Effects of Social Housing Condition on Chemotherapeutic Efficacy in a Shionogi Carcinoma (SC115) Mouse Tumor Model: Influences of Temporal Factors, Tumor Size, and Tumor Growth Rate

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Objective: The objective of this study was to investigate 1) whether social housing condition, tumor size, and tumor growth rate alter responses to chemotherapy and 2) whether the timing of tumor cell injection or chemotherapy initiation (relative to housing condition formation) influences tumor growth rate or the efficacy of chemotherapy.

Methods: Mice were reared individually (I) or in groups (G). In experiment 1, mice were rehoused (IG or GI) or left in group housing (GG) immediately after tumor cell injection. In experiment 2, housing conditions (II, IG, GG, or GI) were formed when tumors weighed 1 g. Chemotherapy (adriamycin 4 mg/kg and cyclophosphamide 61.5 mg/kg IP) and exposure to acute novelty stress (15 min/d, 5 d/wk) were initiated 1 day after housing condition formation.

Results: If chemotherapy was initiated when the tumor burden was undetectable (experiment 1), housing condition did not alter tumor response to chemotherapy, although IG mice lost the most weight and overall had the lowest probability of survival. If chemotherapy was initiated when tumors weighed 1 g (experiment 2), both tumor and host responses to chemotherapy were poorest for IG mice. Timing of tumor cell injection relative to housing condition formation also differentially influenced the rate of tumor growth in mice treated with the drug vehicle; in experiment 1, tumor growth rate was faster in GI and GG mice than in IG mice, whereas in experiment 2, the rate of tumor growth was faster in II mice than in GG and IG mice. Conclusions: Altering the temporal relationships among social housing condition formation, tumor cell injection, and chemotherapy initiation differentially influences the rate of tumor growth and the efficacy of chemotherapy. Effects of housing condition are independent of tumor growth rate at chemotherapy initiation and, in terms of host responses, independent of tumor burden.

Key words: Shionogi carcinoma, psychosocial stress, chemotherapy, tumor and host responses, survival probability.

INTRODUCTION

In humans, stressful life events, the frequency of such events, and the ability to cope with stress have been shown to play a role not only in increased cancer risk and metastasis (1–7) but also in response to chemotherapy, including survival probability (6, 8), time to cancer reoccurrence after chemotherapy (5), and the variable incidences of the toxic effects of chemotherapy (9–13). However, a number of studies have reported little or no support for the association among stressful life events, coping, and cancer progression or chemotherapeutic efficacy (14–18). The complex relationships between psychosocial stressors and the progression of cancer or chemotherapeutic efficacy are difficult to investigate in humans because a number of issues may affect interpretation of the data. For example, the stage of treatment in which the patients are examined (3, 19, 20) as well as the form of psychosocial assessments used (3, 21, 22) may alter the association among psychosocial stressors, coping resources or strategies, and cancer treatment. In addition, timing of a stressful event relative to the initiation of treatment as well as tumor and host factors may affect interpretation of the data (9, 23–27).

Animal models allow investigation of the relationship among stressors, coping mechanisms, tumor growth, and responses to chemotherapy under more controlled conditions. However, even in animal models the data are complex. Factors such as the type of tumor; timing, duration, and severity of the stressor; the species, strain, or gender of the animal; and the ability to cope with the stressor have been shown to influence stress effects on tumor growth or chemotherapeutic efficacy (28–34). In animals, psychosocial stressors such as housing condition and psychological stressors such as forced restraint and rotation have been shown to affect tumor growth rates or metastasis of both transplantable and chemically induced tumors.
(35–40) as well as both tumor and host responses to chemotherapy (41–43).

We have developed an animal tumor model using the transplantable, androgen-responsive Shionogi mouse mammary carcinoma (SC115; Ref. 40). Our data demonstrate that a change in social housing condition as well as the direction of change (40, 44) can significantly influence tumor growth rate. Mice are reared either individually (I) or in groups (G) until 2 to 4 months of age, at which time tumor cells are injected and experimental housing conditions (IG or GI) are formed. Under these conditions tumor growth rate is reduced in IG mice and increased in GI mice compared with mice remaining in their original rearing conditions (II or GG; Refs. 40 and 44). Furthermore, subjecting mice to a daily acute novelty stress increases the difference in tumor growth rate between IG and GI mice (40).

