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Biobehavioral and Neuroendocrine Correlates of Antioxidant Enzyme Activity in Ovarian Carcinoma

Jennifer L. Bayer[1], **Douglas R. Spitz**[2,3], **Desire Christensen**[4], **Michael L. McCormick**[2,3], **Donna Farley**[5], **Koen DeGeest**[6], **Laila Damoush**[7], **Samantha Aust**[1], **Anil K. Sood**[8], and **Susan K. Lutgendorf**[1,3,9,10]

[1]Department of Psychology, University of Iowa

[2]Free Radical and Radiation Biology Program, Department of Radiation Oncology, University of Iowa

[3]Holden Comprehensive Cancer Center, University of Iowa

[4]Carver College of Medicine, University of Iowa

[5]Department of Pharmacology, University of Iowa

[6]Oregon Health and Sciences University

[7]Department of Pathology, University of Iowa

[8]Departments of Gynecologic Oncology, Cancer Biology, and Center for RNA Interference and Noncoding RNA, University of Texas M.D. Anderson Cancer Center

[9]Department of Obstetrics and Gynecology, University of Iowa

[10]Department of Urology, University of Iowa

Abstract

Increased levels of reactive oxygen species (ROS) such as superoxide anions and hydrogen peroxide have been reported in many cancer cells and they have been implicated in carcinogenesis and tumor progression. Antioxidant enzymes, such as Manganese Superoxide Dismutase (MnSOD or SOD2) and Glutathione Peroxidase-1 (GPx1), act coordinately to neutralize ROS. These enzymes are also thought to contribute to cancer cell resistance to conventional radio-chemotherapies. Although some relationships have been reported between psychosocial factors and the regulation of antioxidant enzymes, little is known about these relationships in the context of cancer progression.

Corresponding Author: Susan K. Lutgendorf, Ph.D., University of Iowa, E11 Seashore Hall, Iowa City IA 52242, PH: 319-335-2432, FX: 319-335-0191, Susan-lutgendorf@uiowa.edu.

The current study investigated the levels of MnSOD and GPx1 in confirmed serous, high-grade tumor tissue from 60 ovarian cancer patients, and explored the relationship between the activity of these enzymes, the levels of tumor norepinephrine (NE), and patient mood as determined via pre-operative questionnaires. MnSOD activity was positively related to depressed mood ($p = 0.025$) and tumor NE ($p = 0.023$). In contrast, GPx1 activity was inversely related to fatigue ($p = 0.015$) and tumor NE ($p = 0.009$), and was positively associated with vigor ($p = 0.024$). These findings suggest that psychological state and adrenergic signaling are linked with antioxidant enzyme activity in ovarian cancer and may have implications for patient treatments and outcomes.

Keywords

neuroendocrine; biobehavioral; stress; antioxidant enzymes; ovarian cancer

1. Introduction

Defects in cancer cell metabolism that lead to increased steady-state levels of reactive oxygen species (ROS; i.e., superoxide anion and hydrogen peroxide) have been implicated in carcinogenesis and cancer progression (Reuter, Gupta, Chaturvedi, & Aggarwal, 2010; Zhou, Shao, & Spitz, 2014) Although normal fluctuations in steady-state levels of ROS produced by metabolism are hypothesized to be important in normal cellular signaling (Holmstrom & Finkel, 2014) and associated with normal growth and development (Zhou et al., 2014), increased steady-state levels of ROS are believed to lead to cellular and organismic damage (Reuter et al., 2010) as well as genomic instability, uncontrolled growth, and the inability to properly differentiate that is characteristic of the malignant phenotype (Zhou et al., 2014). Thus, high levels of ROS are believed to activate signaling pathways that contribute to tumor cell proliferation, chemoresistance, invasion, and metastasis (Mates, Segura, Alonso, & Marquez, 2012; Reuter et al., 2010; Zhou et al., 2014).

