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Biochemical relationship between leiomyosarcoma and peroxiredoxin-6 expression level: Clinical implications

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Uterine leiomyosarcomas are tumors with a heterogeneous genetic profiles that respond very poorly to cytotoxic chemotherapy with aggressive progression. We aimed to show the status of peroxiredoxin 6 as a biomarker in leiomyosarcoma progression.Study included 12 patients diagnosed with "leiomyosarcoma" and 13 patients diagnosed with "myoma" (as control) after histopathological examinations of clinical samples. Peroxiredoxin-6 gene expression and protein levels were evaluated on the tumor preparations (blocks) utilizing ELISA and PCR methods.Peroxiredoxin-6 protein was mainly localized in the cytoplasm of leiomyosarcoma cells, and the expression of peroxiredoxin-6 was significantly increased in cancerous tissues compared to normal myoma tissues (3.33±1.7 *vs*. 2.03±1.07fold change; *P*= 0.031). Peroxiredoxin-6 tissue protein levels were also significantly higher in leiomyosarcoma cases (100.54±66.86 *vs*. 183.72±64.54 pg/µg protein; *P*= 0.005). Our findings demonstrate that peroxiredoxin-6 plays a vital role in the emergence and development of leiomyosarcoma and that peroxiredoxin-6 level assessments can be used as a biomarker in guiding better prognosis andtreatment plans while managing leiomyosarcoma.

Keywords: Biomarker, Clinical relevance, Histopathology, Leomyosarcoma, Myoma, Peroxiredoxin-6, Prognosis

Uterine leiomyosarcomas (uLMSs) are rare aggressive tumors that account for approximately 1% of female genital neoplasms[1]. uLMS show a heterogeneous genetic profile and respond very poorly to cytotoxic chemotherapy with aggressive progression[2,3]. Although clinical results have been reported with several drugs in the advanced stages of the disease, the role of postoperative adjuvant therapy to reduce the risk of recurrence in uLMS is rather controversial. This situation has necessited for newer searches in the early diagnosis and treatment of uLMS. Antioxidant therapy, which is one of the most recent research approaches on malignancy, draws attention and the mechanism of its effect on the disease prognosis is still being explored.

A number of reactive oxygen species (ROS), including hydrogen peroxide, hydroxyl radical, superoxide radical, and oxygen, have been shown to play important roles in signal transduction messengers that are associated with cellular transformation, inflammation, and tumor survival[4,5]. There are excessive accumulation of ROS in tumor cells compared to normal cells, which play triggering role(s) in the initiation and progression of neoplastic changes, and may result in resistance to radiotherapy and chemotherapy[6]. The increase in ROS in cells has been shown to be suppressed by various antioxidant systems, including peroxiredoxins (PRDXs)/ thioredoxin (Trx), and glutathione peroxidase (GPx)/ glutathione (GSH)[7]. PRDXs breaks-down hydrogen peroxide in the cell. They are involved in ROS signaling, regulation of cell proliferation, differentiation and apoptosis. PRDX3, which has been reported to play important roles in the antioxidant defence system, also destroys a significant part (90%) of H_2O_2 formed in mitochondria[4]. p53 protein functions as a tumor suppressor, which keeps the growth and proliferation of cells under control. Tumor protein (TP53) mutation is seen in >50% of cancer types. Changes in TP53 have previously been associated with uLMSs and have been suggested to play role(s)in the pathogenesis of uLMS[2,3]. It is known that the mutations in TP53 change the protein structure of p53, inhibit its tumor suppressor function, and results in longer half-life of tumors[2,3].

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PRDXs may choose two different pathways as oncogene or tumor suppressor in cancer development[8]. The importance of these genes in the prognosis of malignant tumors is still complex and contradictory in many ways[9-11]. Recent studies show that PRDX6 is a predictive biomarker for the prognosis of patients with malignant tumors; however, there is no consensus on the results. Isohookana *et al.*[12] reported that decreased PRDX6 expression was associated with a relatively lower survival in patients with larger pancreatic adenocarcinoma tumor size. However, increased expression of PRDX6 was detected in lung cancer development through the Janus kinase 2 (JAK2)/ signal transducer and activator of transcription 3 (STAT3) pathway, glutathione peroxidise (GPx),and independent phospholipase A2 (iPLA2) activities of PRDX6[13,14].

Herein, we aimed to evaluate the status of PRDX6 as a potential biomarker for predicting uLMS progression, thereby adding new information for improved diagnosis and treatment plans.

