Differential Effects of Selenium on Normal and Neoplastic Canine Mammary Cells1,2

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ABSTRACT

Four different canine mammary tumor (CMT) cell lines and a nonneoplastic primary culture of mammary cells were examined for their in vitro responsiveness to selenium supplementation. These cell lines were found to vary in their metabolic response to increasing concentrations of selenium. Sensitivity to selenium, as sodium selenite, increased with increasing concentrations of this trace element in all of the neoplastic lines. These data also suggest that increasing the plating density of tumor cells further increases the sensitivity to selenium. A relatively selenium-sensitive cell line (CMT-13) and relatively insensitive cell line (CMT-11) were characterized on the basis of reduced growth resulting from selenium supplementation. Increasing the concentration of selenium to 0.75 µg/ml depressed the growth of CMT-13 and CMT-11 cells by 75% and 11%, respectively, while no inhibition was observed in nonneoplastic cells. These cell lines also varied in their sensitivity to different forms of selenium. Selenodiglutathione was the most effective form of selenium examined that inhibited tumor cell growth. The sensitivity of the neoplastic lines was selenodiglutathione > sodium selenite > selenocysteine > selenomethionine. None of the forms of selenium examined inhibited the growth of the nonneoplastic mammary cells in culture. Supplementation with sodium selenite (1 µg Se per ml) for 60 min resulted in a dramatic depression in RNA biosynthesis in CMT-13, but not CMT-11 or nonneoplastic cells.

INTRODUCTION

 Dietary factors constitute important variables that may either enhance or suppress tumor development. One factor, implicated as a potential inhibitor of tumor development, is the trace element selenium. Regional and national variation in dietary selenium intake is inversely correlated with mortality from a variety of cancer sites including breast, colon, rectum, prostate, lung, and blood (1, 2). Considerable evidence also indicates that dietary selenium supplementation can reduce the incidence of virally and chemically induced tumors (3–14).

 Weisberger and Suhrland (15) observed that selenocysteine significantly retarded the growth of Murphy’s lymphosarcoma implanted into rats. Our laboratory has shown that selenium is also capable of retarding the in vitro growth of Ehrlich ascites tumor cells (16–18), L1210 leukemia cells (19), SV40-3T3 tumor cells (20), canine mammary tumor cells (21), and human mammary tumor cells (22). The inhibition of tumor development was dependent upon the form and dose of selenium administered. Data obtained with solid transplantable tumors suggest the antitumorigenic properties of selenium are not only due to direct cytotoxicity, but are associated with a decrease in the proliferation of neoplastic cells (20–23).

 The present studies were designed to examine the effect of selenium on the growth of nonneoplastic and neoplastic canine mammary cells in culture. Differences in sensitivity to selenium among cell types, as influenced by different forms of selenium, were also examined. In addition, the effect of selenium on macromolecular biosynthesis was examined.

MATERIALS AND METHODS

Tumor Cells. Four CMT3 cell lines designated CMT 11, 13, 14A, and 14B were used in the following studies. CMT-11 was isolated from a primary neoplasm of a mammary gland of a 9-yr-old Airedale. This tumor had the histological characteristics of a spindle-cell carcinoma. Electron microscopic examination revealed numerous desmosomal junctional complexes. This line was purified and has been maintained in the laboratory of A. Watrach for over 105 passages. Its morphological properties, karyotypic configuration, hormone receptors, and tumorigenicity were defined in athymic nude mice. These cells are essentially epithelial in type and have continued to maintain a modal chromosome number of 78. The CMT-13 cell line was developed from a primary tumor of the mammary gland of an 11-yr-old mixed terrier. This tumor had morphological properties of a cystic adenocarcinoma. This cell line was morphologically stabilized by cultivation and further purified by isolation of colonies arising from single cells in soft agar. Cultures have been continuously propagated through 95 passages in the laboratory of A. Watrach. These cells were determined to be of myoepithelial derivation and have a modal chromosome number of 68. In nude mice these cells consistently produced neoplastic growths with the same morphological characteristics as the original tumor.