Antioxidant enzymes neutralize ROS. The antioxidant enzyme Manganese Superoxide Dismutase (MnSOD) is particularly important in the conversion of superoxide anions produced in mitochondria during mitochondrial respiration to hydrogen peroxide while glutathione peroxidase (GPx1) then converts hydrogen peroxide to water and oxygen in the cytoplasm (Brigelius-Flohe & Maiorino, 2013). Antioxidant enzymes are also thought to act as second messengers (Valko et al., 2007). In early stages of cancer, MnSOD concentration in tumor cells is significantly lower than in normal cells (Oberley & Buettner, 1979). MnSOD is thought to act as a tumor suppressor, low levels of MnSOD may lead to increased tumorigenesis via low tumor suppressor activity. As cancer progresses, metabolism shifts back to aerobic respiration, ROS production increases, and antioxidant enzyme activity also increases (Sarsour et al., 2012). At this point however, instead of acting in a tumor suppressor role, MnSOD is thought to support tumor growth by upregulating hypoxia inducible factor (HIF-1a), a protein associated with angiogenesis (Kim & Dang, 2006).

Stress hormones, including norepinephrine (NE), upregulate cellular metabolism and increase both the concentration of cellular ROS as well as the activity of antioxidant enzymes (Manoli et al., 2007; Picard, Juster, & McEwen, 2014). Antioxidant enzyme

activity appears to be impacted by mental health states as well, however relationships are not consistent. Bilici et al (2001) found that patients with major depression have higher levels of both superoxide dismutase (SOD) and GPx, while Ozcan et al (2004) found lower levels of GPx in depressed patients and no relationship with SOD. Relationships between depression, NE, and antioxidant enzymes have been minimally examined in cancer patients in general and to our knowledge, have not previously been examined in ovarian cancer patients.

Ovarian cancer is the sixth leading type of cancer affecting women in developed countries and the most lethal gynecological cancer (Modugno & Edwards, 2012). Little is known about antioxidant activity in ovarian cancer and about conditions that promote this activity. Depressed mood is quite prevalent in ovarian cancer patients and has been associated with elevated NE in both healthy individuals (Hughes, Watkins, Blumenthal, Kuhn, & Sherwood, 2004) and in ovarian cancer patients (Lutgendorf et al., 2009). Both oxidative stress (Reuter et al, 2010) and adrenergic signaling have been shown to modulate numerous pathways implicated in tumor progression (Thaker, Sood, & Ramondetta, 2013) and thus their interaction could potentially be involved in tumor progression. Therefore, the purpose of this study was to determine levels of antioxidant enzyme activity in primary ovarian tumor tissue and to investigate associations of mood and tumor NE with the antioxidant enzymes MnSOD and GPx. We hypothesized that antioxidant activity would be elevated in patients with higher levels of either depression or tumor NE.

2. Materials and Methods

2.1 Participants

Women with a new diagnosis of a pelvic or abdominal mass suspected to be ovarian cancer were recruited at their pre-surgical clinical visit as part of a larger study examining psychosocial factors, biomarkers and tumor progression. Inclusion required a histologically confirmed diagnosis of primary invasive serous epithelial ovarian, peritoneal, or fallopian tube cancer. Tumor samples were verified as positive for serous histology and containing at least 70% tumor tissue by the study pathologist (LD). Women with a primary cancer of another organ site, a non-serous or non-epithelial ovarian tumor, an ovarian tumor of low malignant potential, use of systemic corticosteroid medication in the last 4 months, comorbidities known to alter the immune response, or age under 18 years were all excluded. All tumor samples were cryopreserved in liquid nitrogen at the time of surgery. Psychosocial questionnaires were completed between the pre-operative appointment and surgery. This research was approved by the Institutional Review Boards at the University of Iowa and University of Miami.