In this same model we have also demonstrated that social housing condition can significantly influence both tumor response to chemotherapy (assessed by tumor growth delay) and the interaction between tumor and host responses to chemotherapy (assessed by overall survival probability). If chemotherapy is initiated when the mean tumor weight of mice in each housing condition reaches 1 g (approximately 14 days after injection of tumor cells) the differential responses to chemotherapy are observed in GI and IG mice (41).

Tumor Propagation and Experimental Animals

The androgen-responsive Shionogi mouse mammary carcinoma subline SC115 class A (50) was maintained by serial transplantation in male mice of the DD/S strain. Tumors weighing approximately 2 g were dissociated to single cells according to our standard protocol (40), and mice were injected subcutaneously in the interscapular region with $2 \times 10^6$ cells suspended in 0.1 ml of DMEM (Stem Cell Technologies Ltd., Vancouver, British Columbia, Canada).

Male DD/S mice between the ages of 2 and 4 months were the experimental subjects in experiment 1 ($N = 113$) and experiment 2 ($N = 176$).

Experiment 1: Effects of Social Housing Conditions and Tumor Size on Tumor and Host Responses to Chemotherapy

Mice were reared either individually or in groups. Immediately after injection of tumor cells (subcutaneous injection of $2 \times 10^6$ cells suspended in 0.1 ml of DMEM) the tumor cell alone (subcutaneous injection of 0.1 ml of DMEM), mice were either rehoused (from individual to group housing [IG] or from group to individual housing [GI]) or remained in their group housing condition (GG) according to our published protocol (40). Chemotherapy or drug vehicle was initiated 1 day later, when tumor burden was undetectable (similar to the adjuvant situation in humans). Mice within each housing condition were randomly assigned into tumor cell injection groups receiving either chemotherapy (TC: $N = 20$ IG, 14 GI, and 9 GG) or drug vehicle (TV: $N = 10$ IG, 8 GI, and 6 GG) or into tumor cell vehicle (no tumor cells) injection groups receiving chemotherapy (NTC: $N = 20$ IG, 15 GI, and GG; Figure 1, A). The II housing condition was not used in this experiment because under the conditions of this study, tumor growth rate and hormone levels in II mice are similar to those in GG mice (40, 51). Beginning the day after rehousing and tumor cell or vehicle injection, all animals were exposed to an acute daily stressor; the stressor consisted of exposure to one of five different novel environments for 15 min/d, 5 d/wk, a treatment that we have shown enhances differences in tumor growth rate between experimental housing conditions (40). The five environments were 1) a clear plastic container, 9 cm in diameter × 7 cm in height; 2) a polystyrene container, 12 × 10 × 4 cm; 3) a cardboard box divided into compartments, 7 × 7 × 14 cm; 4) a polystyrene box, 6 cm in diameter × 10 cm in height; and 5) a standard rodent cage, 18 × 29 × 13 cm, empty of bedding, food, and water.

Experiment 2: Effects of Social Housing Conditions and Tumor Growth Rate on Tumor and Host Responses to Chemotherapy

As in experiment 1, mice were reared either individually or in groups (Figure 1, B). To examine the influence of tumor growth rate on chemotherapeutic efficacy, experimental variables were manipulated such that chemotherapy was initiated when tumors weighed approximately 1 g (as in our initial study; Ref. 41) but were growing at similar rates. To accomplish this, tumor cells ($2 \times 10^6$ cells suspended in 0.1 ml of DMEM) were injected subcutaneously, but mice remained in their original rearing condition (I or G) until mean tumor weights reached 0.8 ± 0.2 g, which occurred approximately 14 days after tumor cell injection. At that time mice were rehoused (IG or GI) or remained in their original rearing condition (II or GG), and chemotherapy or drug vehicle was initiated 1 day later (Figure 1, C).
1, B). Tumor cell–injected mice in each of the experimental housing conditions (II, IG, GG, and GI) were randomly assigned to receive either chemotherapy (TC: N = 9 II, 23 IG, 13 GG, and 16 GI) or drug vehicle alone (TV: N = 12 II, 19 IG, 12 GG, and 14 GI). Mice within each housing condition that were injected with tumor cell vehicle (but no tumor cells) also received chemotherapy to assess the possible toxic side effects of chemotherapy independent of the presence of a tumor (NTC: N = 12 II, 20 IG, 15 GG, and 11 GI; Figure 1, B). As in experiment 1, mice were exposed daily to an acute novelty stress beginning the day after rehousing. Note that in both experiments 1 and 2, the stressor was initiated concurrently with chemotherapy. However, in experiment 1, this occurred 1 day after tumor cell injection, whereas in experiment 2, this occurred 14 days after tumor cell injection.