CMT-14A cells were isolated from a primary neoplasm of the right fifth mammary gland of a 9-yr-old female dachshund. The original tumor had the structural characteristics of a carcinoma of the “clear cell” type (24). These cells are of a distinct epithelial type with numerous desmosomal junctional complexes and a modal chromosome number of 86. The cells have been continuously propagated through 115 passages. In nude mice, CMT-14A cells grow slowly and produce neoplastic growths of the same morphological characteristics as the original tumor. CMT-14B was developed from the same neoplasm as CMT-14A. The CMT-14A and B cell lines were separated early during isolation and developed different cultural and morphological properties. CMT-14B is essentially epithelial like in its structural characteristics and has a strong clonogenic potential. This cell line has been maintained over 104 passages in the laboratory of A. Watrach and has a model chromosomal number of 86. This cell is very aggressive upon transplantation in nude mice and readily gives rise to large tumors, eventually killing the host.

Isolation of Nonneoplastic Cells. A short-term cell line was developed from a normal mammary gland of a 4-yr-old lactating pointer. The gland was surgically removed and processed within 1 h. Small specimens of mammary tissue were trimmed of fat and excess connective tissue and minced with scissors. The minced tissue was then transferred to an Erlenmeyer flask containing sufficient 0.25% trypsin in phosphate-buffered saline to form a suspension. The resulting suspension was constantly stirred at 37°C, utilizing a magnetic stirrer. At intervals the supernatant was harvested and centrifuged, the trypsin was decanted, and each cell pellet was washed once in Earle’s diploid basal medium (25), containing 10% fetal bovine serum. The cells were then plated in plastic flasks, using the same medium supplemented with antibiotics. A majority of cells in the primary cultures had morphological characteristics suggestive of epithelial-like cells. Primary cultures used in the present studies were grown in Earle’s diploid basal medium

1 The abbreviation used is: CMT, canine mammary tumor.

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supplemented with 10% fetal bovine serum and antibiotics.

Selenium Sensitivity. The CMT cell lines and the primary nonneoplastic primary culture were examined for their sensitivity to selenium addition in vitro. Neoplastic and nonneoplastic cultures were maintained with chemically defined Ringer's inclusive phosphate medium and 10% fetal bovine serum. Neoplastic and nonneoplastic cells were maintained at 37°C in an environment of 5% CO2:95% air and a relative humidity of 95%. All subsequent cultures were maintained in this manner.

In Experiment 1, each cell culture, at the time of confluency, was replenished with fresh medium supplemented with selenium as Na2SeO3 (Sigma Chemicals, St. Louis, MO) at concentrations of 0, 0.2, 0.4, 0.6, 0.8, or 1.0 μg Se per ml. Cells were harvested by trypsinization at 24-h intervals for 72 h following medium replenishment for determination of selenium toxicity and total cell number. Viabilities were determined by the trypan blue dye viable exclusion technique (26, 27) on a Bright-Line hemocytometer (American Optical Corporation, Buffalo, NY). Cell survival is expressed as a percentage of cells excluding trypan blue, in relation to control cultures at the same time interval. Duplicate assays were performed on each concentration of selenium for each cell line at each of the time points.

In Experiment 2, the effect of selenium on the growth of CMT-11, CMT-13, and nonneoplastic canine mammary cell cultures was examined during a 4-day experiment. In this study all lines were plated at 1×10^5 cells per flask. After 24 h, selenium, as sodium selenite at concentrations ranging from 0.0 to 0.75 μg/ml, was added to each cell line. Attached cells were harvested by trypsinization and counted at 24, 48, and 72 h after the addition of selenium. Cells were counted with a Coulter Counter (Coulter Electronics, Hialeah, FL). Four flasks per concentration of selenium were examined at each time point.

