Advances in the role of GPX3 in ovarian cancer (Review)

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Abstract. Ovarian cancer (OC) is the 5th most common malignancy in women, and the leading cause of death from gynecologic malignancies. Owing to tumor heterogeneity, lack of reliable early diagnostic methods and high incidence of chemotherapy resistance, the 5-year survival rate of patients with advanced OC remains low despite considerable advances in detection and therapeutic approaches. Therefore, identifying novel therapeutic targets to improve the prognosis of patients with OC is crucial. The expression of glutathione peroxidase 3 (GPX3) plays a crucial role in the growth, proliferation and differentiation of various malignant tumors. In OC, GPX3 is the only antioxidant enzyme the high expression of which is negatively correlated with the overall survival of patients. GPX3 may affect lipid metabolism in tumor stem cells by influencing redox homeostasis in the tumor microenvironment. The maintenance of stemness in OC stem cells (OCSCs) is strongly associated with poor prognosis and recurrence in patients. The aim of the present study was to review the role of GPX3 in OC and investigate the potential factors and effects of GPX3 on OCSCs. The findings of the current study offer novel potential targets for drug therapy in OC, enhance the theoretical foundation of OC drug therapy and provide valuable references for clinical treatment.

Contents

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1. Introduction

Glutathione peroxidase 3 (GPX3) is a highly conserved selenoprotein. As a member of the GPX family, it catalyzes the reduction of glutathione (GSH), detoxifies water-soluble lipid hydroperoxide and protects cells. GPX3 also provides a greater survival advantage in response to exogenous oxidative stress, including chemotherapy (1). Furthermore, GPX3 plays a crucial role in the growth regulation and differentiation of various malignant tumor cells, exhibiting dual roles in different tumors. In certain cancer types, including gastric, breast, renal clear cell, colorectal and endometrial cancer, and myeloid leukemia, the absence of GPX3 expression often indicates a poor prognosis and the development of resistance to chemotherapy in patients (2). However, GPX3 expression is elevated in epithelial ovarian cancer (OC) and clear cell carcinoma of the ovary (3). This shows that GPX3 serves as a tumor suppressor and pro-survival protein (4). Moreover, GPX3 is the only extracellular GPX in the oxidoreductase family. In OC, it is the sole antioxidant enzyme with high expression that is negatively associated with the overall survival of patients (4-6).

OC is the 5th most common malignancy in women and the leading cause of death from gynecologic malignancies (6). Usually, patients with OC exhibit non-specific symptoms such as abdominal distension, pain, appetite loss, or increased frequency of urination during early development. The most common sign in patients with advanced disease is abdominal swelling due to the accumulation of ascites (7). Among the five major epithelioid OC tissue types recognized by the World Health Organization criteria in 2014, high-grade serous OC (HGSOC) is the most common histological subtype in the clinic, accounting for 70-80% of OC deaths (8). As there is no reliable early screening method, most patients are diagnosed only at stages III and IV (International Federation of Gynecology and Obstetrics staging) (7). Substantial advances have been made in OC detection and therapeutic approaches in recent years; however, the 5-year survival rate for patients with advanced OC remains low (49%, 2022) due to tumor heterogeneity, lack of reliable early diagnostic methods and the high incidence of chemotherapy resistance. Therefore, gaining a deeper understanding of GPX3 and identifying new therapeutic targets to improve the prognosis of patients with OC are crucial (9).

The aim of the current study was to review the role of GPX3 in OC and investigate the potential factors and effects of GPX3 on OC stem cells (OCSCs). The current study focused

on summarizing the mechanism of action of GPX3 in OC and OCSCs, as well as identifying potential targets for clinical intervention.

2. GPX3

What is GPX3? The GPX family, which consists of eight isozymes (GPX1-8), is the most prominent group of proteins in the crucial redox system of mammalian cells (10). These proteins have a substantial influence on the multifaceted functions of nearly all cellular processes. GPX1-8, which are antioxidant enzymes, assist in combating oxidative stress and maintaining redox homeostasis (11). Each member of the GPX family has a different mechanism and site of action in maintaining redox homeostasis (9). A total of ~70% GPX3 is secreted by the basolateral membrane of renal proximal tubule cells and is predominantly present in the extracellular fluid. It catalyzes the reduction of hydrogen peroxide (H_2O_2), hydroperoxides and lipid hydroperoxides via reduced GSH (12). Additionally, GPX4 is capable of reducing complex lipid compounds and it is the only enzyme in the GPX family that directly reduces and destroys lipid hydroperoxides. GPX5 is mainly expressed in the epididymal tissue, where it plays a role in protecting sperm from oxidative stress. GPX7 and 8 are both located in the endoplasmic reticulum and are essential enzymes involved in the oxidative folding of endoplasmic reticulum proteins. GPX8 also plays an important role in regulating Ca^{2+} in the endoplasmic reticulum (13).