Body and Tumor Weight Measurements

In both experiments body weights were measured and mice were palpated every second day. Once the tumors were measurable (approximately 8–10 days after tumor cell injection), caliper measurements were taken every second day and tumor weights were calculated according to the following formula (tumor weight measured in grams; length and width measured in centimeters) (52):

\[
\text{Tumor Weight} = \left(\frac{\text{Length} \times \text{Width}^2}{2}\right)
\]

Chemotherapy

Chemotherapy consisted of a combination of adriamycin (4.0 mg/kg; Adria Laboratories of Canada Ltd., Mississauga, Ontario, Canada) and cyclophosphamide (61.5 mg/kg; Procytox, Horner, Montreal, Quebec, Canada) in NaCl solution (drug vehicle). Drugs were administered intraperitoneally every 7 days for a total of three injection rounds. The doses of drugs selected for this study have been shown to be optimal for SC115 tumor regression with minimal toxic side effects (53). Mice were monitored every second day for drug toxicity (as assessed by morbidity, ie, body weight loss) and daily for mortality (survival probability).

Statistical Analyses

Tumor response to chemotherapy was analyzed using tumor growth delay, defined as the mean time for tumors in chemotherapy-

Fig. 1. Experimental design of experiments 1 (A) and 2 (B).
treated mice to reach a specific weight minus the mean time for tumors in drug vehicle–treated mice to reach the same weight. Host response to chemotherapy was analyzed by 1) the percentage of body weight loss over the course of chemotherapy and 2) overall survival probability. Percentage of body weight loss was calculated as follows: Body Weight Loss = [(C2 or C3 − C1) − C1] × 100, where C1 = body weight on day of chemotherapy initiation; C2 = body weight on day of second round of chemotherapy; and C3 = body weight on day of third round of chemotherapy. Negative values indicate weight loss between chemotherapy rounds. Only the data from mice that were still alive 70 days after the first round of chemotherapy were considered censored. Tumor growth rate in drug vehicle–treated mice to reach the same weight minus the mean time for tumor formation immediately after SC115 tumor cell injection formed immediately after SC115 tumor cell injection (41), analysis of tumor growth rate in mice treated with the drug vehicle in the present study revealed a significant group-by-days interaction \( F(8.72) = 24.209, p < .001; \) Figure 2, A). Tukey’s post hoc analysis indicated that on days 15 and 17 after tumor cell injection and formation of experimental housing conditions, tumor growth rates were significantly faster in both GI and GG mice than in IG mice \( (\text{GI} > \text{GG} > \text{IG}, p \text{ values} < .001) \). Consequently, survival probability was also greater in IG mice than in both GI and GG mice \( (\text{IG} > \text{GI} = \text{GG}, \chi^2 = 12.42 \text{ and } 20.18, \text{ respectively, } p \text{ values} < .001; \) Figure 3, A). Analysis of the percentage of body weight loss similarly revealed a significant group-by-days interaction \( F(2.14) = 3.629, p = .05; \) Table 1, probably reflecting a somewhat greater initial weight loss in IG and GG mice than in GI mice. However, post hoc analyses failed to reach significance.

**Experiment 2.** Tumor growth rates in drug vehicle–treated mice were similar for individually and group-housed mice from 0 days until approximately 14 days after tumor cell injection, when mean tumor weights of mice in both conditions reached approximately 1 g, at which time experimental housing conditions (II, IG, and GI) were further analyzed by Tukey’s post hoc tests.