Influence of Different Forms of Selenium on Cell Growth. In Experiment 3, the relatively selenium-insensitive (CMT-11), selenium-sensitive (CMT-13), and the nonneoplastic mammary cell cultures were exposed to different forms of selenium to determine their efficacy in reducing growth. Neoplastic, CMT-11, and CMT-13 cell lines were plated at 1×10^5 cells per flask and allowed to attach for 24 h. After 24 h the medium was replenished, and the flasks were divided into groups and treated with 0.75 μg of selenium per ml as selenomethionine, selenocysteine, sodium selenite, and selenodiglutathione. All selenium compounds were purchased from Sigma Chemical Co., St. Louis, MO. Selenodiglutathione was prepared and separated on a series of Dowex 50W×4 (200–400 mesh hydrogen form) columns according to the method of Ganther (28) as modified by Vernie et al. (29). Cells were harvested by trypsinization and counted at 24 and 48 h after the addition of selenium. Four flasks per experimental treatment were counted at each time period. All data were analyzed by analysis of variance with a least significance test applied for mean comparison.

Biosynthesis of Macromolecules. In Experiment 3, CMT-11, CMT-13, and NCM cells were grown to subconfluency before replenishment with medium containing 0 or 1 μg of Se per ml. To each group of flasks was added either 2.5 μCi of [5-3H]thymidine (17 Ci/mmol), 5.0 μCi of [5-3H]uridine (29 Ci/mmol), or 25 μCi of [4,5-3H]leucine (36 Ci/mmol) (Amersham Corporation, Northbrook, IL). All flasks were incubated for an additional 60 min before the medium was decanted. The cells were washed twice with phosphate-buffered saline and removed by scraping. DNA, RNA, and protein were fractionated by centrifugation using a neutral cesium chloride density gradient. For these samples the cell pellet was lysed with sodium dodecyl sulfate (0.5% in 0.02 M Tris-HCl, pH 7) and mixed with 150% CsCl (1.5:1.0 CsCl:0.05 M Tris-HCl, pH 7.0). The gradient was spun to equilibrium at 105,000 × g in a Beckman Ti 70.1 rotor for 48 h. Total RNA was determined by the method of Ceriotti (31). An adaptation of the method of Taylor and Milthorpe (32) was used to estimate DNA spectrophotometrically using the DNA-specific fluorochrome 4,6-diamidino-2-phenylindole (Boehringer Mannheim, West Germany). A standard curve was generated and found to be linear between 0.5 and 10 μg of DNA per ml. Protein was determined by the method of Lowry et al. (33). The purity of each fraction was assessed for contamination by the other macromolecules and found to be minimal. Any cross-contamination of the fractions was corrected for in the calculation of radioactivity per unit of the macromolecule. Radioactivity in each of the macromolecular fractions was determined with a Beckman LS9000 liquid scintillation counter (Beckman Instrument Co., Palo Alto, CA). Statistical analysis was performed by the Student t test. Mean differences with P < 0.05 were considered statistically significant.

RESULTS

Growth Response to Selenium. In Experiment 1, two of the four canine tumor cell lines, CMT-13 and CMT-14B, were sensitive to the addition of 0.2 μg of selenium per ml (Fig. 1). CMT-14A cells were not sensitive to the addition of this quantity of selenium, and they had viabilities reduced only by about 20% when the medium was supplemented with 0.6 μg of selenium per ml. Greater quantities of selenium were effective in suppressing the viability of these cells. The CMT-11 cell line was also extremely resistant to selenium supplementation. Concentrations of selenium of 0.8 μg/ml or more were required to cause a modest, less than 20%, decrease in the viability of this cell line. Incubation of CMT-13, CMT-14A, and CMT-14B with this quantity of selenium resulted in a 97, 51, and 40% decrease in viabilities within 48 h. Although the CMT-11 cell line was relatively insensitive to selenium supplementation, it was approximately 4 times more sensitive to 1 μg of selenium per ml than was the primary culture of nonneoplastic canine mammary cells. Viabilities of nonneoplastic canine mammary

![Fig. 1](cancerres.aacrjournals.org)
cells were not altered by selenium supplementation up to 0.8 μg/ml. Addition of 1.0 μg of Se per ml decreased cell number less than 10% in these nonneoplastic canine mammary cells.

