette C3b-coated SRBC, generally only activated macrophages phagocytose the particles (3). Rosetting of EAC was 98% with both beige and +/+ activated macrophages and 86 and 92% with beige and +/+ resident macrophages, respectively (Table 2). The CHS mutation also did not affect C3b-mediated phagocytosis. Less than 5% of the resident macrophages of either strain were phagocytic for EAC, while 67% of the C. parvum macrophages from both beige and +/+ mice showed phagocytosis of EAC. The number of EAC phagocytosed per 100 adherent cells was 200 for beige and 253 for +/+ C. parvum macrophages.

Several reports have indicated that microtubules in the CHS

### Table 1

Response of beige and C57BL/6J +/+ mice to C. parvum

<table>
<thead>
<tr>
<th>Mouse strain</th>
<th>Treatment with C. parvum</th>
<th>Spleen wt (mg)</th>
<th>Increase in spleen wt</th>
<th>Total cell yield/mouse (x 10⁶)</th>
<th>% of macrophages</th>
<th>Increase in peritoneal macrophages</th>
</tr>
</thead>
<tbody>
<tr>
<td>C57BL/6J-/+</td>
<td>+</td>
<td>284.4 ± 11.3 (21)</td>
<td>3.5-fold</td>
<td>3.5 ± 0.8 (12)</td>
<td>48.7 ± 4.0 (10)</td>
<td>2.7-fold</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>80.0 ± 2.1 (21)</td>
<td></td>
<td>2.5 ± 0.2 (16)</td>
<td>24.9 ± 2.5 (13)</td>
<td></td>
</tr>
<tr>
<td>C57BL/6J-bg'/bg'</td>
<td>+</td>
<td>319.1 ± 13.0 (16)</td>
<td>3.2-fold</td>
<td>3.0 ± 0.6 (10)</td>
<td>44.6 ± 4.0 (10)</td>
<td>2.2-fold</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>99.7 ± 5.6 (23)</td>
<td></td>
<td>2.6 ± 0.4 (13)</td>
<td>23.1 ± 2.4 (13)</td>
<td></td>
</tr>
</tbody>
</table>

* As determined by acridine orange.

* Average ± S.E.

* Numbers in parentheses, number of determinations.

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chicine, was used to determine if microtubules in macrophages of the beige mouse were more susceptible to the effects of colchicine on C3b-mediated phagocytosis than were +/+ macrophages. Colchicine treatment had no effect on rosetting by macrophages of either mouse strain. At 10^-6 M colchicine, both +/+ and beige mouse C. parvum-elicited macrophages showed similar reductions in the proportion of cells phagocytosing EAC (49 and 48% reduction, respectively) and the number of EAC phagocytosed per 100 cells (73 and 68% reduction, respectively). However, at 10^-5 M colchicine, C57BL/6J-+/+ macrophages showed a marked decrease in levels of 5'-nucleotidase and alkaline phosphodiesterase I ectoenzyme activities, as compared with resident macrophages (23). These changes were observed in C. parvum-elicited macrophages from both mouse strains. With regard to 5'-nucleotidase, beige mouse C. parvum macrophages showed 0.49 specific activity as compared with the 17.4 specific activity of resident macrophages, while +/+ C. parvum macrophages showed 2.6 specific activity as compared with 24.7 specific activity of the resident cells. With regard to alkaline phosphodiesterase activity, beige mouse C. parvum macrophages showed 1.6 specific activity compared with the 8.8 specific activity of resident macrophages, while +/+ C. parvum macrophages showed 1.6 specific activity compared with the 13.7 specific activity of the resident cells.

Another indication of macrophage activation is change in surface ectoenzymes (9, 10, 23). We have demonstrated previously that C. parvum-elicited peritoneal macrophages show a marked decrease in levels of 5'-nucleotidase and alkaline phosphodiesterase I ectoenzyme activities, as compared with resident macrophages (23). These changes were observed in C. parvum-elicited macrophages from both mouse strains. With regard to 5'-nucleotidase, beige mouse C. parvum macrophages showed 0.49 specific activity as compared with the 17.4 specific activity of resident macrophages, while +/+ C. parvum macrophages showed 2.6 specific activity as compared with 24.7 specific activity of the resident cells. With regard to alkaline phosphodiesterase activity, beige mouse C. parvum macrophages showed 1.6 specific activity compared with the 13.7 specific activity of resident macrophages, while +/+ C. parvum macrophages showed 1.6 specific activity compared with the 13.7 specific activity of the resident cells.

