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Expression and function of peroxiredoxins in gynecological malignancies

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1. ABSTRACT

A large family of peroxiredoxin proteins plays essential roles in the regulation of multiple redox-sensitive cellular activities related to cell signaling, cell proliferation and apoptosis. The involvement of these proteins in protecting cells from oxidative damage, induced by reactive oxygen species, points to their potential role in human cancers. According to some studies, the peroxiredoxin proteins in gynecological malignancies, promote tumors development and progression, whereas others indicate that peroxiredoxin proteins function as onco-suppressors in these cancers. Here, we review the utilization of peroxiredoxin proteins as novel biomarkers for screening and early diagnosis of gynecological malignancies, and as the specific therapy targets and prognostic factors as well.

2. INTRODUCTION

Peroxiredoxins, a large family of proteins, were initially identified as thiol-specific antioxidant enzymes, which can protect cells from oxidative damage induced by reactive oxygen species (ROS) produced in the presence of dithiothreitol (1-4). They are found in a wide range of species ranging from protozoa to mammals (5, 6). Six Peroxiredoxin isoforms have been reported in human, namely, peroxiredoxin 1, 2, 3, 4, 5, 6 (7). Peroxiredoxin proteins share a common reactive Cys residue in the N-terminal region, and are capable of breaking down H_2O_2 as a peroxidase and involve thioredoxin and/or glutathione as the electron donor (9, 10). Besides serving a general protective role for the cell, peroxiredoxin proteins also play crucial role in a wide variety of redox-sensitive

cellular activities, such as the regulation of cell signaling, cell proliferation and apoptosis (11-13).

Over the past several years, there are accumulated evidences that peroxiredoxin proteins may play dichotomous role in human carcinogenesis, where they can exhibit strong tumor-promoting or tumor-suppressive functions. Many investigations have suggested that peroxiredoxin proteins were up-regulated in several cancers, which included increased expression of peroxiredoxin 4 in colorectal neoplasms (14) and prostate cancer (15), elevated peroxiredoxin 3 in prostate cancer (15) and malignant mesothelioma (16) and up-regulated peroxiredoxin 5 in malignant mesothelioma (16). With regard to peroxiredoxin 2, several studies showed that peroxiredoxin 2 overexpressed in malignant mesothelioma (16) and castration-resistant prostate cancer (17), while lower expression of peroxiredoxin 2 was reported to correlate with poor prognosis of colorectal cancer (18). As for peroxiredoxin 1 and 6, researchers found that they might be involved in the pathogenesis of numerous human cancers, colorectal adenocarcinoma (19), malignant mesothelioma (16), esophageal carcinoma (20, 21), and follicular adenomas (22), as either oncogenes or onco-suppressors. Therefore, the involvement of peroxiredoxin proteins in tumor development is complex and far from being clarified. The issue of possible contribution of peroxiredoxin proteins to carcinogenesis has gradually attracted the attention of basic and clinical researchers.

To date, there appears to be contradictory data describing a supporting or a possibly inhibitory role for peroxiredoxin proteins in gynecological cancers (23-25). Thus, in this review, we will focus our discussion on the role of peroxiredoxin proteins family in gynecological cancers development and progression. The possible utilization of peroxiredoxin proteins as novel biomarkers of gynecological cancers for cancers screening and early diagnosis is also reviewed. In addition, peroxiredoxin proteins are proposed to be used as prognostic factors and as specific targets in the treatment of gynecological cancers.

3. THE ROLE OF PEROXIREDOXINS IN CERVICAL CANCER

3.1. The change of peroxiredoxins in cervical carcinogenesis

3.1.1. The change of peroxiredoxin 2 in the cervical carcinogenesis

Kim *et al.* (26) reported that peroxiredoxin 2 was clearly over-expressed in most cervical cancer tissues compared with normal tissues by immunoblotting. In addition, peroxiredoxin 2 was also found to be highly expressed in high-grade cervical intraepithelial neoplasia and cervical cancer, while undetectable or weakly expressed in normal and low-grade cervical intraepithelial neoplasia. These data indicate that peroxiredoxin 2 is up-regulated during the cervical cancer carcinogenesis.

3.1.2. The change of peroxiredoxin 3 in the cervical carcinogenesis

Li *et al.* (27) showed that the apoptotic percentage was significantly higher in cervical cancer cells with peroxiredoxin 3-knockdown than that without peroxiredoxin 3-knockdown. Additionally, they then confirmed that the ROS level was significantly increased in peroxiredoxin 3 down-regulated cancer cells, in comparison with control cancer cells. These findings suggest that peroxiredoxin 3 is an indispensable ROS scavenger, which protects cervical cancer cells against oxidation-induced apoptosis.