In Experiment 2, selenium, as sodium selenite, inhibited the growth of both the CMT-11 and 13 cell lines but not the growth of the primary culture of the nonneoplastic cells (Figs. 2 and 3; Table 1). Growth of the CMT-13 cells was more sensitive to selenium supplementation than was CMT-11, as observed in the viability studies of Experiment 1. Sodium selenite supplementation caused a greater depression in the growth rate in CMT-13 cells in the first 24 h than after longer incubations. Within 24 h 0.1 μg of Se per ml resulted in a significant inhibition of growth of CMT-13 cells (Fig. 2). Addition of 0.05 μg of Se per ml actually stimulated the growth of the CMT-11 cell line (Fig. 3). Increasing the concentration of selenium to 0.1 μg/ml in the CMT-11 cells reduced growth compared to that observed with no selenium supplementation. Concentrations of selenium greater than 0.5 μg/ml were required to induce a significant inhibition of growth in CMT-11 cells. Even this concentration required approximately 48 h of incubation to detect a depression in growth. The percentage of growth inhibition caused by selenium supplementation of cultures of CMT-11 was reduced after 3 days of incubation, indicating some adaptation occurs in these cells.

Selenium supplementation up to 0.1 μg/ml had no influence on the growth of nonneoplastic mammary cells (Table 1). The growth of these cells was stimulated by greater than 0.5 μg of Se per ml by Day 3 of incubation (Table 1). Increasing the concentration of Se to 0.75 μg/ml reduced the time required to detect a growth stimulation in the nonneoplastic cells.

Growth Response to Different Forms of Se. CMT-13 was more sensitive than CMT-11 to all forms of selenium examined. Selenocystine inhibited the growth of CMT-13 by 29.1% but had no effect on the growth of CMT-11 cells. Selenomethionine had minimal effects on cellular growth in both cell lines when present 48 h (Table 2). In other studies longer incubation with this concentration has been found to retard the growth of CMT-13 cells but not CMT-11 cells (data not presented). Selenium, as selenodiglutathione and sodium selenite, markedly inhibited the growth of both the CMT-13 and CMT-11 cell lines but had no adverse effects on nonneoplastic canine mammary cells (Table 2). Selenodiglutathione completely inhibited the growth and resulted in cell killing of CMT-13 cells in less than 24 h. Only a 39% decrease in growth occurred after exposure to selenodiglutathione in the CMT-11 cell line during this same time of incubation. The percentage of growth inhibition increased to 76% after 2 days of exposure to selenodiglutathione in CMT-11 cells. Sodium selenite supplementation at 0.75 μg/ml inhibited the growth of CMT-13 by 21% at 24 h but had no detectable effect on the growth of CMT-11 cells. However, after 2 days of treatment with selenite the inhibition of CMT-13 was 51% and CMT-11 was 42%.

Macromolecular Biosynthesis. Addition of sodium selenite for 60 min at a concentration of 1 μg of Se per ml significantly increased the incorporation of thymidine into DNA in both the CMT-11 and nonneoplastic cells. However, incorporation of
RESPONSIVENESS OF CMT CELL LINES TO SELENIUM

label into the DNA of CMT-13 cell was not influenced by selenium supplementation during this incubation time. Protein synthesis was actually depressed by approximately 15% in only the nonneoplastic mammary cells. RNA biosynthesis was decreased approximately 50% in CMT-13 but was not significantly altered in either the CMT-11 or nonneoplastic cultures exposed to selenium for 60 min (Table 3).

DISCUSSION

Increasing information strongly suggests that selenium has an inhibitory effect on the proliferation of neoplastic tissue. However, little information exists to explain the mechanism by which selenium exerts its antiproliferative effect. Broghamer et al. (34) reported that increased concentrations of blood selenium in some cancer patients are associated with tumors remaining confined to the region of origin, fewer distant metastasis, reduced numbers of primary neoplasms, and decreased frequency of recurrences. Neoplastic tissue, regardless of cellular origin, is known to concentrate a variety of selenium compounds at levels higher than that of normal differentiating tissue (35). Human and animal experiments suggest the incorporation of selenium in neoplastic tissue is negatively correlated with the degree of differentiation of the tissue (34–38). The ability of selenium to inhibit the growth of neoplastic but not nonneoplastic cells in the present experiments is consistent with this hypothesis.