### RESULTS

**Tumor Growth Rates, Body Weight Loss, and Survival Probability in TV Mice**

**Experiment 1.** Consistent with the data from our initial study, in which social housing conditions were also formed immediately after SC115 tumor cell injection (41), analysis of tumor growth rate in mice treated with the drug vehicle in the present study revealed a significant group-by-days interaction \( F(8.72) = 24.209, p < .001; \) Figure 2, A). Tukey’s post hoc analysis indicated that on days 15 and 17 after tumor cell injection and formation of experimental housing conditions, tumor growth rates were significantly faster in both GI and GG mice than in IG mice \( (\text{GI} > \text{GG} > \text{IG}, p \text{ values} < .001) \). Consequently, survival probability was also greater in IG mice than in both GI and GG mice \( (\text{IG} > \text{GI} = \text{GG}, \chi^2 = 12.42 \text{ and } 20.18, \text{ respectively, } p \text{ values} < .001; \) Figure 3, A). Analysis of the percentage of body weight loss similarly revealed a significant group-by-days interaction \( F(2.14) = 3.629, p = .05; \) Table 1, probably reflecting a somewhat greater initial weight loss in IG and GG mice than in GI mice. However, post hoc analyses failed to reach significance.

**Experiment 2.** Tumor growth rates in drug vehicle–treated mice were similar for individually and group-housed mice from 0 days until approximately 14 days after tumor cell injection, when mean tumor weights of mice in both conditions reached approximately 1 g, at which time experimental housing conditions (II, IG, and GI) were further analyzed by Tukey’s post hoc tests.

### TABLE 1. Percentage of Body Weight Loss (mean ± SE) in Mice Over the Course of Chemotherapy or Drug Vehicle Treatment in Experiments 1 and 2

<table>
<thead>
<tr>
<th>Housing Condition</th>
<th>Body Weight Loss (%)</th>
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<tbody>
<tr>
<td></td>
<td>TC</td>
</tr>
<tr>
<td><strong>Experiment 1</strong></td>
<td></td>
</tr>
<tr>
<td>IG</td>
<td>−19.33 ± 1.36&lt;sup&gt;b&lt;/sup&gt; (15)</td>
</tr>
<tr>
<td>GG</td>
<td>−11.96 ± 1.63&lt;sup&gt;d&lt;/sup&gt; (9)</td>
</tr>
<tr>
<td>GI</td>
<td>−12.96 ± 1.22 (12)</td>
</tr>
<tr>
<td><strong>Experiment 2</strong></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>−19.72 ± 3.18&lt;sup&gt;e&lt;/sup&gt; (9)</td>
</tr>
<tr>
<td>IG</td>
<td>−16.78 ± 1.55&lt;sup&gt;i&lt;/sup&gt; (23)</td>
</tr>
<tr>
<td>GG</td>
<td>−13.68 ± 2.83 (13)</td>
</tr>
<tr>
<td>GI</td>
<td>−12.29 ± 1.96 (16)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Percentage of body weight (BW) loss from first to third chemotherapy rounds = [(C3 − C1) − C1] × 100, where C3 = body weight (gross body weight − tumor weight) on day of third round of chemotherapy and C1 = body weight on day of initiation of chemotherapy. Negative values indicate weight loss between chemotherapy rounds. Numbers in parentheses indicate number of mice per group.

<sup>b</sup> IG > GI = GG; p values < .01.

<sup>c</sup> IG > GI > GG; p values < .01.

<sup>d</sup> IG > GI; p = .07.

<sup>e</sup> IG > GI; p = .05.

<sup>f</sup> IG > GI = GG; p values < .01.

<sup>g</sup> II > GI = GG; p values < .05.