Kim *et al.* (26) showed that peroxiredoxin 3 was highly expressed in high-grade cervical intraepithelial neoplasia and cervical cancer, whereas undetectable or weakly expressed in normal and low-grade cervical intraepithelial neoplasia. Recently, Hu *et al.* (28) also confirmed that the number of positive cells for peroxiredoxin 3 in invasive squamous cervical cancer areas was significantly higher as compared to that in non-cancerous areas. They further found that the positive cells for peroxiredoxin 3 in cervical cancer were correlated with the expression of human papilloma virus (HPV) 16 E6/E7.

Safaeian *et al.* (29) investigated 18,310 tag single nucleotide polymorphisms (SNPs) from 1113 genes in 416 cervical intraepithelial neoplasia 3 (CIN3)/cancer cases, 356 women with persistent carcinogenic HPV infection and 425 randomly selected cases without HPV infection or HPV persistent infection. They found that peroxiredoxin 3 rs7082598, the SNP in peroxiredoxin 3 gene, was associated with significant decreased risk of cervical cancer compared to controls, which was observed for both progression (CIN3/cancer compared to HPV-persistence) and HPV-persistence (persistence compared to non-persistence). This finding suggests an involvement of SNP in peroxiredoxin 3 in cervical carcinogenesis.

3.2. The relationship of peroxiredoxins with the clinicopathological feature of cervical cancer

Hu *et al.* (28) investigated 68 patients with invasive squamous cervical cancer, including 30 in the International Federation of Gynecology and Obstetrics (FIGO) stage I and 38 in stage II and found that the expression of peroxiredoxin 3 was significantly negatively associated with cell differentiation (grade).

3.3. The role of peroxiredoxins in the diagnosis of cervical cancer

In a study of immunohistochemistry-based analysis of several marker proteins during squamous cell cervical carcinogenesis, Lomnytska *et al.* (30) found

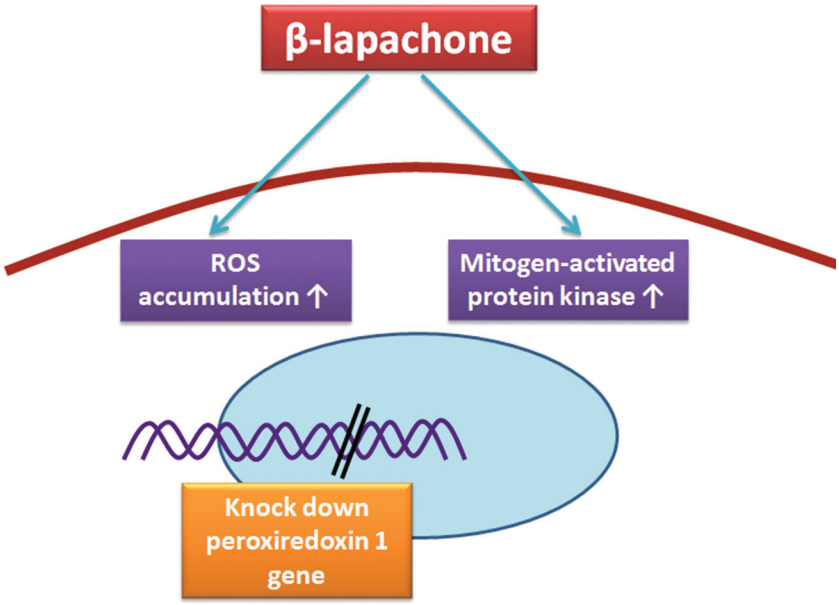

Figure 1. HeLa cell with peroxiredoxin 1 knockdown in response to β-lapachone. When the HeLa cell is knocked down of peroxiredoxin 1, both the accumulation of reactive oxygen species (ROS) and the activation of facilitated mitogen-activated protein kinase are increased, resulting in an increased response to β-lapachone.

that the expression of peroxiredoxin 2 in the cytoplasm of dysplastic cells increased from cervical intraepithelial neoplasia 2/3 to microinvasive cancer. However, expression of peroxiredoxin 2 in microinvasive cancer was similar to that in squamous cervical epithelial, which was higher than in invasive squamous cell cervical cancer. In addition, invasive squamous cell cervical cancer with the highest sensitivity and specificity differed from normal epithelium and from microinvasive squamous cell cervical cancer by the expression of peroxiredoxin 2 in the cytoplasm. These findings indicate that detection of expression changes of peroxiredoxin 2 in squamous cell cervical cancer precursor lesions may aid current cytological and pathological diagnosis.