The use of established cell lines provides a good model to study the mechanism of selenium-induced inhibition of tumor growth. In vitro differences in the growth of cultured normal, preneoplastic, and neoplastic murine mammary cells treated with selenium have been reported (39). This differential response is also reflected in the various canine mammary cell lines used in the present studies. The range of response to selenium in the present studies was from relatively sensitive to relatively resistant. The inhibiting effects of selenium on these cells were dependent on the total concentration and form, the length of exposure, cell type and growth state, or plating density.

Comparison of confluent and growing cultures indicates that cell density modifies the sensitivity to selenium (Figs. 1–3). These data are consistent with the data of Medina et al. (40) showing that the inhibition of COMMA-D cells caused by selenium increased with cell density. The reason for this increased sensitivity is unknown.

The present studies are consistent with previous observations from our laboratory showing that the form of selenium is an important factor determining the ability of this trace element to inhibit tumor growth (16, 19, 23). Vernie et al. (29) reported that selenodiglutathione was a potent inhibitor of protein biosynthesis in cells in culture. This inhibition is thought to occur as a result of a depression in the synthesis of the elongation factor eIF-2 (29). Selenodiglutathione was the most potent form of selenium examined in this study. However, not all cells responded identically to this form of selenium. Whether the differences in efficacy of the forms of selenium examined in our studies are related to cellular uptake or metabolism of selenium within the cell is unknown.

The quantity and form of selenium accumulated by these cells and their ability to metabolize selenium may explain their differences in sensitivity to this trace element. Whether the form of selenium present in the CMT-11 cell differs from that found in the CMT-13 or nonneoplastic cell line is unknown. Our data suggest that the CMT-11 cell line may be more efficient in acclimating to higher concentrations of selenium as a function of time (Fig. 3). The ability to acclimate suggests that the rate of selenium detoxification may be a factor in the sensitivity of cells to this trace element.

The inhibitory effects of selenium on the growth of tumor cells are not completely understood. Gruenwedel and Cruikshank (41) reported that, after incubating HeLa cells with 2, 5, and 10 μM sodium selenite, the synthetic activity of RNA, DNA, and protein was significantly decreased. However, the inhibition of one of these macromolecules may lead to alterations in the synthesis or degradation rates of the other macromolecules. Medina and Oborn (39) observed that the growth response of a selenium-responsive tumor cell as measured by [3H]thymidine incorporation into DNA was altered 72 h, following the addition of selenium to the medium. Lewko et al. (42) have also reported a progressive depression in the growth of human breast cancer lines after the addition of sodium selenite from 0.1 to 1.0 μg of Se per ml. Accompanying this depression in growth was a depression in protein biosynthesis in cells cultured for 24 h. In the present studies, only nonneoplastic cells exposed to selenium were found to have depressed incorporation of leucine into protein. These cells are less sensitive to selenium since they are able to withstand relatively high selenium concentrations without an inhibition of growth. At present, it is unknown if protein biosynthesis remains depressed in these cells or if they are able to compensate for

Table 2 Effect of different forms of selenium on the growth of CMT-13, CMT-11, and nonneoplastic canine mammary cells

