Manganese Superoxide Dismutase Expression Correlates with p53 Status and Local Recurrence of Cervical Carcinoma Treated with Radiation Therapy

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ABSTRACT

Manganese superoxide dismutase (Mn-SOD) inactivates the radiation effect by removal of radiation-induced toxic superoxide radicals. The purpose of this study was to assess the correlation among Mn-SOD, radiation sensitivity, and prognosis following radiation therapy.

The Mn-SOD, p53 oncoprotein, and c-erbB-2 oncoprotein expressions in 52 specimens from patients with cervical cancer treated with radiation therapy were investigated immunohistochemically. The frozen sections were stained using antihuman Mn-SOD, anti-p53 monoclonal antibodies, and anti-c-erbB-2 oncoprotein polyclonal antibody followed by the avidin-biotin peroxidase complex method. Correlations among Mn-SOD expression, prognosis, and failure patterns were analyzed. Additionally, correlations between p53 and c-erbB-2 oncoproteins and Mn-SOD expression were investigated.

Positive expression of Mn-SOD in cervical carcinoma was 48.1%. No significant difference in positivity of Mn-SOD expression was noted according to stage and histological subtypes. The 5-year survival rate of Mn-SOD-positive patients was 42.5%, significantly poorer than the 77.0% of Mn-SOD-negative patients (P < 0.05). Analysis of the failure patterns revealed that patients with Mn-SOD expression showed a significantly higher incidence of local recurrence than those without. However, there was no difference in distant metastasis between them. Although both p53 and c-erbB-2 oncoprotein expressions were significantly associated with the prognosis of the same patients, Mn-SOD expression was associated with p53 oncoprotein expression but not with that of c-erbB-2 oncoprotein.

Our results demonstrate that the Mn-SOD level of cancer cells is correlated with local control and is an important prognostic factor in radiation therapy for cervical cancer. The Mn-SOD level may help explain the intrinsic radiosensitivity of cervical cancer cells.

INTRODUCTION

Mn-SOD is an enzyme that catalyzes the reaction \( \text{O}_2^- + \text{O}_2^- + 2\text{H}^+ \rightarrow \text{H}_2\text{O}_2 + \text{O}_2 \). This enzyme is believed to protect against toxic by-products of oxygen metabolism (1). Radiation produces superoxide radicals as a consequence of both radiolysis of water in tissues and the subsequent recombination of primary free radicals (2). Radiation-induced superoxide radicals in the presence of oxygen increase the radiation response of tumors. This is known as the "oxygen effect" and is an important modification factor in radiation therapy (3). An increase in Mn-SOD activity after X-irradiation was reported in the mouse heart (1, 4). It is supposed that Mn-SOD removes toxic superoxide radicals and protects against the damaging effects of ionizing radiation. Thus, under oxygenated conditions, Mn-SOD probably decreases the oxygen effect and may be involved in the induction of radiation resistance of normal tissues and malignant neoplasms. The expression of Mn-SOD by transfection of human Mn-SOD cDNA into murine spontaneous fibrosarcoma, FSa-II, which does not express Mn-SOD, was reported to increase radiation resistance (5). Moreover, a decrease in Mn-SOD activity has been reported in radiation hypersensitivity syndromes such as xeroderma pigmentosum, Fanconi's anemia, and acute radiation syndrome (6-9). Nevertheless, in animal experiments any association between radiation sensitivity and the SOD level has remained a matter of controversy (10, 11). In the clinical field, no reliable assessment of whether the SOD level of cancer cells is associated with radiation sensitivity or local control in radiation therapy has been reported.

Superoxide has been proposed to play a role in carcinogenesis, cardiopulmonary disease, chemical toxicity, radiation injury, inflammation, arthritis, and aging (12). Especially, the protective effects of SOD have been assumed to be related to the mechanisms of carcinogenesis (13). Some evidence has been presented that the Mn-SOD gene is a potential tumor suppressor gene (14, 15). Increased Mn-SOD expression suppresses the malignant phenotype of human melanoma cells (15). Furthermore, the SOD level of various cancer cells was reported to be lower than that of normal cells (6, 16). In contrast, it was also reported that the Mn-SOD level varied in different cancers, and that some cancers showed substantial amounts of Mn-SOD (17). In ovarian cancer, the serum SOD level varied and was apparently associated with tumor progression (18). These findings indicate that the Mn-SOD activity in human cancers remains controversial and requires further study.