Macrophage Antitumor Activity. Defects were apparent in macrophage antitumor functions of beige mice. The cytostatic ability of C. parvum-elicited macrophages from the beige mouse was significantly delayed (Table 3). Activated macrophages from beige mice showed much less cytostatic ability at 3 and 6 hr (90 and 42% less activity) than did C. parvum macrophages from the +/+ mice. In this experiment, by 12 hr activated macrophages from both strains showed complete inhibition of DNA synthesis. In some experiments in which complete inhibition of DNA synthesis required 24 hr to become manifest, C. parvum macrophages of the beige mouse were still less cytostatic at 12 hr. Resident macrophages did not show significant cytostasis.

The kinetics of macrophage cytotoxicity also showed an initial delay. At 12 hr, the C. parvum macrophages from +/+ mice were significantly more cytotoxic than were macrophages from beige mice (Table 3). This difference decreased over the next 36 hr, although the C. parvum macrophages from the beige mouse showed slightly less activity than did the +/+ mouse macrophages. At a macrophage:target cell ratio of 25:1, a similar delay in cytotoxicity occurred; at 12 hr, beige and +/+ C. parvum macrophages showed 9 and 64% cytotoxicity, respectively (p < 0.001), again with differences decreasing over the next 36 hr.

Thus, C. parvum-elicited macrophages from beige mice showed delays in both cytostasis and cytotoxicity but eventually reached levels similar to the control. Consistent with these data, C. parvum macrophages from beige mice were as effective as were activated +/+ macrophages in the morphological antitumor assay (Fig. 1). After 72 hr of incubation, the +/+ and beige mouse C. parvum macrophages showed 75 ± 8% (S.E.) and 94 ± 8% cytotoxicity, respectively.

Growth of the Lewis Lung Carcinoma in Beige and +/+ Mice. To determine whether the early delay in macrophage antitumor activity that was observed in vitro was also apparent in vivo, growth of the Lewis lung carcinoma was monitored in beige and +/+ mice. The size of the tumor in the footpad and the mean survival time of mice were similar in beige and +/+ mice (Table 4). There was a trend toward greater growth of the primary tumor in the +/+ mice than in the beige mouse, but the mean survival time of the groups was not different.

DISCUSSION

After C. parvum or Brewer’s thioglycolate broth stimuli, the increases in numbers of total cells or macrophages in the

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**Table 2**

<table>
<thead>
<tr>
<th>Mouse strain</th>
<th>C. parvum</th>
<th>% of rosettes</th>
<th>% of phagocytosis</th>
<th>Phagocytic index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beige</td>
<td>-</td>
<td>96.5 ± 0.7</td>
<td>66.6 ± 2.9</td>
<td>200 ± 36</td>
</tr>
<tr>
<td>C57BL/6J-+/+</td>
<td>+</td>
<td>98.8 ± 0.6</td>
<td>67.1 ± 4.2</td>
<td>253 ± 69</td>
</tr>
<tr>
<td>Beige</td>
<td>-</td>
<td>88.3 ± 5.3</td>
<td>&lt;5</td>
<td>&lt;15</td>
</tr>
<tr>
<td>C57BL/6J-/+</td>
<td>-</td>
<td>92.5 ± 3.7</td>
<td>&lt;5</td>
<td>&lt;15</td>
</tr>
</tbody>
</table>

*a* A macrophage with 3 or more attached SRBC was considered positive.

*b* A macrophage with one or more phagocytosed SRBC was considered positive.

*c* The number of phagocytosed SRBC per 100 adhered cells.

*d* Mean percentage positive ± S.E.

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**Table 3**

<table>
<thead>
<tr>
<th>Mouse strain</th>
<th>C. parvum treatment</th>
<th>3 hr</th>
<th>6 hr</th>
<th>12 hr</th>
<th>24 hr</th>
<th>12 hr</th>
<th>24 hr</th>
<th>48 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beige</td>
<td>+</td>
<td>645 ± 28</td>
<td>359 ± 19</td>
<td>194 ± 67</td>
<td>65 ± 12</td>
<td>1,581 ± 360</td>
<td>15,536 ± 1,738</td>
<td>25,530 ± 254</td>
</tr>
<tr>
<td>C57BL/6J-+/+</td>
<td>+</td>
<td>284 ± 29</td>
<td>98 ± 12</td>
<td>68 ± 7</td>
<td>54 ± 6</td>
<td>4,945 ± 124</td>
<td>18,330 ± 1,310</td>
<td>29,787 ± 1,966</td>
</tr>
<tr>
<td>Beige</td>
<td>-</td>
<td>695 ± 56</td>
<td>528 ± 15</td>
<td>1,790 ± 166</td>
<td>5,275 ± 383</td>
<td>7 ± 205</td>
<td>3,140 ± 1,002</td>
<td>2,392 ± 575</td>
</tr>
<tr>
<td>C57BL/6J-/+</td>
<td>-</td>
<td>569 ± 20</td>
<td>522 ± 26</td>
<td>1,678 ± 192</td>
<td>4,864 ± 653</td>
<td>179 ± 446</td>
<td>3,192 ± 231</td>
<td>1,125 ± 433</td>
</tr>
<tr>
<td>Cell control</td>
<td></td>
<td>866 ± 24</td>
<td>714 ± 51</td>
<td>2,176 ± 87</td>
<td>7,037 ± 238</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*a* Corrected for spontaneous release from tumor cell controls. Total releasable cpm were 76,132.