Materials and Methods

Patients and Specimens

The present study included 12 patients whose clinical samples were diagnosed as "leiomyosarcoma" after histopathological examination and 13 patients diagnosed with "myoma" (served as control) in our tertiary care hospital between the years 2010 and 2020. Detailed pathology reports and clinical information of the cases were obtained through archive scanning. As a result of the information obtained, it was seen that the patients routinely underwent either myomectomy or hysterectomy and bilateral salpingo-oophorectomy, as well as pelvic and/or para-aortic lymphadenectomy procedures, according to the standard protocol and the results thus obtained from the frozen examination. Tumor cell necrosis, cellularity, atypia and mitotic index findings of each patient diagnosed with LMS were examined and staging was performed using the 2009 International Federation of Gynecology and Obstetrics (FIGO) classification system[15]. Tumor preparations of the cases from the pathology archives were re-evaluated and chondoadherin gene expression and protein levels were assessed with appropriate blocks utilizing polymerase chain reaction (PCR) and enzyme-linked immunosorbent assay (ELISA) methods, respectively.

Ethics

The study was carried out in accordance with the Declaration of Helsinki and the guidelines approved by the Zeynep Kamil Women's and Children's Diseases Training and Research Hospital Ethics Committee. All patients consented for treatment according to the institutional guidelines with informed consent, and all patients consented for anonymous evaluation and analysis of data and treatment outcomes.

Gene Expression of Peroxiredoxin-6 by qRT-PCR

From each paraffin block, five tissue sections (each 10 μM thick) were collected into 1.5 mL microfuge tubes. RNA isolation from tissues were determined in duplicate through the use of a commercially available formalin-fixed paraffin-embedded (FFPE) RNA isolation kit (Invitrogen™; Waltham, MA, USA; Catalogue Number K156002). A total of 1 μg RNA was reverse transcribed using High Capacity cDNA Reverse Transcription Kit (Applied Biosystems®, Foster City, CA, USA) following the manufacturer's protocols. Ready-to-order primers (NM004905 for Peroxiredoxin-6, KiCqstart, Sigma-Aldrich, St. Louis, MO, USA) were used for amplification. One-hundred nanograms of cDNA was amplified using SYBRGreen PCR Master Mix (Applied Biosystems®, Foster City, CA USA) on the ABI StepOnePlus™ detection system (Applied Biosystems®, Foster City, CA, USA), programmed for 95°C for 10 min, then 40 cycles of: 95°C for 15 sec, and 60°C for 1 min. The results were analyzed using StepOne Software v2.3 (Applied Biosystems™, Foster City, CA), and normalized to the corresponding GAPDH (glyceraldehyde-3-phosphate dehydrogenase) results. Data were expressed as fold induction relative to the control values.

Peroxiredoxin-6 Protein Levels Determination by ELISA

Four FFPE tissue sections (each 10-15 μM thick) were collected into a 1.5 mL centrifuge tube. Samples were incubated with 250 μL buffer (pH 7.5, 0.05 M Tris, 1 mM EDTA, and 0.5% Tween 20). Protein extraction of all samples were performed as previously described[16]. Protein concentrations were measured with Bradford's method[17]. Peroxiredoxin-6 levels were measured with the sandwich-ELISA in accordance with the manufacturer's protocols (Fine Test®, Bayrakli/Izmir, Turkey; Catalogue Number EH1911) with inter-assay coefficient of variation (cv): <12% and intra-assay cv: <10%, respectively. The mean minimum detectable quantity of human peroxiredoxin-6 was 9.375 pg/mL. Peroxiredoxin-6 values presented as pg/μg protein. All ELISA measurements were performed at least in duplicate using a microplate reader (BioTek Epoch, Winooski, VT, USA). Results are provided as milliliter per milligram (mL/mg) of protein.

Histopathologic Evaluations

After fixation, samples were embedded in paraffin blocks and cut into 5 μM thick sections using a Leica RM2125RTS microtome device (Leica Biosystems, Nussloch, Germany). Selected paraffin sections were stained with hematoxylin and eosin (H&E) staining for morphological evaluation. All slides were examined under a light microscope (Olympus BX-51, Olympus, Tokyo, Japan).

Statistical Analyses

Data are shown as the means±standard error (SE) from at least three independent experiments. One-way analysis of variance (ANOVA) was applied to evaluate the differences among the multiple groups. Student's *t*-test was used to perform the statistical comparisons between two groups. If the variances were homogeneous, two groups were compared using the least significance difference (LSD) method. Otherwise, Dunnett's T3 method was included to analyze non-homogeneous variances between two groups. All statistical tests were two-sided, and $P< 0.05$ (*) and $P< 0.01$ (**) were considered statistically "significant" and "highly significant", respectively. All analyses were performed using SPSS version 18.0 software program.