2.2 Assessments

The Center for Epidemiological Studies Depression Scale (CES-D) is a 20-item questionnaire assessing depressive symptomatology over the last week (Radloff, 1977). Scores of 16 or greater indicate “probable cases of depression” (Weissman, Sholomskas, Pottenger, Prusoff, & Locke, 1977). The CES-D has four subscales that have been confirmed using factor analysis: depressed affect, vegetative depression, positive affect, and interpersonal relationships (Sheehan, Fifield, Reisine, & Tennen, 1995). There are no

thresholds for the subscales, higher scores are associated with greater difficulty for the depressed affect, vegetative depression, and interpersonal relationships subscales while a higher score on the positive affect subscale reflects more positive mood.

The Profile of Mood States – Short Form (POMS-SF) measures participants' agreement with 37 adjectives to describe their mood over the past week, ranging from 0 (not at all) to 4 (extremely). Scores are summed to create six subscales. The subscales do not have clinical cut offs; higher scores indicate greater distress for the negative mood subscales: anxiety, depression, anger, fatigue, and confusion or higher levels of the positive subscale: vigor (Shacham, 1983).

2.3 Biological Measures

2.3.1 Norepinephrine—Tumor samples were analyzed for NE content as previously described (Lutgendorf et al., 2009). Briefly, dissected 2–3 mm tumor tissue samples, cryopreserved in liquid nitrogen, were pulverized and homogenized prior to the adsorption of catechols onto acid-washed alumina. Catechols were immediately eluted from the alumina using dilute acetic acid and NE levels were determined by high performance liquid chromatography with electrochemical detection (HPLC-ED) as previously described (Hoffman, Sinkey, Dopp, & Phillips, 2002; Lutgendorf et al., 2009). A 5-point calibration curve was obtained using known concentrations of pure standards and linear regression analysis was used to determine catecholamine concentrations in the tissue samples. The lower limit of detection was 0.1 pg/mg tumor.

2.3.2 Antioxidant enzyme activity—MnSOD activity of cell homogenates was determined as previously described (Spitz & Oberley, 1989) using an indirect competitive inhibition spectrophotometric assay. This assay uses xanthine/xanthine oxidase to generate superoxide and measures the inhibition of the superoxide-dependent reduction of nitroblue tetrazolium (NBT) to blue formazan in the presence of increasing concentrations of purified SOD enzymes or tumor tissue homogenates. The percent inhibition of NBT reduction was plotted against protein concentration for each sample assay reaction series. One unit of MnSOD activity was defined as the amount of protein that results in 50% of maximum inhibition. GPx1 was determined spectrophotometrically as previously described (Lawrence & Burk, 1976). Enzyme activities were normalized to protein content as determined by the method of Lowry (Lowry, Rosebrough, Farr, & Randall, 1951).

2.4 Statistical Analyses

Statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS) version 22 (Armonk, NY). For purposes of homogeneity, only high grade tumors were analyzed. Distributions were assessed for normality and outliers. MnSOD, GPx1, and tumor NE were log transformed to normalize the distributions. A bivariate Pearson correlation was used to evaluate the relationship between the two antioxidant enzymes. Hierarchical regressions were conducted to test relationships between variables. Stage of cancer and age at recruitment were covariates entered in the first level of the regression, followed by the independent variable of interest to assess its unique contribution to each antioxidant enzyme.

3. Results

3.1 Participant Characteristics

Sixty women met inclusion criteria. Participants were primarily married, non-Hispanic Caucasians with a mean age of 58.9 years. The majority of participants had advanced stage and depressed mood (Table 1).