<sup>h</sup> II = IG > GG; p values < .05.
GG and GI were formed (Figure 1, B). Analysis of tumor growth rates after the formation of experimental housing conditions revealed a significant group-by-days interaction (F(6,92) = 2.395, p < .05; Figure 2, B). Post hoc analysis indicated that when the temporal relationship between tumor cell injection and formation of experimental housing conditions is altered, compared with that of our original experimental paradigm, tumor growth rates among the different housing conditions are also altered. Specifically, 5 days after formation of experimental housing conditions (approximately 19 days after tumor cell injection), tumor growth rates were significantly faster in II mice than in both IG and GG mice (II > IG = GG, p values < .01; Figure 2, B). GI mice had intermediate tumor growth rates that did not differ significantly from those of mice in the other experimental housing conditions. In addition, II mice had a marginally reduced survival probability compared with IG mice (II < IG, χ² = 3.243, p = .072; Figure 4, A). For body weight loss, the significant main effect of group (F(3,48) = 4.207, p = .01) indicated that both II and IG mice lost significantly more weight than GG mice (II = IG > GG, p values < .05; Table 1), suggesting that body weight loss did not relate to tumor growth rate. Weight loss for GI mice did not differ significantly from that of mice in any other housing condition (Table 1).

Tumor Response to Chemotherapy, Body Weight Loss, and Survival Probability in TC Mice

Experiment 1. Tumor response to chemotherapy was similar among mice in all experimental housing conditions. That is, no tumors were palpable in any mouse for up to 70 days after chemotherapy initiation, suggesting that chemotherapy initiated 1 day after tumor cell injection is equally effective in containing tumor growth in all mice regardless of housing condition. Similarly, no significant differences in overall survival probability were observed among mice in the different experimental housing conditions (Figure 3, A). However, host response to chemotherapy, assessed by body weight loss over the course of chemotherapy, revealed significant effects of both group (F(2,32) = 10.760, p < .001) and days (F(2,32) = 312.936, p < .001). Both GI and GG mice lost significantly less weight than IG mice (GI = GG < IG, p values < .01; Table 1).

As expected, survival probability for chemotherapy-treated mice was significantly greater than that for drug vehicle–treated mice (TC > TV, χ² = 38.371, p < .001; Figure 3, A), and mice treated with chemotherapy lost significantly more weight than those receiving drug vehicle (TC > TV, p < .001; Table 1). In addition, for all mice treated with chemotherapy, tumor cell–injected mice lost significantly more weight than tumor cell vehicle–injected mice regardless of experimental housing condition (TC > NTC, p values < .05; Table 1). Interestingly, however, no significant differences in survival probabilities were observed between tumor cell–injected and tumor cell vehicle–injected mice receiving chemotherapy (Figure 3, A and B).

Experiment 2. Social housing condition significantly affected both tumor and host responses to chemotherapy. Analysis of tumor responses, measured by tumor growth delay, revealed a significant effect of group (F(3,159) = 3.624, p = .01); GI mice had a
significantly longer delay in tumor growth than II mice (GI > II, \( p < .01 \)) and a marginally longer delay than IG mice (\( p = .098 \); Table 2). Similarly, analysis of host response to chemotherapy, measured by the percentage of body weight loss over the course of chemotherapy treatment, revealed a significant main effect of group (\( F(3,35) = 4.170, p = .01 \)); GI mice lost significantly less weight than IG mice (GI < IG, \( p < .05 \); Table 1) and marginally less weight than II mice (\( p = .07 \); Table 1). However, social housing condition did not influence the overall survival probabilities among tumor cell–injected, chemotherapy-treated mice. For GG mice, both tumor growth delay and percentage of body weight change did not differ significantly from those of mice within the other social housing conditions.

Once again, as expected, overall survival probability was greater for chemotherapy-treated mice than for drug vehicle–treated mice (TC > TV, \( \chi^2 = 57.778, p < .001 \); Figure 4, A), and mice treated with chemotherapy lost significantly more weight than those receiving drug vehicle (TC > TV, \( p < .001 \); Table 1). In addition, survival probability was significantly greater for tumor cell–injected, chemotherapy-treated mice (NTC > TC, \( \chi^2 = 32.561, p < .001 \); Figure 4, A and B). However, no significant differences in body weight loss were observed between
tumor cell–injected and tumor cell vehicle–injected mice receiving chemotherapy.