Results

According to the FIGO classification, four patients diagnosed with LMS were stage 1a, six patients were stage 1b, one patient was stage 2a, and one patient was stage 2b. The mean age of patients with LMS was 54.3±8.9 years (range: 42-71).

Peroxiredoxin-6 protein was mainly localized in the cytoplasm of leiomyosarcoma cells, and the expression of peroxiredoxin-6 was significantly increased in cancerous tissues compared to normal myoma tissues (3.33±1.7 vs. 2.03±1.07fold change; $P= 0.031$) (Table 1) (Fig. 1A). Peroxiredoxin-6 tissue protein levels were also significantly higher in leiomyosarcoma cases (100.54±66.86 pg/μg vs. 183.72±64.54 pg/μg; $P= 0.005$) (Fig. 1B).

In the correlation analysis, a positive correlation was observed between PRDX6 protein expression and PRDX6 protein expression (r= 0.662, $P< 0.001$) (Table 2).

As shown in Table 3, there was no significant correlation between PRDX protein expression and hemoglobin, while a negative correlation was observed between PRDX6 gene expression and hemoglobin (r= −0.339, $P= 0.049$). A negative correlation was seen between PRDX6 protein expression and mean corpuscular hemoglobin (r=-0.434, $P= 0.015$). A positive correlation was seen between PRDX6 gene expression and red cell distribution width (r= 0.432, $P= 0.016$). A positive correlation was observed between

Table 1 — Tissue PRDX6 gene expression and protein levels in patients with LMS

Biomarker	Group	N	Mean±SE	*P*-Value
PRDX6/GAPDH	Control	13	2.03±1.07	0.031
	LMS	12	3.33±1.70	
PRDX6 (pg/μg protein)	Control	13	100.54±66.86	0.005
	LMS	12	183.72±64.54	

SE: Standard error, PRDX6: Peroxiredoxin-6, GAPDH: Glyceraldehyde-3-Phosphate Dehydrogenase, LMS: Leiomyosarcoma.

Statistically significant values are in bold

Table 2 — Correlation between PRDX6 gene expression and protein levels in patients with LMS

Spearman's correlation test		PRDX6
PRDX6/GAPDH	rho	0.662
	p	<0.001

PRDX6: Peroxiredoxin-6, GAPDH: Glyceraldehyde-3-Phosphate Dehydrogenase, LMS: Leiomyosarcoma. Pearson correlation coefficient (r)

Statistically significant values are in bold

Table 3 — Correlation between blood parameters, PRDX6 gene expression, and protein levels in patients with LMS

		PRDX6 (pg/μg protein)	PRDX6/ GAPDH
Tumor size	rho	0.105	0.370
	p	0.309	0.034
Grade	rho	-0.081	0.190
	p	0.351	0.181
LVSI	rho	0.136	0.114
	p	0.258	0.294
Mitose	rho	0.334	0.529
	p	0.051	0.003
A type	rho	-0.091	0.234
	p	0.333	0.130
Necrose	rho	0.065	0.442
	p	0.379	0.014
Hb	rho	0.070	-0.339
	p	0.369	0.049
MCH	rho	-0.434	-0.219
	p	0.015	0.147
RDW	rho	0.136	0.432
	p	0.258	0.016
MPV	rho	0.071	0.359
	p	0.369	0.039

Pearson correlation coefficient (r), PRDX6: Peroxiredoxin-6, GAPDH: Glyceraldehyde-3-Phosphate Dehydrogenase, LMS: Leiomyosarcoma, LVSI: Lymphovascular Space Invasion, Hb: hemoglobin, MCH: Mean corpuscular hemoglobin, RDW: Red cell distribution width, MPV: Mean platelet volume.