3.4. Therapeutic potential of peroxiredoxins in cervical cancer

3.4.1. Therapeutic potential of peroxiredoxin 1 in cervical cancer

In our previous study (31), we investigated paired samples of early-stage bulky squamous cervical cancer before and after cisplatin-based neoadjuvant chemotherapy from a total of 16 patients (9 with the International Federation of Gynecology and Obstetrics stage IB and 7 with stage IIA) who responded to neoadjuvant chemotherapy. We found that 16 proteins were down-regulated and 15 proteins including peroxiredoxin 1 were up-regulated after neoadjuvant chemotherapy relative to the level before neoadjuvant chemotherapy by 2-dimensional gel electrophoresis and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry. Then, through western blot and immunohistochemistry, we also confirmed that the expression of peroxiredoxin 1 was statistically higher after neoadjuvant chemotherapy as compared with that before chemotherapy, suggesting that peroxiredoxin 1 may play a role in neoadjuvant chemotherapy.

He *et al.* (32) found that HeLa cell line with the peroxiredoxin 1 gene stably knockedown (peroxiredoxin 1-) exhibited increased sensitivity to β-lapachone, but not the other three ROS-generating agents as compared with a corresponding control cell line (peroxiredoxin 1+). Then β-lapachone was also reported to induce more death in peroxiredoxin 1−cells than peroxiredoxin 1+ cells. Additionally, they demonstrated that knockdown of peroxiredoxin 1 increased ROS accumulation and facilitated mitogen-activated protein kinase activation significantly in response to β-lapachone, suggesting that peroxiredoxin 1 knockdown may enhance the cytotoxicity of β-lapachone through modulating ROS accumulation and mitogen-activated protein kinase activation (Figure 1).

3.4.2. Therapeutic potential of peroxiredoxin 2 in cervical cancer

Lee *et al.* (33) found that HeLa cervical cancer cells stably transfected with a vector encoding a dominant negative mutant (DN) form of peroxiredoxin 2, which were shown to act as DN cells for cytosolic 2-cys peroxiredoxin, resulted in the additional increase of intracellular reactive oxygen species level and apoptotic cell death induced by combined treatment of tumor necrosis factor-alpha and cycloheximide when compared

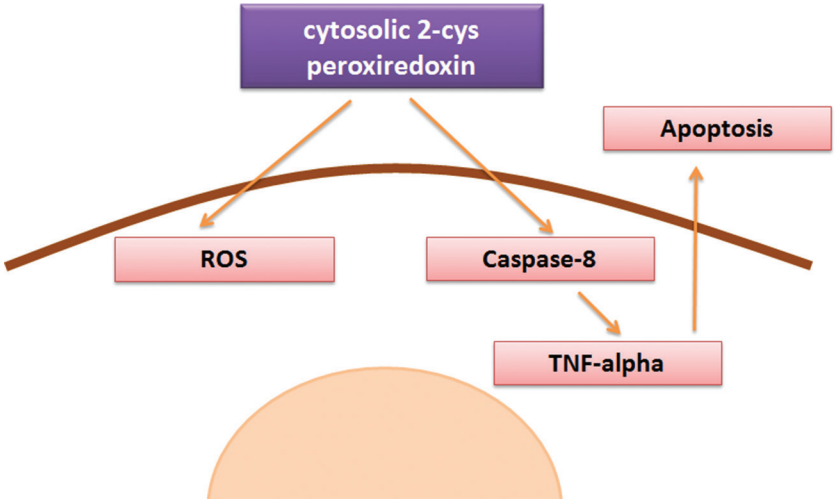

Figure 2. The cytosolic 2-cys peroxiredoxin in HeLa cell. In HeLa cell, cytosolic 2-cys peroxiredoxin regulated intracellular reactive oxygen species (ROS), and induce apoptosis by TNF-alpha in a caspase-8-dependent manner.

to HeLa cells transfected with control vector. The results showed that cytosolic 2-cys peroxiredoxin regulated intracellular reactive oxygen species, played a crucial role in the TNF-alpha-induced apoptotic death of HeLa cells in a caspase-8-dependent manner (Figure 2). As cytosolic 2-Cys peroxiredoxin was shown to assume a high molecular weight complex structure that has a highly efficient chaperone function when exposure to oxidative stress, Moon *et al.* (34) demonstrated that HeLa cells overexpressing native human 2-Cys peroxiredoxin showed obvious resistance to H_2O_2-induced cell death, whereas HeLa cells transfected with or without the empty vector were sensitive to H_2O_2-exposure. This result suggests that cytosolic isotype of human 2-Cys peroxiredoxin can protects HeLa cells from H_2O_2-induced cell death.