Effects of Social Housing Condition on Body Weight Loss and Survival Probability in NTC Mice

Experiment 1. For tumor cell vehicle–injected, chemotherapy-treated mice, survival probability was significantly less for IG than for GI mice (IG < GI, $\chi^2 = 4.588$, $p < .05$; Figure 3, B); survival probability for GG mice did not differ significantly from that of IG and GI mice. Analysis of body weight loss over the course of chemotherapy revealed a significant group-by-days interaction ($F(2,43) = 4.332$, $p < .05$). Similar to the results in their tumor cell–injected counterparts, tumor cell vehicle–injected, chemotherapy-treated IG mice lost significantly more weight over the course of chemotherapy than GI mice, which in turn lost more weight than GG mice (IG > GI > GG, $p$ values = 0.01; Table 1).

Experiment 2. For tumor cell vehicle–injected, chemotherapy-treated mice, survival probability for IG mice was significantly less than for both II and GG mice (IG < II, $\chi^2 = 7.626$, $p < .01$ and IG < GG, $\chi^2 = 5.752$, $p < .05$) and marginally less than for GI mice ($\chi^2 = 2.812$, $p = .094$; Figure 4, B). Similarly, analysis of body weight loss over the course of chemotherapy revealed a significant group-by-days interaction ($F(3,52) = 3.918$, $p = .01$); IG mice lost significantly more weight than mice in all other housing conditions (IG > II = GG = GI, $p$ values < .01; Table 1). It is possible that the decreased survival probability in tumor cell vehicle–injected, chemotherapy-treated IG mice was due to a poor host response to chemotherapy (possibly reflecting greater toxic side effects of chemotherapy), at least as assessed by body weight loss.

### DISCUSSION

Overall our studies demonstrate that both tumor and host responses to chemotherapy are significantly influenced by experimental housing conditions and that these effects are independent of tumor growth rate at the time of chemotherapy initiation and, at least in terms of host response to chemotherapy, are independent of tumor burden. Importantly, these data also demonstrate that the temporal relationship among formation of housing conditions, tumor cell injection, and chemotherapy initiation plays a critical role in determining the direction and magnitude of the effects of social housing conditions on both tumor growth rate and chemotherapeutic efficacy.

If chemotherapy was initiated 1 day after tumor cell injection and formation of social housing conditions (experiment 1), a time when tumor burden is undetectable (similar to the adjuvant situation in humans), social housing condition did not influence tumor response to chemotherapy. That is, no tumor masses were palpable for up to 70 days after chemotherapy initiation, suggesting that chemotherapy was equally effective in containing tumor growth in mice in all housing conditions. Moreover, there were no significant differences in overall survival probability among mice in the different housing conditions. However, host responses to chemotherapy were better in GI and GG mice than in IG mice; GI and GG mice lost less weight than IG mice. If chemotherapy was initiated 1 day after formation of social housing conditions but approximately 14 days after tumor cell injection (experiment 2), a time when tumors weigh approximately 1 g and are growing at similar rates, GI mice showed longer tumor growth delay and lost less weight than IG and II mice. However, as in experiment 1, overall

### TABLE 2. Tumor Growth Delay (mean ± SE) in Chemotherapy-Treated Mice in Experiment 2

<table>
<thead>
<tr>
<th>Housing Condition</th>
<th>Tumor Weight (g)</th>
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<tbody>
<tr>
<td></td>
<td>1.5</td>
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<tr>
<td>II</td>
<td>0.75 ± 0.39</td>
</tr>
<tr>
<td>(8)</td>
<td>(8)</td>
</tr>
<tr>
<td>IG</td>
<td>4.00 ± 1.13</td>
</tr>
<tr>
<td>(16)</td>
<td>(13)</td>
</tr>
<tr>
<td>GG</td>
<td>0.50 ± 0.57</td>
</tr>
<tr>
<td>(10)</td>
<td>(9)</td>
</tr>
<tr>
<td>GI$^{bc}$</td>
<td>6.19 ± 3.22</td>
</tr>
<tr>
<td>(16)</td>
<td>(16)</td>
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</tbody>
</table>

$^a$ Tumor growth delay is defined as the mean time, in days, for tumors to reach a specific weight in chemotherapy-treated mice minus the mean time for tumors in drug vehicle–treated mice to reach the same weight. Numbers in parentheses indicate the number of mice per group.

$^b$ GI > II; $p = .01$.