Statistically significant values are in bold

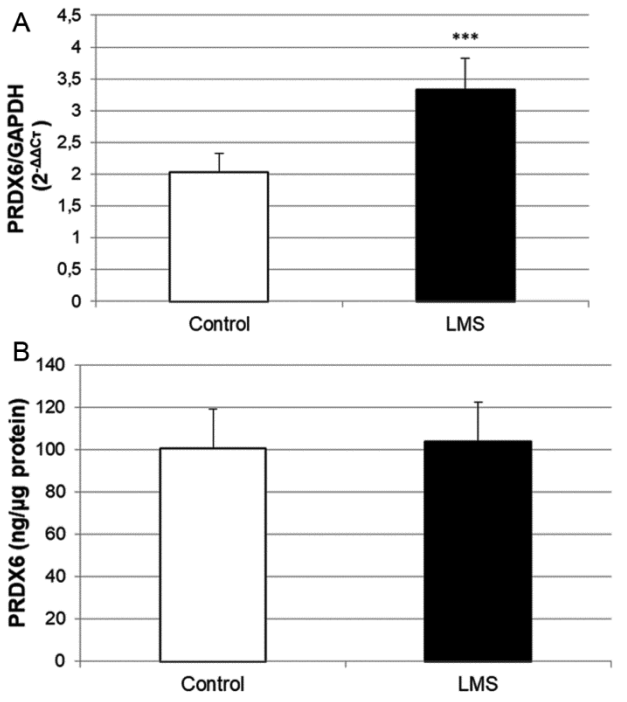

Fig. 1 — Graph of mean (A) protein level; and (B) PRDX6 gene expression values between leiomyosarcoma patients and the control (myoma) group. PRDX6: peroxiredoxin; GAPDH: glyceraldehyde-3-phosphate dehydrogenase; LMS:Leiomyosarcoma

PRDX6 gene expression and mean platelet volume (r=0.359, *P*= 0.039) (Table 3).

There was a positive correlation between PRDX6 gene expression and tumor size (r= 0.370, *P*= 0.034). Also, there was a positive correlation between PRDX6 gene expression and mitose (r= 0.529, *P*= 0.003). A positive correlation (r= 0.442, *P*= 0.014) was also found between PRDX6 gene expression and necrose (Table 3).

Discussion

It has been observed that PRDX6 is highly expressed in various cancer cells such as lung, ovarian, tongue, and breast cancers[14,18]. Studies have associated the over expression of PRDX6 in carcinomas with cancer cell proliferation and aggressive progression[19,20]. In the present study, we found that PRDX6 protein level and gene expression increased in uLMS, which is one of the aggressive cancer types, compared to myoma tissue. To the best of our knowledge,the present study is first attempt to examine the relationship between PRDX6 and uLMS overexpression.

PRDXs is a highly sensitive and specific biomarker for metastatic cancers, which catalyzes peroxide reduction and form the antioxidant mechanism[21,22]. Many cytotoxic regimens are recommended in uLMS, and generally doxorubicin, ifosfamide, gemcitabine, docetaxel, trabectedin, dacarbazine, and pazopanib are used as single agents or in combination therapy[23]. The response with chemotherapy varies between 10% and 50%, but the effect of these treatments on the prognosis of the disease is insufficient[23]. Many studies have shown that PRDXs are associated with chemotherapy drug resistance of cancers. For example, over expression of PRDX6 was found to decrease ROS levels in SKOV-3 ovarian cancer cells, attenuate cisplatin-induced apoptosis, and increase cisplatin resistance[24]. Another study showed that increased expression of PRDX3, PRDX5, and PRDX6 could lead to chemotherapy resistance in ovarian cancer, and therapeutic strategies targeting these molecules could be an effective new treatment modality for ovarian cancer[25]. The fact that we found PRDX6 protein level to be significantly higher in LMS compared to normal myoma tissue in the present study confirms the findings of other studies.

Although apoptosis is a fundamental process during embryogenesis, it has an important role in cellular hemostasis[26]. The formation and development of neoplasia is associated with apoptosis[26]. Decrease in PRDX6 expression increases susceptibility to oxidative stress[27]. It has been shown that over expression of PRDX6 significantly suppresses cisplatin-induced apoptosis in ovarian cancer cells[24,28]. It has been shown that the expression of PRDX6 plays a role in the progression of neoplasms such as lung, thyroid, and colorectal cancers[29-31]. Chang *et al*.[32] found that increased PRDX6 expression stimulated the invasive phenotype of metastatic breast carcinoma. An increase in the expression level of PRDX6 has been shown in cervical squamous cell carcinoma tissues compared to normal cervical tissue[33,34]. In recent studies, the authors recommended the use of PRDX6 inhibitor such as MJ33 [1-hexadecyl-3-(trifluoroethyl)-snglycero2-phospho-methanol] to prevent and control the development of PRDX6[34].

Conclusion

In patients with rapidly growing uterine fibroids or in postmenopausal women with growing uterine fibroids, underlying malignancies of the uterus are often suspected in clinical practice. Based on our finding, it can be suggested that the PRDX6 expression level may be useful for excluding the diagnosis of fibroids and uLMS tissues. It is to be

noted that to the best of our knowledge, currently there are no such studies and/or data supporting this strategy, hence the present study is first attempt in this regard. Indeed, further translational studies would be desirable to explore the potential role of PRDX6 in differential diagnosis of uterine leiomyosarcomas.

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Conflict of interest

All authors declare no conflict of interests.

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