Yue *et al.* (35) found that five purified ganoderic acids including ganoderic acid F, ganoderic acid K, ganoderic B, ganoderic acid D and ganoderic acid AM1, can inhibited the proliferation of HeLa cells. By using proteomic method, they then demonstrated that peroxiredoxin 2 in HeLa cells decreased after treatment of these five ganoderic acids, suggesting peroxiredoxin 2 may contribute to the cytotoxicity of ganoderic acids and be target-related proteins of ganoderic acids.

4. THE ROLE OF PEROXIREDOXINS IN BREAST CANCER

4.1. The change of peroxiredoxins during breast carcinogenesis

4.1.1. The change of peroxiredoxin2 during breast carcinogenesis

Using a high-throughput proteomic analysis, Somiari *et al.* (23) showed that peroxiredoxin 2 displayed lower abundance in the entire four poorly differentiated human breast infiltrating ductal carcinomas, in relation to non-neoplastic mammary tissue. However, many reports showed the higher expression of peroxiredoxin 2 in breast cancer tissues. In a study of Chinese, Malay and Indian patients with infiltrating ductal breast carcinoma in Malaysia, Liang *et al.* (36) reported that the expression levels of peroxiredoxin 2 was significantly higher in the breast cancerous tissues compared to the normal breast tissues in 78%, 88% and 83%, 50% of all, Chinese, Malay and Indian patients, respectively. These data indicate that peroxiredoxin 2 may have a significant role in the development of infiltrating ductal breast carcinoma and could be an ethnic-related potential marker for Chinese and Malay patients. Cha *et al.* (24) found that peroxiredoxin 2 over-expressed in human breast carcinoma in comparison to normal breast tissues, which was consistent with the results found in the study of Noh *et al.* (37).

In vitro, Tehan *et al.* (38) compared mRNA and protein expression of peroxiredoxin 2 gene in the MCF-7 breast cancer cell line with that in the noncancerous MCF-10A cell line and found that MCF-7 cell line exhibited significantly up-regulated peroxiredoxin 2 mRNA and protein level, as compared to MCF-10A cell.

4.1.2. The change of other peroxiredoxin isoforms during breast carcinogenesis

Goncalves *et al.* (39) demonstrated an increased expression of peroxiredoxin 1 in the MCF-7 mammary adenocarcinoma cell line compared to that in noncancerous MCF-10A cell, which was supported by Bae *et al.* (40). Cha *et al.* (24) examined peroxiredoxin 1 expression in 204 samples of breast cancer tissues and normal tissues and found that peroxiredoxin 1 was expressed at a significantly higher level in human breast carcinoma in relation to normal counterparts.

Noh *et al.* (37) conducted a study of 24 patients with breast cancer and found that peroxiredoxin 3 was up-regulated in the cancer tissues of 19 patients (79.2%), as compared to matched normal mammary tissues. In a study of 106 cases of archival invasive ductal breast cancer sections, Chua *et al.* (41) reported that highly invasive MDA-MB-231 breast cancer cells transfected with si- peroxiredoxin 3 exhibited decreased cell proliferation as compared with vector treated cells. Additionally, down-regulation of the peroxiredoxin 3 was also found to increase the percentages of cells in sub-G1 and G1 phases and decrease the percentages of cells in the S and G2/M phases, which indicated that peroxiredoxin 3 might play an essential role in cell cycle regulation and serve as a potential proliferation marker in breast cancer.

Tehan *et al.* (38) found that MCF-7 cell line exhibited significantly up-regulated peroxiredoxin 4 and peroxiredoxin 5 mRNA and protein expression, as compared to MCF-10A cell. As to peroxiredoxin 6, mRNA level of which slightly increased in the cancer cells and its protein levels were similar between the two cell types, which was supported by Goncalves *et al.* (39). *In vivo*, Karihtala *et al.* (42) also found that peroxiredoxin 4 and peroxiredoxin 5 showed higher levels in carcinomatous breast tissues, especially in progesterone receptor positive cases, when compared with those of nonmalignant tissues.