3.2 Psychosocial Factors and Antioxidant Enzymes

Patients reporting higher levels of depressed mood (CES-D, depression subscale) had significantly higher levels of tumor MnSOD, adjusting for age and stage (n= 60, $R^2 = 0.136$, $\beta=0.288$, $p=0.025$, Figure 1A). No relationships were found between MnSOD and the other CESD subscales (all p values > 0.11). In contrast, patients with higher tumor GPx1 had significantly greater vigor (n = 57, $R^2 = 0.113$, $\beta = 0.309$, $p = 0.024$, Figure 1B) and lower levels of fatigue (n = 57, $R^2 = 0.159$, $\beta = -0.326$, p = 0.015). Patients with higher GPx1 activity showed a trend towards lower levels of vegetative depression (n=60, $R^2 = 0.135$, $\beta = -0.227$, $p = 0.077$) and greater positive mood (n=59, $R^2 = 0.063$, $\beta=0.254$, $p = 0.060$), but no relationship was seen with depressed mood (p = 0.645). MnSOD was not related to vigor, fatigue, positive mood, or vegetative depression (all p values > 0.507). MnSOD and GPx1 activity were inversely related, ($r(60) = -0.299$, $p = 0.020$).

3.3 Tumor Norepinephrine and Antioxidant Enzyme Activity

Patients with higher levels of tumor NE had significantly higher MnSOD (n=59, $R^2 = 0.127$, $\beta = 0.302$, p = 0.023, Figure 1C) and significantly lower levels of GPx1 (n=59, $R^2 =.0154$, $\beta = -0.344$, $p = 0.009$, Figure 1D).

4. Discussion

The purpose of this study was to investigate relationships of mood and stress hormones with antioxidant enzyme activity in primary ovarian tumors. The key findings were that MnSOD was related to greater depressed mood and higher levels of tumor NE in ovarian cancer patients, adjusting for clinical covariates, whereas GPx1 was related to vigor, lower levels of fatigue, as well as lower tumor NE. We found an inverse relationship between MnSOD and GPx1.

Sympathetic nervous system activity has been shown to elicit greater mitochondrial activity in specific tissues as part of the energy mobilization in the fight or flight response (Weber et al., 2002). These effects are known to be true in many tissue types but have not been previously described in tumor tissue. The positive association of tumor NE with MnSOD may reflect adrenergic elicitation of greater mitochondrial activity in tumor tissue (Manoli et al., 2007) which would have downstream effects described below. As adrenergic signaling has been associated with a variety of pro-tumor activities including enhanced angiogenesis, invasion, and evasion of anoikis, it is possible that mitochondrial activity plays a part in enhancing these tumor activities.

The role of MnSOD in cancer is not completely understood. Oberley and Buettner (1979) showed that MnSOD was significantly lowered if not absent in cancer cells, and that

MnSOD acts as a tumor suppressor, protecting cells from tumorigenesis in the presence of superoxide (Oberley & Buettner, 1979). Nishida et al (1993), however, showed elevated levels of MnSOD in tumors of ovarian cancer patients. One explanation given for this is that MnSOD is downregulated when tumors are developing but becomes upregulated after the tumor is established (Dhar & St Clair, 2012). This would parallel the findings of Dhar et al (2011) that cancer cells use aerobic glycolysis early in their development but transition back to aerobic respiration as they progress. In culture, when cancer cells are in proliferative stage, they have low levels of MnSOD but have high levels when the cells are confluent (Sarsour, Kalen, & Goswami, 2014). In fact, MnSOD might play a role in the shift from the Warburg effect, a metabolic shift from aerobic respiration to glycolysis in the presence of oxygen, back to normal aerobic respiration as cancer cells increase in aggressiveness (Dhar & St Clair, 2012). The regulation of cellular metabolism in cancer is quite complex and not signaled by MnSOD alone. The proto-oncogene Ets-1, when overexpressed as it commonly is in cancer cells, has been shown to shift ovarian cancer cells to aerobic glycolysis while suppressing aerobic respiration (Verschoor, Verschoor, & Singh, 2013).