$^c$ GI > IG; $p = .098$.

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survival probability was not significantly different among mice in the different housing conditions.

The present data are in contrast to those of our previous study (41), in which experimental housing conditions were formed immediately after tumor cell injection and chemotherapy was initiated 14 to 18 days later, at a time when tumors weighed 1 g but were growing at different rates. Under those conditions, IG mice had a better tumor response to chemotherapy (longer tumor growth delay), a better host response to chemotherapy (less weight loss, unpublished results), and a greater overall survival probability than GI mice.

The finding that social housing condition did not influence tumor response to chemotherapy if chemotherapy is initiated when tumor burden is undetectable was not entirely surprising. It is recognized that when tumor burden is small, there is a greater chance for drugs to eradicate tumor cells, possibly because of the presence of fewer cells or proximity of the blood supply to the tumor cells and thus greater exposure of the cells to cytotoxic drugs. Furthermore, it is less likely that alterations in host physiological profiles (eg, endocrine or immune activity) could influence the development of tumor cell populations resistant to chemotherapy (56–58). Nevertheless, taken together our data demonstrate that altering the timing of chemotherapy initiation relative to tumor cell injection and formation of experimental housing conditions significantly influences both tumor and host responses to chemotherapy.

Altering the temporal relationship between tumor cell injection and formation of experimental housing conditions also differentially affects SC115 tumor growth rate, assessed in drug vehicle–treated mice. Data from both our initial study (41) and experiment 1 of the present study demonstrate that if social housing conditions are formed immediately after SC115 tumor cell injection, GI mice have significantly faster tumor growth rates than IG mice and GG mice have intermediate tumor growth rates. In contrast, if mice remain in their original individual or group housing conditions after tumor cell injection and experimental housing conditions are formed approximately 14 days later, as in experiment 2 of the present study, II mice have significantly faster tumor growth rates than both IG and GG mice, whereas GI mice have intermediate tumor growth rates. Interestingly, it seems that the differential tumor growth rates observed in drug vehicle–treated mice from the different experimental housing conditions cannot be used to predict tumor response to chemotherapy. In our previous study (41), mice that had the slowest tumor growth rates had the best tumor response to chemotherapy (longest tumor growth delay), whereas in the present study mice that had intermediate tumor growth rates (GI) had the longest tumor growth delay.

The differential effects of social housing condition on both tumor growth rates and chemotherapeutic ef-
Housing Condition, SC115, and Chemotherapy

Psychosocial stressor–induced or chemother-
apy-induced changes in endocrine function may be involved. We have shown previously that for male mice in our standard laboratory housing condition (group housed and not subjected to daily novelty stressors), SC115 tumor response to adriamycin and cyclophosphamide can be modulated by altering the level of exogenous testosterone administered after castration (53). It has also been shown that the anti-tumor effects of cyclophosphamide on ascitic Ehrlich tumors in mice can be suppressed by increased activity of endogenous or exogenous corticosterone through acceleration of drug metabolism (67). Furthermore, we have demonstrated that over the first 7 days after tumor cell injection and formation of experimental housing conditions, basal testosterone levels are higher in GI than in IG mice, whereas basal corticosterone levels are higher in IG mice than in mice in all other housing conditions (51). Therefore, in the present study, altered hormone profiles among mice in the different housing conditions at the time of chemotherapy initiation may have differentially affected tumor responses to chemotherapy.

Differential tumor response to chemotherapy may also be mediated through changes in immune function. Such changes may occur either directly through chemotherapy-induced changes in immune function or indirectly through psychosocial stressor–induced changes in hormonal activity that in turn alter immune function. We have shown that the SC115 tumor differentially stimulates natural killer cell activity in mice in the different housing conditions at 7 days after tumor cell injection and formation of experimental housing conditions (68, 69). In addition, preliminary evidence from our laboratory suggests that the SC115 tumor stimulates a tumor-specific cytolytic immune response (unpublished data). Several studies have shown that chemotherapy treatment is optimized when combined with an increase in immune activity (61, 62, 70–73). Thus, differential immune activity in mice in the different experimental housing conditions could alter tumor response to chemotherapy. Alternatively, chemotherapy in itself may differentially affect both endocrine and immune activities of mice in the different housing conditions, thereby altering tumor response to chemotherapy. In animal studies, both adriamycin and cyclophosphamide have been shown to affect the immune and/or endocrine responses (47, 74, 75).