4.2. The relationship of peroxiredoxins with the clinicopathological feature of breast cancer

Cha *et al.* (24) measured peroxiredoxin 1 mRNA in normal and malignant breast tissues ranging from 0 to IV grade and demonstrated that the expression level of peroxiredoxin 1 was associated with tumor grade. Contrarily, in a study of a tissue microarray of 224 patients with primary invasive early stage breast cancer, Woolston *et al.* (43) found that peroxiredoxin 1 was not correlated with tumor grade. Karihtala *et al.* (42) also reported that peroxiredoxin 1 did not have significant association with any clinicopathological parameters such as tumor size, the presence of lymph node metastases, or tumor grade, supported by Noh *et al.* (37).

In the study by Karihtala *et al.* (42), moderate expression of peroxiredoxin 2 was reported to be related to poorly differentiated breast cancer, although not significantly. However, peroxiredoxin 2 showed no statistical association with other clinicopathological features, such as tumor size, or the presence of either lymph node or other metastases. Conversely, several studies reported association between peroxiredoxin 2 and lung metastases. España *et al.* (44) examined tumors, metastases in lymph node, lung, and bone, and bloodstream surviving cells by a metastasis model in which MDA-MB 435 breast cancer cells were transfected with the anti-apoptotic gene Bcl-xL(435/Bcl-xL tumor cells). Twelve proteins including peroxiredoxin 2 were significantly over-expressed in 435/Bcl-xL lung metastasis with regard to the 435/Bcl-xL tumor, but not in lymph node metastasis. Then, in other study (45), they also found that levels of peroxiredoxin 2 expression in lung metastatic variants of MDA-MB-435 cells (435-L2, 435-L3 and 435-L2/5) was higher than in parental cells (435-P) and lymph node (435-N) or bone (435-B) metastatic variants. Additionally, peroxiredoxin 2 knockdown was shown to inhibit the growth of 435-L3 cells in the lungs, whereas lymph node metastasis remained unaffected. These findings indicate that peroxiredoxin 2 is a putative marker involved in the selective growth of metastatic breast cancer cells in the lungs.

Noh *et al.* (37) showed that there was no significant association between peroxiredoxin 3 over-expression and clinicopathological parameters of breast cancer such as tumor size, lymphatic invasiveness and tumor grade. By contrast, in a study of 79 women with local or locally advanced breast cancer, Karihtala *et al.* (46) found that nuclear peroxiredoxin 3 expression was over-expressed within the T1 tumor population and in grade I-II disease, which suggested that peroxiredoxin 3 was related to less aggressive breast cancer characteristics. España *et al.* (44) also reported that peroxiredoxin 3 was significantly over-expressed in 435/Bcl-xL lung and lymph node metastasis as compared to the parental 435/Bcl-xL tumor, indicating that peroxiredoxin 3 may play a potential role in protecting phenotypes mediated by Bcl-xL in breast cancer cells during transit from the primary tumor to the metastatic state.

Woolston *et al.* (43) found that cytoplasmic expression of peroxiredoxin 5 was associated with grade of breast cancer. Karihtala *et al.* (42) also demonstrated that peroxiredoxin 5 was connected to a larger tumor size, positive lymph node status and lower differentiation of breast cancer. Furthermore, they reported that peroxiredoxin 4 showed significantly increased expression in poorly differentiated breast cancer.

Li *et al.* (47) showed that peroxiredoxin 6 was up-regulated in the highly metastatic variant of human MDA-MB-435 breast cancer cell line as comparison with its parental counterparts by comparative proteomic analysis. Additionally, they revealed that expression of peroxiredoxin 6 was significantly associated with the presence of lymph node metastasis in breast cancer patients, indicating that peroxiredoxin 6 may play a role in breast cancer metastasis. In their other study (48), similar results were found in cases of high metastatic MDA-MB-231 breast cancer cells. They also demonstrated that overexpression of peroxiredoxin 6 enhanced the proliferation and invasion of breast cancer MDA-MB-231 and MDA-MB-435 cells, which were further confirmed by RNA interference experiments *in vitro*. Similarly, an *in vivo* assay showed that peroxiredoxin

6-transfected MDA-MB-231 and MDA-MB-435 cells grew faster and had more pulmonary metastases than their control counterparts, verified by knockdown experiments as well. It has been suggested that peroxiredoxin 6 expression may contribute to a more invasive phenotype and metastatic potential in human breast cancer.