Many oncogene expressions, including c-erbB-2, c-myc, H-ras, and p53, have been studied in terms of tumor progression, and their relationship with poor prognosis was reported (19-26). Moreover, these oncogenes are involved not only in cell cycle regulation mechanisms (26, 27) but also in intrinsic radiation sensitivity (28, 29). As for Mn-SOD activity, it is known to vary according to the cell cycle (30). Therefore, the question arises as to whether Mn-SOD activity may be associated with these oncogenes. The present study was performed to analyze the correlation between the Mn-SOD level of malignant tumors and the outcome of patients with cervical cancer treated with radiation therapy. Additionally, the Mn-SOD expression was analyzed in relation to p53 and c-erbB-2 oncoprotein expressions.

MATERIALS AND METHODS

Fifty-two patients with invasive squamous cell carcinoma of the uterine cervix, who received radiation therapy alone at the National Institute of Radiological Sciences Hospital (Chiba, Japan) between 1988 and 1990, were analyzed. The minimum follow-up period was 4.5 years, and most of the patients were followed up for more than 5 years. Clinical stages and histological subtypes are summarized in Table 1. The clinical staging and histological classification were based on the criteria of the International Federation of Gynecology and Obstetrics (London, England) classification (31) and the World Health Organization (Geneva, Switzerland) classification (32), respectively. The numbers of patients with stages I, II, III, and IV were 2, 13, 32, and 5, respectively. As for histological subtype, those with keratinizing, small cell nonkeratinizing and large cell nonkeratinizing types were 11, 12, and 29, respectively.

Radiotherapeutic Protocol. Patients were treated with a combination of external and high-dose rate intracavitary irradiation. Details of the protocol have been reported elsewhere (33). External whole pelvis irradiation was performed with anterior-posterior and posterior-anterior parallel opposing
ports, with a dose of 1.8 Gy/fraction, five times per week, to a total dose of 30.6 Gy. This was followed by a central shielding pelvis field, with a dose of 2 Gy/fraction, five times per week, to a total dose of 20 Gy. Along with the central shielding irradiation, these patients also received intracavitary irradiation by a remote afterloading system using 192Co sources; they received four insertions (one per week) with fraction doses of 550–600 cGy at point A. The total doses ranged from 22 Gy to 24 Gy.

**Histopathological Study.** All specimens were excised from cervical tumors before radiation therapy. All of the fresh biopsy specimens were divided into two parts: one was fixed with 10% formaldehyde solution for conventional H&E staining, and the other was quickly frozen for immunostaining for Mn-SOD, p53 protein, and c-erbB-2 protein. The specimens were sectioned with a cryostat at 6-μm thickness, air-dried, and fixed with cold 4% parafomaldehyde solution for 30 min. Then the sections were reacted for 1 h at room temperature with mouse anti-Mn-SOD monoclonal antibody (PG-11; a gift from Dr. N. Taniguchi, Osaka University, Osaka, Japan; Ref. 34), an antibody specific for Mn-SOD without any reaction to copper SOD and zinc SOD. Similarly, the same specimens were reacted with mouse PAb1801 (Oncogene Science, Inc., Uniondale, NY) for p53 protein staining and polyclonal rabbit anti-c-erbB-2 oncoprotein antibody (Dako, Copenhagen, Denmark) for 1 h. The sections were followed by reaction with biotinylated second antibodies for 30 min and treated using the avidin-biotin complex method (Ref. 35; Vector Laboratories, Burlingame, CA) for 30 min. Then the sections were reacted with 3,3'-diaminobenzidine tetrahydrochloride solution (Dojin Chemicals, Tokyo, Japan) with 0.01% (w/v) hydrogen peroxide for 2 to 5 min at room temperature and counterstained with hematoxylin. Control staining was done by incubation with normal control serum instead of primary antibodies.