The effects of antioxidant enzyme activity on cancer progression are likely not limited to effects on cellular metabolism. MnSOD activity has been shown to increase and decrease as cells progress through cell cycle, indicating that MnSOD might be involved in the signaling of cells to proliferate (Sarsour et al., 2012). Higher levels of ROS can independently signal cells to proliferate (Ogrunc et al., 2014; Wallace, 2012). MnSOD upregulates hypoxia inducible factor (HIF-1α) which helps cancer cells withstand the oxygen-poor environment created when the tumor grows but blood vessels have not yet infiltrated the new tumor (Holley, Dhar, & St Clair, 2013). Additionally, cancer cells favor a redox balance within the cell and will activate the transcription factor Nrf2, which upregulates the expression of antioxidant enzyme genes (van der Wijst, Brown, & Rots, 2014; Yang, Soga, & Pollard, 2013). Thus adrenergic enhancement of MnSOD, may support tumor growth and progression via a variety of pathways.

Like MnSOD, the role GPx1 plays in cancer progression is complex and not fully characterized. It has been proposed that, as cancer progresses, GPx1, like MnSOD, might be associated with poor outcomes as cancer cells capitalize on the anti-apoptotic properties of antioxidant enzymes (DeNicola et al., 2011). While high levels of GPx1 have been associated with increased cellular proliferation (Jin et al., 2015), colorectal cancer cells had decreased concentration of GPx1 compared to healthy tissue (Nalkiran et al., 2015). GPx1 has also been shown to be decreased (Kodydkova et al., 2009; Maes et al., 2011; Rybka et al., 2013; and Stefanescu et al., 2012) or not different (Galecki et al., 2009) in depressed patients compared to healthy controls. While we found no relationship between GPx1 and depressed mood, we did show increased activity associated with positive mood states. Biochemically, GPx1 was associated with lower NE, which based on other work from this group tends to indicate more favorable outcomes. Further work must be done to assess the impact of GPx1 levels on ovarian tumor growth and on long-term outcomes in ovarian cancer patients.

Limitations

This study is cross sectional, and thus we are not able to determine the causal direction of relationships, or if there is another factor underlying observed relationships. The existence of a relationship between MnSOD and GPx1 variants and cancer risk has been suggested (Blein et al., 2014). Thus, future pre-clinical work should establish causality and the role of genetic variants so that therapeutic interventions can be appropriately targeted.

This study is the first to demonstrate that antioxidant enzymes in tumor are related to catecholamines and psychological characteristics in ovarian cancer patients. These findings, while not definitive, suggest that psychological state and adrenergic signaling are linked with oxidative stress in ovarian cancer. This may have implications for patient treatments and outcomes. More research is needed to determine the molecular pathways that link psychological state and stress hormones to antioxidant activity.

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Highlights

- Antioxidant enzyme activity was associated with tumor NE and mood in ovarian cancer
- MnSOD activity was positively related to depressed mood and tumor NE
- GPx1 activity was inversely related to fatigue and tumor NE
- GPx1 was positively associated with vigor