4.3. Peroxiredoxins as biomarkers for early diagnosis of breast cancer

In a study of 69 prospective breast cancer patients, Gromov *et al.* (49) showed that a set of 26 proteins including peroxiredoxin 2 were up-regulated in the tumor interstitial fluids as compared to the normal interstitial fluids counterparts by gel-based proteomics in combination with mass spectrometry. They also confirmed that expression of peroxiredoxin 2 was up-regulated in breast cancer tissue when compared with normal/benign tissue by immunohistochemistry based on breast cancer tissue array. These data suggest that peroxiredoxin 2 in the fluid bathing the tumor cell microenvironment may be used as a potential serological marker for early detection of breast cancer. Liu *et al.* (50) also confirmed that 773 proteins including peroxiredoxin 2 and 6 were up-regulated in the serum of breast cancer patients in comparison with the healthy volunteers by screening immunohistochemistry maps of human breast cancer proteins.

4.4. The role of peroxiredoxins in treatment of breast cancer

4.4.1. The role of peroxiredoxins in chemotherapy of breast cancer

Kalinina *et al.* (51) studied the expression of peroxiredoxin 1, 2, 3, 6 in human breast carcinoma MCF-7 cells during cisplatin resistance development and demonstrated a pronounced rise in the expression of peroxiredoxin 1, 2, 3, 6 genes in MCF-7 cells resistant to cisplatin, in comparison with sensitive cells. This result indicates that peroxiredoxin 1, 2, 3, and 6 genes may contribute to the development of cisplatin resistance of breast cancer cells. Using two-dimensional gel electrophoresis, Smith *et al.* (52) investigated protein expression profiles of the MCF-7 breast cancer cell line and a novel derivative MCF-7CR displaying significant resistance to cisplatin. They found 15 differentially expressed proteins including peroxiredoxin 4, which was down-regulated in the MCF-7CR cell line in comparison with the parental MCF-7 cell line and confirmed by western blotting, proposing a potential role for peroxiredoxin 4 as a biomarker to predict response to chemotherapy in breast cancer *in vivo*.

In a study of 44 breast tumor tissues sampled by biopsy before treatment with docetaxel, Iwao-Koizumi *et al.* (53) found that peroxiredoxin 1 gene was up-regulated in nonresponders as compared with responders by gene expression profiling. Then they transfected MCF-7 cells that were sensitive to docetaxel normally with peroxiredoxin 1 gene and demonstrated that peroxiredoxin 1 gene could protect MCF-7 from docetaxel-induced cell death. These findings provide further insights into the complex mechanisms of chemoresistance and represent an attractive starting point for the identification of potential markers to predict the clinical response to docetaxel in breast cancer.

McDonald *et al.* (54) showed higher resistance to doxorubicin-induced toxicity and peroxiredoxin proteins expression in MCF-7 cells in comparison with non-cancer MCF-10A cells. Suppression of four of six of the peroxiredoxin proteins (1, 2, 3, 5) in MCF-7 cells also resulted in increased doxorubicin-induced cell death. They further selected a doxorubicin-resistant MCF-7 subline and demonstrated that expression of peroxiredoxin 2, 3, 4 and 5 elevated after treatment with doxorubicin, supporting the protective role for the peroxiredoxins overexpression in breast cancer cell resistance to doxorubicin.

He *et al.* (55) analyzed proteomic differences in 28 HER2-positive tumors from patients with locally advanced breast cancer collected from a neoadjuvant clinical trial (15 received Taxotere/Carboplatin and 13 received Taxotere/Carboplatin and Herceptin before surgery). They demonstrated that 100% (4/4) nonresponders and 85.7.% (6/7) pathologically complete response were correctly grouped by 20 selected proteins, of which high level of peroxiredoxin 5 was found only in the nonresponders. This result indicates that high levels of peroxiredoxin 5 in HER2-positive breast cancers may be linked to poor response to neoadjuvant therapy and targeting peroxiredoxin 5 may sensitize breast cancers to neoadjuvant therapy.

Liu *et al.* (56) reported that 4-amino-5-(4-chlorophenyl)-7-(t-butyl) pyrazolo (3,4-d) pyrimidine (PP2) could inhibit the proliferation of MCF-7 cells and induced mitochondria-mediated apoptosis. Then they found that peroxiredoxin 3 was down-regulated at the protein and transcription levels after PP2 treatment. Further study by up-regulating and knockdowning of peroxiredoxin 3 supported the crucial role of peroxiredoxin 3 in regulation of PP2-induced apoptosis, which suggested that down-regulation of peroxiredoxin 3 could potentiate PP2-induced apoptosis in MCF-7 cells and it might be target-related protein of PP2.