<table>
<thead>
<tr>
<th>Forms of selenium</th>
<th>CMT-13</th>
<th>CMT-11</th>
<th>Non-neoplastic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>5.77 ± 0.42</td>
<td>5.09 ± 0.54</td>
<td>1.72 ± 0.27</td>
</tr>
<tr>
<td>Selenomethionine</td>
<td>5.87 ± 0.75</td>
<td>4.78 ± 0.20</td>
<td>1.81 ± 0.23</td>
</tr>
<tr>
<td>Selenocystine</td>
<td>5.79 ± 0.59</td>
<td>5.33 ± 0.51</td>
<td>2.15 ± 0.44</td>
</tr>
<tr>
<td>Sodium selenite</td>
<td>4.57 ± 0.38</td>
<td>4.94 ± 0.22</td>
<td>1.84 ± 0.12</td>
</tr>
<tr>
<td>Selenodiglutathione</td>
<td>0.0 ± 0.12</td>
<td>3.09 ± 0.34</td>
<td>1.68 ± 0.18</td>
</tr>
<tr>
<td>Day 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>9.30 ± 0.62</td>
<td>15.21 ± 0.51</td>
<td>4.40 ± 0.26</td>
</tr>
<tr>
<td>Selenomethionine</td>
<td>8.94 ± 0.74</td>
<td>13.26 ± 0.74</td>
<td>4.46 ± 0.22</td>
</tr>
<tr>
<td>Selenocystine</td>
<td>6.59 ± 1.10</td>
<td>14.25 ± 0.51</td>
<td>4.56 ± 0.12</td>
</tr>
<tr>
<td>Sodium selenite</td>
<td>4.55 ± 0.60</td>
<td>8.78 ± 1.00</td>
<td>4.28 ± 0.16</td>
</tr>
<tr>
<td>Selenodiglutathione</td>
<td>0.0 ± 0.12</td>
<td>3.60 ± 0.16</td>
<td>4.46 ± 0.27</td>
</tr>
</tbody>
</table>

* Selenium was added to the medium in each form at 0.75 μg/ml.
Days 1 and 2 indicated in Table 3 and 48 h after selenium treatment, respectively.

Table 3 Effect of selenium treatment on macromolecular biosynthesis in canine mammary tumors

<table>
<thead>
<tr>
<th>Se treated</th>
<th>Control</th>
<th>Se treated</th>
<th>Control</th>
<th>Se treated</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>RNA biosynthesis (dpm [3H]uridine/μg RNA)</td>
<td>2955 ± 154δ</td>
<td>6295 ± 176δ</td>
<td>8891 ± 558δ</td>
<td>8471 ± 39δ</td>
<td>2246 ± 206δ</td>
</tr>
<tr>
<td>DNA biosynthesis (dpm [3H]thymidine/μg DNA)</td>
<td>22.9 ± 1.1δ</td>
<td>23.8 ± 0.3δ</td>
<td>10.0 ± 0.2δ</td>
<td>6.6 ± 1.2δ</td>
<td>4.2 ± 0.1δ</td>
</tr>
<tr>
<td>Protein biosynthesis (dpm [3H]leucine/μg protein)</td>
<td>724 ± 21δ</td>
<td>787 ± 23δ</td>
<td>992 ± 91δ</td>
<td>1005 ± 36δ</td>
<td>482 ± 2δ</td>
</tr>
</tbody>
</table>

* CMT-13 is selenium-responsive, and CMT-11 is selenium-nonresponsive canine mammary tumor cell line. NCMC area is nonneoplastic, nonresponsive primary cell line.

Horizontal paired means ± SE with unlike superscripts differing, P < 0.05.
exposure to this concentration of this trace element. Nevertheless, an inhibition of protein biosynthesis does not appear to be the principal factor accounting for the enhanced sensitivity of CMT-13 cells to selenium.

In the present studies, the incorporation of uridine into RNA was modified only in the selenium-sensitive cell line (CMT-13). These data suggest RNA may be the first crucial macromolecule to change after selenium supplementation. This early detection of depressed RNA synthesis in the selenium-sensitive cell line may indicate a specific site of action for selenium in tumor cell metabolism. Abdullaev et al. (30) reported that selenite significantly inhibited the incorporation of [3H]uridine into RNA of mussels (Mytilus foissus) embryos at the gastrula stage. The effect was first detected with incubation medium supplemented with 10 mM sodium selenite after 60 min of incubation. Such information suggests that selenium, in addition to inhibiting protein biosynthesis, may alter RNA transcription leading to specific alterations in RNA translation and ultimately depressed protein biosynthesis. Increased time of exposure to selenium would likely have modified the incorporation of precursors into DNA and protein in the neoplastic cells examined in the present studies. Our growth data suggest that concentration, form, and time of exposure to selenium are factors that determine when macromolecule biosynthesis will be altered. Support for this hypothesis comes from the delay in cell death in confluent cultures of canine mammary tumors as the selective agent.

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