Body weight change has been shown to influence the effectiveness of chemotherapy (76–78), possibly through alterations in hormone (eg, glucocorticoids and insulin) levels that may modulate, directly or indirectly, the activity of drug-metabolizing enzymes (9, 10, 79–81) or change the growth kinetics of tumor cells (53, 60, 82). Similar to other studies (83–85), our studies demonstrate that body weight loss over the duration of chemotherapy is inversely proportional to the tumor response to chemotherapy. In our previous study (41), IG mice lost less weight and had better tumor response to chemotherapy than GI mice, and in experiment 2 of the present study, GI mice lost less weight and had a better tumor response to chemotherapy than mice in other housing conditions.

In the present study, increased weight loss and reduced survival probability experienced by IG mice may have been influenced by the increased fighting that occurs when the IG condition is formed. Previously we showed that 1 day after formation of experimental housing conditions, fighting and defensive behaviors are significantly increased in IG mice compared with mice in all other housing conditions.
characterized by increased corticosterone secretion to
quences lasting from hours up to weeks (86) and is
been shown to have marked physiological conse-
ence with a stressor in the form of social defeat has
established social groups (41). However, a single experi-
possibly increasing chemotherapeutic efficacy in es-
may play a role in reducing tumor growth rate and
fighting may represent a form of coping response that
(44). We (40, 44) and others (38) have suggested that
fighting may represent a form of coping response that
may play a role in reducing tumor growth rate and
possibly increasing chemotherapeutic efficacy in es-
This, the initial physiological effects of fighting
the day of chemotherapy initiation could play a role
in increasing the probability of weight loss and toxic
effects of chemotherapy and in decreasing survival
probability.
Stressor-induced changes in hormones and cyto-
kines may influence the toxic side effects of drugs, possibly including chemotherapeutic agents (47, 68, 89–92). We and others have demonstrated that for
mice allowed to adapt to new social housing condi-
tions, the impact of the change in social housing condi-
tion on endocrine and immune functions is reduced
(44, 59, 86, 88). The present study demonstrates that if
chemotherapy is initiated 1 day after the formation of
experimental housing conditions (at a time when hor-
mones and immune activity is differentially altered
among social housing conditions; Refs. 51, 68, and 69).
IG mice lose more weight and have a lower survival
probability compared with GI or GG mice. Conversely,
if chemotherapy is initiated 14 to 18 days after forma-
tion of social housing condition (at a time when hor-
mones and immune activity may be similar among so-
cial housing conditions), mice in the IG housing
condition lose less weight and have a higher survival
probability compared with GI mice (41). By 14 days
after the initiation of chemotherapy, social hierarchies
among mice in the IG housing condition have become
established and mice have adapted to the new housing
condition, as evidenced by the reduction in fighting
among mice within the IG housing condition (44).
Thus, different physiological profiles may exist be-
tween IG mice rehoused 1 day before initiation of
chemotherapy and those rehoused 14 days before che-
motherapy; as a consequence, differential tumor and
host responses to chemotherapy were observed.
In summary, the present study and our previous
study (41) together demonstrate that social housing
conditions can significantly influence the efficacy of
chemotherapy and highlight the importance of the
temporal relationship between formation of social
housing conditions and initiation of chemotherapy on
chemotherapeutic efficacy. These studies suggest that
the effects of social housing conditions on chemother-
apeutic efficacy may be independent of tumor growth
rate at the time of chemotherapy initiation and, at least
in terms of host response to chemotherapy, are inde-
pendent of tumor burden. Finally, these studies high-
light the possible impact of social housing condition
on the complex interrelationship among the host en-
vironment, tumor growth, and chemotherapeutic effi-
cacy. Although it is difficult to extrapolate from the
animal to the human situation, these data may help to
emphasize the role that psychosocial stressors may
play in the often unpredictable and highly variable
differences in tumor responses to chemotherapy as
well as in the toxic side effects of chemotherapy ob-
served among cancer patients.

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