The specimens were histologically examined and classified into two groups according to the degree of stained cells as follows: Mn-SOD expression—positive, marked nuclear and cytoplasmic staining (Fig. 1); negative, no or slight staining; p53 expression—positive, marked nuclear staining (Fig. 2); negative, no or slight nuclear staining; and c-erbB-2 expression—positive, marked cell membrane staining (Fig. 3); negative, no or slight cell membrane staining.

To rule out the possibility of bias, the specimens were classified into the two groups by one investigator without knowledge of patient status and outcome.

**Statistical Analysis.** Cumulative survival rates were statistically analyzed using the Peto log rank test (36). Correlations between Mn-SOD and the expressions of p53 and c-erbB-2 oncoproteins were analyzed using the χ² test.

**RESULTS**

The overall Mn-SOD positivity was 48.1%. Positivity according to stage and histological subtype is shown in Table 1. There was no significant difference in positivity among the stages, although stage II tended to be somewhat lower. Histological subtypes also showed no differences in Mn-SOD positivity, but small cell types showed a tendency to have a lower rate.

Mn-SOD was expressed in the cytoplasm of cancer cells as shown in Fig. 1. Fig. 2 shows p53 antigen expression in the nucleus, and Fig. 3 shows the c-erbB-2 oncoprotein on the cell membrane of cancer cells.

Table 2 illustrates that there was a significant correlation between Mn-SOD and p53 expressions. All tumors with Mn-SOD expression were positive for p53, whereas only 70.7% of those lacking the expression were p53 positive (P < 0.005). There was no significant correlation between Mn-SOD and c-erbB-2.

Cumulative survival rates according to Mn-SOD positivity are shown in Fig. 4. Mn-SOD-positive patients had a significantly poorer 5-year survival than Mn-SOD-negative patients (42.5 versus 77.0%,
Table 2  Correlation between Mn-SOD, p53, and c-erbB-2 expressions

<table>
<thead>
<tr>
<th>Mn-SOD</th>
<th>p53</th>
<th>c-erbB-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>8</td>
<td>19</td>
</tr>
<tr>
<td>+</td>
<td>17</td>
<td>14</td>
</tr>
</tbody>
</table>

\[ P < 0.005 \]

Table 2 shows the failure patterns of the patients according to Mn-SOD status. Ten (40%) of 25 Mn-SOD-positive patients and 3 (11%) of 27 negative patients had recurrences. This higher incidence in Mn-SOD-positive patients was statistically significant \( P < 0.05 \). However, there was no correlation between the Mn-SOD status and metastasis.

Table 4 shows the cumulative 5-year local control rates according to Mn-SOD, p53, and c-erbB-2 expressions. The local control rate was significantly associated with Mn-SOD and c-erbB-2 expressions, but the correlation between Mn-SOD and p53 was not statistically significant.

DISCUSSION

In human tumors, no relationship between sensitivity to ionizing radiation and content of enzymes has been reported \((17, 37)\). The present study demonstrated that tumors expressing Mn-SOD showed significantly lower survival than those of negative Mn-SOD. Analysis of the failure patterns following radiation therapy revealed that the difference was due to higher local recurrence in the patients with positive Mn-SOD. This suggests that Mn-SOD is associated with local control by protecting cancer cells from radiation damage. This seems to be the first confirmation of the possibility that SOD in human tumor cells protects against radiation effects on the tumor in radiation therapy. Similarly, radiation hypersensitivity of Down syndrome fibroblasts was associated with low Mn-SOD levels \((38)\). In addition, this hypersensitivity in xeroderma pigmentosum cells was also correlated with reduced SOD activity, but not with excision repair \((8, 9)\). These results, then, suggest that one of the roles of Mn-SOD in human tumors is to protect against radiation damage.