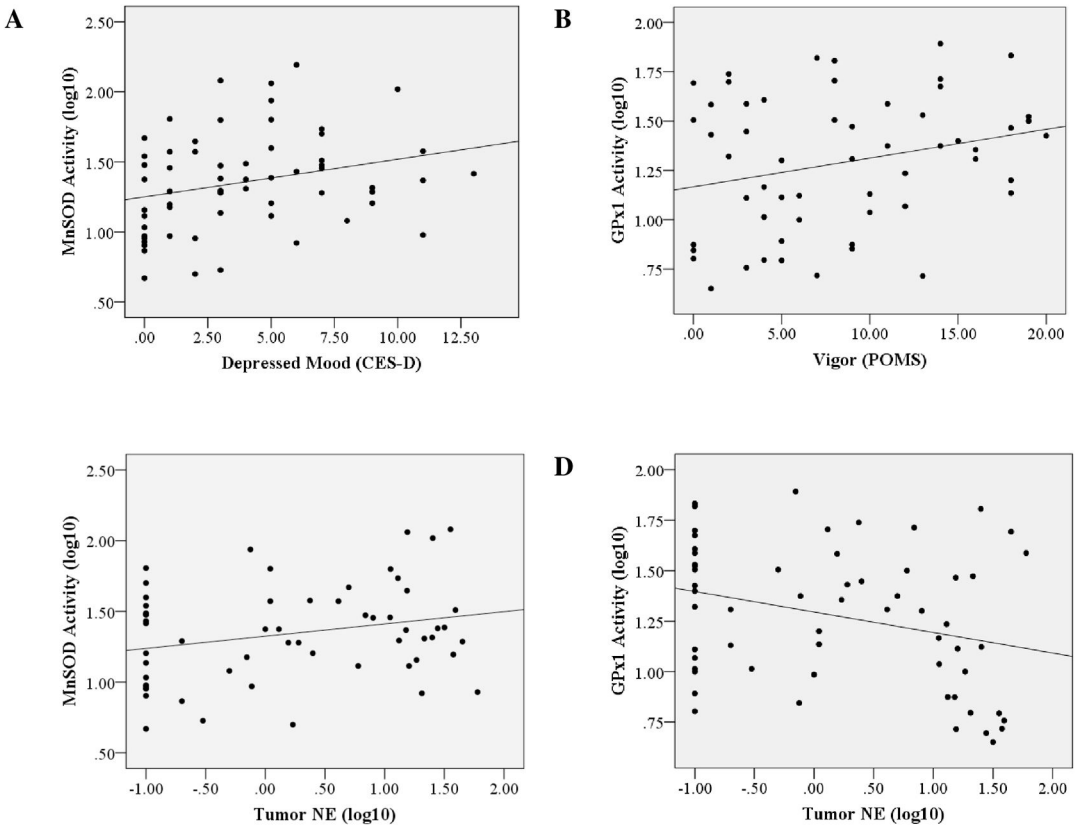

Figure 1.

A: MnSOD was significantly related to depressed mood (CESD: depressed mood subscale), controlling for stage and age (n= 60, R^2 = 0.136, β=0.288, *p*=0.025). B: GPx1 was positively related to feeling energetic and lively (POMS vigor subscale), controlling for stage and age (n=57, R^2 = 0.113, β=0.309, *p* = 0.024). C: MnSOD was positively related to tumor NE (n=59, R^2 = 0.127, β = 0.302, p = 0.023). D: GPx1 was negatively related to tumor NE (n=59, R^2 =.0154, β = −0.344, *p* = 0.009).

Table 1

Participant Characteristics

Characteristic	Ovarian Cancer Patients
Age, years	
Mean (S.D.)	58.9 (11.9)
Ethnicity	
Non-Hispanic	95.0%
Hispanic	5.0%
Race	
American/Indian/Alaska native	1.7%
Asian	1.7%
Pacific Islander	0.0%
Black/African American	0.0%
White	96.6%
Education	
Less than high school graduate	3.4%
High school graduate	37.3%
Trade school/some college	33.9%
College graduate	16.9%
Postgraduate	8.5%
Marital status	
Single/Widowed/Separated/Divorced	26.6%
Married/Living with Partner	73.3%
Stage	
I	11.7%
II	8.3%
III	68.3%
IV	11.7%
Medication use at pre-surgery	
Antidepressants	13.3%
Beta blockers	28.3%
CES-D, Mean (S.D.)	17.3 (9.9)
Depressed mood	4.0 (3.5)
Vegetative symptoms	7.4 (4.0)
Positive mood	7.3 (3.3)
Interpersonal Difficulties	1.6 (1.3)
POMS, Mean (S.D.)	
Fatigue	8.5 (5.8)
Vigor	8.3 (6.0)
Biochemical Markers, Mean (S.D.)	

Characteristic	Ovarian Cancer Patients
NE, (log10)	0.20 (1.00)
Beta-blocker	−0.03 (1.08)
No beta-blocker	0.29 (0.96)
MnSOD, (log10)	1.36 (0.35)
Beta-blocker	1.26 (0.31)
No beta-blocker	1.39 (0.36)
GPx1, (log10)	1.27 (0.34)
Beta-blocker	1.27 (0.31)
No beta-blocker	1.27 (0.36)