Lee *et al.* (57) found that the transcript/protein expression of peroxiredoxin 4 in MCF-7 cells was significantly increased after treatment with 16alpha-hydroxyestrone (OHE1). Additionally, peroxiredoxin 4-specific siRNA significantly inhibited the 16alpha- OHE1-induced proliferation of MCF-7 cells, suggesting that peroxiredoxin 4 may play a crucial role in the 16alpha-OHE1-induced proliferation of MCF-7 cells.

4.4.2. The role of peroxiredoxins in radiotherapy of breast cancer

Wang *et al.* (58) identified that expression level of peroxiredoxin 2 was significantly up-regulated in radio-resistant breast cancer cells (MCF+FIR3) compared with that in MCF+FIS4 breast cancer cells, which were relatively sensitive to radiation. Then small interference RNA experiment showed that down-regulation of peroxiredoxin 2 partially reversed the resistant phenotype of MCF+FIR3 cells. Additionally, they demonstrated that ionizing radiation contributed to an increase resistant level in peroxiredoxin 2 over-expressing MCF+FIS4 cells compared to vector-transfected control ones. These data indicated that peroxiredoxin 2 was a potential novel therapeutic target that might be targeted to overcome the increased resistance of breast cancer cells to ionizing radiation. In another study, they further showed that silencing peroxiredoxin 2 gene expression increased cellular toxicity through altering cellular thiol status, inhibiting Ca^{2+} efflux from the cells, and perturbing the intracellular Ca^{2+} homeostasis, rendering MCF+FIR3 cells more sensitive to ionizing radiation (59).

4.5. Prognostic value of peroxiredoxins for breast cancer

Karihtala *et al.* (42) studied 642 breast cancer samples and found that peroxiredoxin 3 and 4 was related to better prognosis, while peroxiredoxin 5 was connected with shorter survival, probably resulting from their connection with a positive hormone receptor status. By contrast, they demonstrated that cytoplasmic peroxiredoxin 3 immunostaining had a nearly significant association with poorer breast cancer-specific survival in another study (46). Woolston *et al.* (43) also found that high cytoplasmic expression of peroxiredoxin 3 and 4, and high nuclear expression of peroxiredoxin 6, approached correlating with a worse prognosis. In addition, they showed that both high cytoplasmic expression of peroxiredoxin 1 alone and the combination (high cytoplasmic/low nuclear) had a greater chance of local recurrence, indicating that peroxiredoxin 1 is independently linked to risk of local recurrence in these early stage breast cancer patients.

5. THE ROLE OF PEROXIREDOXINS IN OVARIAN CANCER

5.1. Effect of peroxiredoxins on ovarian carcinogenesis

Sova *et al.* (25) reported that endometriosis-associated ovarian cancer cells had significantly weaker nuclear peroxiredoxin 2 expression than benign endometriotic epithelial cells. They also found that cytoplasm expression of peroxiredoxin 2 was weaker in cancer cells than in endometriosis epithelial cells in endometriosis-associated ovarian cancer. These results support that peroxiredoxin 2 may play a reversed role in the endometriosis-associated ovarian carcinogenesis.

In an animal model of TOV-112D ovarian endometrioid cancer, Tang *et al.* (60) identified more than 200 human proteins including peroxiredoxin 6 in the mouse serum by a in-depth 4-D protein profiling method. Using label-free multiple reaction monitoring mass spectrometry, they then found that peroxiredoxin 6 was elevated significantly in sera from late-stage ovarian carcinoma patients as compared with normal controls, but not benign ovarian tumors patients, which suggested that peroxiredoxin 6 might has oncogenic potential in ovarian cancer.

5.2. The relationship of peroxiredoxins with the clinicopathological feature of ovarian cancer

In a study of tissues from 22 women with benign endometriosis and 33 women with endometriosis-associated ovarian cancer, Sova *et al.* (25) demonstrated that nuclear peroxiredoxin 6 was overexpressed in low-grade tumors. However, there was no significant difference in expression of peroxiredoxin 2 or peroxiredoxin 6 between patients with different stages of endometriosis-associated ovarian cancer. Wang *et al.* (61) showed no association between peroxiredoxin 3 protein expression and different pathological classifications, histological grades or surgical pathology stages of ovarian cancer.