X-irradiation produces superoxides and induces Mn-SOD in mouse tissues. This induction is dose and time dependent \((4)\). Jaworska and Rosiek \((10)\) reported that SOD might be a radioprotective enzyme in lymphoma LY strains, and that LY-S cells are particularly sensitive to superoxide radicals as a result of relatively low SOD activity. They considered that the sensitivity was due to the higher initial level of DNA DSBs, which are less readily repaired. The relationship between

\[ P < 0.05 \]. As for p53 protein expression, the 5-year survival rate for positive patients was 52.8%, significantly poorer than the 100% of negative patients \((Fig. 5, P < 0.05)\). The 5-year survival rate of c-erbB-2-positive patients was 41.9%, a rate significantly lower than the 74.2% of the c-erbB-2-negative patients \((Fig. 6, P < 0.025)\).

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Fig. 4. Cumulative survival rates according to Mn-SOD expression in cervical cancer. Mn-SOD-positive patients had a significantly poorer 5-year survival than Mn-SOD-negative patients (42.5 versus 77.0%, \( P < 0.05 \)).

Fig. 5. Cumulative survival rates according to p53 expression in cervical cancer. The 5-year survival rate of p53-positive patients was 52.8%, which was significantly poorer than the p53-negative ones (52.8 versus 100%, \( P < 0.05 \)).

Fig. 6. Cumulative survival rates according to c-erbB-2 expression in cervical cancer. The 5-year survival rate of c-erbB-2-positive patients was 41.9%, which was significantly poorer than the c-erbB-2-negative ones (41.9 versus 74.2%, \( P < 0.025 \)).
Moreover, diethildithiocarbamate, an SOD inhibitor, sensitized experimental animals enhanced the resistance against radiation (10). Deficient mutants actually appear to be radiation resistant. It is obvious that activity alone did not prevent oxidation damage caused by ionizing radiations of superoxide anion radicals. In support of this, previous studies have demonstrated that the administration of extracellular Mn-SOD protects organisms against oxygen-mediated radiation damage (39, 40). Urano et al. (5) demonstrated that the transfection of human Mn-SOD cDNA into murine spontaneous fibrosarcoma, FSA-II, which itself had no Mn-SOD activity, increased the Mn-SOD level and reduced radiation sensitivity under aerobic conditions. Similarly, some enzymes which augment the Mn-SOD level in various tissues of experimental animals enhanced the resistance against radiation (10, 41). Moreover, diethildithiocarbamate, an SOD inhibitor, sensitized the radiation response of *in vivo* tumors in mice (42). On the other hand, Scott et al. (11) reported that enhanced endogenous Mn-SOD activity alone did not prevent oxidation damage caused by ionizing radiation (11). In fact, exaggerated Mn-SOD activity has been reported to accelerate oxygen-mediated radiation damage. Mn-SOD-deficient mutants actually appear to be radiation resistant. It is obvious from the various findings that the function of SOD in radiation protection still needs to be clarified.

There are wide variations of radiation sensitivity among human cancers. Tumors such as lymphoma, seminoma, dysgerminoma, and neuroblastoma are sensitive, but others such as melanoma, osteosarcoma, and fibrosarcoma are resistant. This variety in radiation sensitivity has been analyzed in terms of cell cycle kinetics and the proliferative activity of tumors (43–46). However, these factors do not sufficiently explain such a wide variety of radiation sensitivities of tumors of different sites and histological types. Recently, it has been proposed that oncopgenic sequences modulate the intrinsic radiosensitivity of human tumorogenic cell lines and murine fibroblasts. In particular, the ras oncogene has been implicated in the increase in inherent radioresistance of transfected murine cells (28). Mutant p53 transfected into rat embryo cells increased the intrinsic radiation resistance (29). p53 gene is considered to be a tumor suppressor because the wild type negatively regulates cell growth and division (26). Besides its role in cell cycle progression, p53 gene products also regulate the cellular response to DNA damage and apoptosis, and apoptosis also correlated with radiation sensitivity (47). We consider that the variety in SOD activity in cancer cells is one of the reasons for the heterogeneity of intrinsic radiation sensitivity.