*b* p < 0.001 compared with C57BL/6J-+/+ control.

*c* Mean ± S.E.

*d* p < 0.05 compared with C57BL/6J-+/+ control.
peritoneal exudate were similar in both beige and +/+ mice. Additional data showing activation of the mononuclear phagocyte system come from the comparable blood cell changes and splenomegaly observed in C. parvum-treated beige of +/+ mice. Apparently, the beige mouse can mobilize a normal macrophage inflammatory response, similar to the normal neutrophil response previously reported with the beige mouse (18, 22, 35).

Receptors and phagocytic activity of the macrophage population also appear normal. Macrophages of both the beige and +/+ mice showed rosetting and phagocytosis via the IgG Fc receptor. Consistent with this, IgG Fc receptor-mediated antibody-dependent cell-mediated cytotoxicity against chicken erythrocytes, presumably mediated by macrophages, has recently been reported to be normal in the beige mouse (31) and in CHS patients (15). By C3b receptor-mediated phagocytosis, generally considered an indicator of activation (3), beige mice also demonstrated normal proportions of activated macrophages in the C. parvum-elicited populations. However, the activated macrophages of the beige mouse appeared to be somewhat more susceptible than +/+ cells to inhibition of C3b-mediated phagocytosis by colchicine, a microtubule-disrupting agent. These data are consistent with reports of beige mouse microtubule defects with capping and chemotaxis (28), although recent morphological studies of resting cells have shown relatively normal microtubules or actin structures with beige mouse fibroblasts (13).

The kinetics of macrophage-mediated antitumor activity of beige mouse macrophages was abnormal. In both cytotoxicity and cytostasis of tumor cells, the beige mouse macrophages showed a considerable delay (about 12 hr) in inhibiting DNA synthesis and in lysing the target cells. Over the long term in these assays and in the morphological antitumor assay, the final activity was at normal levels, suggesting that a delay in induction or expression of an early step in effector function may be involved. The apparent acceleration of activity (implied by normal levels of activity after the initial delay) is interesting to consider. Our current hypothesis is that beige mouse macrophages recognize and bind the target cells normally and therefore initiate the macrophage effector cell function but are delayed in expression of that function. Thus, for example, if antitumor activity involved release of mediators, as the macrophage responded the mediators might be synthesized to the proper levels but not released initially. The mediators would therefore accumulate within the macrophage and finally be released at higher (and effective) levels, thereby causing an apparently accelerated effect. This would be equally true if lysosomal function were involved; the lysosomes or lysosomal components might be transferred in greater quantity when effector function is expressed after the delay.

Using a system involving bone marrow promonocytes, activated in vitro by concanavalin A lymphokine, and the P815 target cell, Roder and Duwe (31) recently reported normal activity of beige mouse monocytes; no kinetic studies were included. Our preliminary results with beige mouse peritoneal macrophages activated in vitro by BCG/PPD lymphokine have also indicated normal antitumor activity in the long-term morphological assay.¹

Neutrophils from the beige mouse and other CHS homologs exhibit a delay in bactericidal function (32) analogous to the delay that we have observed in macrophage antitumor activity. Ultrastructural studies of the PMN suggest that the bactericidal abnormality may be due to delayed fusion of the bacteria-containing phagosome with lysosomes (27, 31). It has been suggested that lysosomal mechanisms may be involved in macrophage tumoricidal activity (7, 16). Whether abnormal lysosomal fusion or transfer is responsible for the delay in antitumor activity, and whether lysosomes are involved at all cannot yet be determined. Abnormalities in nucleotide metabolism have also been described in CHS (2, 5) and may affect the ability of the beige mouse macrophage to induce the dysfunctions in target cell nucleotide metabolism that have been associated with macrophage antitumor activity (19, 34).

Finally, some enzymes in PMN, such as neutral protease and peroxidase, are reduced or abnormally secreted in CHS (18, 35, 36). Some evidence suggests that such enzymes may be involved in macrophage tumor cell cytotoxicity (1, 8). Unfortunately, it is not known whether beige mouse macrophages exhibit enzyme defects similar to those of the PMN. In fibroblasts from Aleutian mink, secretion of lysosomal enzymes such as β-hexosaminidase was normal (28), and beige mouse macrophages appeared to show normal patterns of ectoenzyme activities.