5.3. Implication of peroxiredoxins in the diagnosis of ovarian cancer

Hoskins *et al.* (62) used proteomic analysis to identify tumor specific proteins from tissue interstitial fluid and ascites from patients with papillary serous epithelial ovarian cancer. They found an aggregate identification of 569 and 171 proteins respectively from tissue interstitial fluid and ascites, among which peroxiredoxin 1 was confirmed to be present in serum and shown by enzyme-linked immunosorbent assay to be increased by nearly 6-fold in 20 patients with stage II or higher epithelial ovarian cancer, as compared to 16 patients with a benign ovarian pathology. These data suggest that peroxiredoxin 1 may be identified as a potential diagnostic biomarker for epithelial ovarian cancer in the future.

5.4. Implication of peroxiredoxins in the treatment of ovarian cancer

Kalinina *et al.* (51) found that there was an appreciable increase of the expression of peroxiredoxin 1, peroxiredoxin 2, peroxiredoxin 3, peroxiredoxin 6 genes in SKOV-3 cells resistant to cisplatin, in comparison with sensitive cells, supporting the important contribution of peroxiredoxin 1, 2, 3, and 6 genes into the development of cisplatin resistance of ovarian cancer cells. Pak *et al.* (63) investigated the protection of cisplatin-induced cytotoxicity by peroxiredoxin 6 in SKOV-3 ovarian cancer cells and found that over-expression of peroxiredoxin 6 protein blocked the apoptotic effect of cisplatin by reducing reactive oxygen species levels and inhibiting the caspase signaling pathway, indicating that reactive oxygen species scavenging and antioxidant enzyme

activity may be involved in the crucial mechanism of chemoresistance.

In vivo, Wang *et al.* (61) showed that ovarian cancer tissue from patients in the platinum-resistant group had higher expression of peroxiredoxin 3 as compared with that from the platinum-sensitive group, which suggested the possible role of peroxiredoxin 3 in the resistance of ovarian cancer to platinum anticancer drugs.

6. THE ROLE OF PEROXIREDOXINS IN ENDOMETRIAL CANCER

Han *et al.* (64) showed that the expression levels of peroxiredoxin 3 and 5 were elevated in endometrial cancer as compared to normal endometrium and endometrial hyperplasia, which supported that peroxiredoxin 3 and 5 might be involved in the development of endometrial cancer and serve as tumor markers to predict the progression of endometrial cancer. In addition, they then confirmed that a high expression of peroxiredoxin 5 in endometrial cancer, but not other isoforms, was significantly associated with a worse survival rate, suggesting that peroxiredoxin 5 may be a potential prognostic biomarker for endometrial cancer.

7. CONCLUSIONS

Peroxiredoxins, a family of antioxidantes enzyme that can protect cells from oxidative damage induced by reactive oxygen species, exist in multiple tissues and their presence in gynecological malignancies has been confirmed for many years. There are conflicting data concerning the role of peroxiredoxin proteins in the carcinogenesis of gynecological cancers, due to diverse roles of six isoforms in cancer. It appears that the expression of peroxiredoxins was significantly negatively associated with cell differentiation, such as peroxiredoxins 3 in cervical cancer and peroxiredoxin 4, 5 in breast cancer. Many researches consistently showed that peroxiredoxin 2, 3, 6, but not the other isoforms, were associated with metastases from breast cancer, especially lung metastases. Some isoforms of peroxiredoxins might be used to early detect gynecological caner, for example, peroxiredoxin 1 be used in epithelial ovarian cancer or peroxiredoxin 2 and 6 be used in breast cancer. Peroxiredoxin 1, 2, 3, and 6 have been reported to have significant correlation with cisplatin resistance in breast and ovarian cancer. In addition, a high expression of peroxiredoxin 5 in endometrial cancer or breast cancer was significantly associated with poor prognosis, suggesting that peroxiredoxin 5 may be a potential prognostic biomarker for endometrial and breast cancer. Knowledge of the role and mode of activity of peroxiredoxin proteins in specific gynecological malignancies may allow us to formulate more effective targeted therapies in the future. Indeed, peroxiredoxin proteins might act as a new target for the adjuvant treatment of cancers. Further studies will require building whole animal models and generating transgenic and knockout mice models for each peroxiredoxin isoforms.

8. ACKNOWLEDGEMENTS

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Abbreviations: ROS: reactive oxygen species; HPV: human papilloma virus; SNPs: single nucleotide polymorphisms; CIN3: cervical intraepithelial neoplasia 3; FIGO: Federation of Gynecology and Obstetrics; DN: dominant negative mutant; PP2: 4-amino-5-(4-chlorophenyl)-7-(t-butyl) pyrazolo (3,4-d) pyrimidine; OHE1: 16alpha-hydroxyestrone

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