The present study demonstrated a positive correlation between the expressions of Mn-SOD and p53 protein. This might in part be due to the fact that Mn-SOD and p53 are associated with DNA damage induced by various agents including radiation and oxidative agents (26). In support of this, Kastan *et al.* (27) suggested that p53 may participate in the cellular response to DNA damage. The present study showed a somewhat positive correlation between p53 expression and prognosis. Some investigators reported that cancer cells overexpressed p53 protein, and that this was associated with tumor grade or poor prognosis in various cancers (16, 26, 48). These results, taken together, suggest that the interrelationship of the Mn-SOD expression and p53 gene may be involved in intrinsic radiation sensitivity.

c-erbB-2 oncoprotein expression is associated with tumor proliferative status and malignancy in many cancers (14, 25), including cervical cancer reported by us (49). The present study demonstrated that local control was associated with c-erbB-2 oncoprotein expression and confirmed that the prognosis was poorer in c-erbB-2 overexpression. However, no correlation between the expressions of Mn-SOD and c-erbB-2 oncoprotein was observed. Bize *et al.* (50) reported that Mn-SOD activity was decreased in fast and medium growth rate hepatomas but was slightly increased in the slowest growth rate hepatomas. Mn-SOD activity was significantly reduced in the cell cycle in the epidermis (30). Along with our result that the Mn-SOD expression was not associated with c-erbB-2 oncoprotein expression or with metastatic activity, the poor local control with Mn-SOD expression might be due to intracellular radiosensitivity rather than to proliferative activity.

The Mn-SOD level of cancer cells appears to be associated with radiation sensitivity and local control in radiation therapy of cervical cancer. Mn-SOD expression on tumor cells is an important prognostic factor different from that which reflects tumor malignancy such as the c-erbB-2 oncoprotein. The clinical significance, then, of our findings is that the treatment modality of radiation therapy may be able to be decided based on the immunohistochemical detection of Mn-SOD expression in cancer cells. Controlling the SOD level of cancer cells may be a first step toward overcoming the radioresistance of certain cancers.

### REFERENCES


### Table 3 Correlation between Mn-SOD and prognosis

<table>
<thead>
<tr>
<th>Stage</th>
<th>SOD(−)</th>
<th>SOD(+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>II</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>III</td>
<td>15</td>
<td>17</td>
</tr>
<tr>
<td>IV</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
<td>25</td>
</tr>
</tbody>
</table>

No., number of patients; Rec, recurrence; Met, metastasis; NS, not significant.

### Table 4 Local control rates by Mn-SOD, p53, and c-erbB-2 expressions

<table>
<thead>
<tr>
<th>Expression</th>
<th>5-yr local control (%)</th>
<th>Statistical value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mn-SOD(−)</td>
<td>88.7</td>
<td>4.75</td>
</tr>
<tr>
<td>Mn-SOD(+)</td>
<td>61.4</td>
<td>2.60</td>
</tr>
<tr>
<td>p53(−)</td>
<td>100</td>
<td>5.27</td>
</tr>
<tr>
<td>p53(+)</td>
<td>71.4</td>
<td>2.60</td>
</tr>
<tr>
<td>c-erbB-2(−)</td>
<td>89.1</td>
<td>2.60</td>
</tr>
<tr>
<td>c-erbB-2(+)</td>
<td>60.0</td>
<td>5.27</td>
</tr>
</tbody>
</table>

P < 0.05

**Note:** The present study demonstrated a positive correlation between the expressions of Mn-SOD and p53 protein. This might in part be due to the fact that Mn-SOD and p53 are associated with DNA damage induced by various agents including radiation and oxidative agents (26). In support of this, Kastan *et al.* (27) suggested that p53 may participate in the cellular response to DNA damage. The present study showed a somewhat positive correlation between p53 expression and prognosis. Some investigators reported that cancer cells overexpressed p53 protein, and that this was associated with tumor grade or poor prognosis in various cancers (16, 26, 48). These results, taken together, suggest that the interrelationship of the Mn-SOD expression and p53 gene may be involved in intrinsic radiation sensitivity.

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