The recent reports of abnormal NK cell activity in the beige mouse (30, 31) and CHS patients (15) are of considerable interest. The delay in antitumor activity observed in the present experiments is probably due to a macrophage defect rather than to defective NK cell activity. Nonadherent cells were removed in the experiments, and this should have eliminated most of the NK cells. Assays for NK activity generally require effector:target cell ratios of 50:1 to 100:1, while the adherent cells (which were >98% macrophages by acridine orange staining) showed antitumor activity at ratios as low as 2:5:1. Moreover, NK activity usually reaches a plateau by 4 to 6 hr,

Fig. 1. Morphological tumoricidal activity of PEC from beige and +/+ mice for Lewis lung carcinoma cells. PEC were adhered for 2 hr in the wells of an 8-chamber Lab Tek slide (Miles Laboratories, Naperville, Ill.). Nonadherent cells were then rinsed off, target cells (4 x 10⁶/well) were added, and the slides were incubated for 68 hr at 37°. After incubation, slides were fixed with methanol, stained with Giemsa stain, and scored for cytotoxicity. (Cytotoxicity values expressed in text are averages of 4 wells, 2 at PEC:target cell ratio of 10:1 and 2 at 5:1.) Left, Lewis lung carcinoma cell (LL):macrophage (MΦ) ratio. Macrophage source shown under respective slide. C57, +/+ controls. Both C. parvum-elicited and resident (saline, from mice receiving only pyrogen-free 0.9% NaCl solution on Day − 7 preceding PEC collection) control slides are shown.

¹ Unpublished observations.
while macrophage-mediated antitumor activity requires 24 to 48 hr (19). Roder (30) has recently shown that NK cells are present in the beige mouse have normal capacity to bind to target cells, but appear to lack the cytolytic mechanism. It is intriguing to speculate that abnormal lysosomes in NK cells (presumably of pre-T-cell origin) may be involved in the antitumor cytolytic action.

Both NK cells and macrophages are effector cells against tumors. Whether defects in macrophages or NK cells play a role in the increased susceptibility to the lymphoma-like condition that frequently develops in CHS patients is not known. Beige mice do not show a greater incidence of spontaneous neoplasms than do the +/+ mice, unless the beige gene is in association with the satin gene (21). Karre et al. (20) have recently reported that beige mice are more susceptible to leukemia progression after inoculation of syngeneic EL-4 or radiation leukemia virus-induced P-52 leukemia cells, showing an increased tumor incidence and decreased mean survival time. Metastatic growth of certain lines of B-16 melanoma cells may also be increased in beige mice. In our experiments with the Lewis lung carcinoma, however, we found no evidence for increased susceptibility of the beige mouse. Whether these differences are due to differences in tumor sensitivities to macrophages or NK cells, to routes of tumor cell inoculation, or to differences between tissue culture and animal-derived tumors will require further investigation. Our present data on normal exudation and receptor functions and delayed cidal activities support the close association of mononuclear phagocytes and granulocytes in cell lineage and the separation of NK cells from this lineage. The beige mouse provides an excellent animal model in which to determine the relative role of NK cells and macrophages in antitumor activities and to define the early stages in macrophage "effector functions."

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REFERENCES


N. Hanna, personal communication.

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Table 4
Growth of Lewis lung carcinoma in beige and +/+ mice

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Mice</th>
<th>No.</th>
<th>Tumor volume (cu mm) at following times after tumor</th>
<th>Survival time (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 days</td>
<td>15 days</td>
</tr>
<tr>
<td>A</td>
<td>Beige</td>
<td>10</td>
<td>14.2 ± 23 (NS)</td>
<td>24.9 ± 6.6</td>
</tr>
<tr>
<td></td>
<td>C57BL/6J/+</td>
<td>13</td>
<td>10.6 ± 2.3 (NS)</td>
<td>43.5 ± 17.8</td>
</tr>
<tr>
<td>B</td>
<td>Beige</td>
<td>15</td>
<td>75.4 ± 14.0</td>
<td>279.3 ± 30.7</td>
</tr>
<tr>
<td></td>
<td>C57BL/6J/+</td>
<td>14</td>
<td>77.8 ± 13.3</td>
<td>418.0 ± 66.3</td>
</tr>
</tbody>
</table>

a Mean ± S.E.

b NS, not significant.

c p values, mean tumor volume in beige mice versus mean tumor volume in C57BL/6J mice; p < 0.05 is considered significant, p = 0.1 is marginal, and p > 0.1 is nonsignificant.
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