Serum GPX3 is a highly conserved selenoprotein. The human GPX3 gene consists of five exons in the 5q32 region of chromosome 5, it is 10 kb in length and it encodes a 23-kDa protein that forms a homotetramer (14). Lee *et al* (12) showed that the secreted isoform of the GPX3 protein is a homotetramer consisting of 226 amino acids with two arginine sites that bind to GSH. Selenocysteine is the substance at the center of the catalytic activity of GPX (GSH-Px), and its activity is closely related to the selenium content in the body. Each GPX3 monomer has selenocysteine as the active center and forms a tetramer with glutamine, tryptophan and asparagine (9).

Functions and adjustment of GPX3. GSH-Px, thioredoxin reductase and the thyroid hormone deiodinase are involved in intracellular signaling, redox homeostasis and thyroid hormone metabolism regulation (15). GSH scavenges excess free radicals in the body by oxidizing the sulfhydryl group (-SH) of GSH to produce oxidized GSH (GSSG) through the catalysis of GSH-Px, which consumes H_2O_2 to produce water (13). By contrast, GSH reductase uses nicotinamide adenine dinucleotide phosphate to catalyze the reduction of GSSG to generate GSH, thereby reducing reactive oxygen species (ROS) in the intracellular cyclic environment and maintaining redox homeostasis (16). GPX3 catalyzes the reduction of hydroperoxides, including H_2O_2 and soluble lipid hydroperoxides, using GSH (17). Additionally, GPX3 can interact with GSH and thioredoxin reductase, or with thioredoxin alone, to produce electrons for GSH in the presence of GSH depletion (18), which in turn protects the cells from ROS-induced deoxyribonucleic acid (DNA) and cellular damage (15).

Extracellular GPX3 relies on the presence of a cysteine encoded by the UGA opal codon in its active catalytic site to undergo conversion into a functional protein (19). Typically, UGA codons serve as signals for translation termination (20). However, in the case of selenoprotein messenger ribonucleic acid (mRNA), the 3'untranslated region contains selenocysteine insertion sequence (SECIS) elements, which allow for the recognition of UGA as a selenium cysteine codon rather than a stop signal (21). Consequently, a deficiency in selenoproteins would result in loss of GPX3 expression (22). Deficiency of selenium can result in insufficient GPX3 biosynthesis, potentially elevating the susceptibility to neurological symptoms, thyroid disorders, reduced fertility, complications during pregnancy and other diseases that are dependent on selenium (Fig. 1) (12). Moreover, previous studies have demonstrated that the expression of GPX3 is regulated by peroxisome proliferator-activated receptor γ (PPARγ) (11,23,24). Zhou *et al* (11) provided evidence that alterations in the mRNA levels of the antioxidant factor GPX3 in ovarian tissues of rats with polycystic ovary syndrome are associated with PPAR-γ activity. Similarly, elevated levels of GPX3 and PPARγ expression have been observed during episodes of obesity (23,24).

Mechanisms of GPX3 effects on various cancers. GPX3 exhibits its activity within the cytoplasmic lysosomes and plasma membranes of mammalian cells located in various organs such as the kidney, heart, lungs, liver, brain, adipose tissue, mammary glands and gastrointestinal tract (25). The mechanism of GPX3 function in different types of cancers is shown in Fig. 2.

GPX3 and promoter hypermethylation. The expression level of GPX3 is strongly associated with the density of DNA methylation (26). In various types of cancers, including gastric (5), lung (27), breast (17,28), endometrial (29), cervical (30), prostate (31) and head and neck tumors (21), the downregulation or complete silencing of GPX3 gene expression, along with hypermethylation of CpG in the CpG island of the GPX3 promoter, have been observed (32). These molecular alterations are indicative of a negative prognosis for patients (Table I) (32,33,34). In the context of prostate cancer, the interaction between GPX3 and p53-induced gene 3 has been observed (35). However, the expression of GPX3 is inhibited by promoter hypermethylation, resulting in the loss of cellular antioxidant capacity. This loss may contribute to the development of breast tumorigenesis (36). Similarly, in patients with breast cancer, the inhibition of GPX3 expression through promoter hypermethylation has been associated with the proliferation, migration and invasion of tumor cells. Additionally, GPX3 hypermethylation has been linked to platinum-based chemoresistance in head and neck cancer (32). Platinum-based drugs can induce oxidative stress and elevate intracellular ROS, leading to apoptosis and elimination of proliferative signals. Therefore, alterations in the intracellular redox state can affect the cellular response to chemotherapeutic agents. Similarly, in cisplatin-induced renal injury, microRNA (miR)-4835p (37) promotes the expression of GPX3, thereby mitigating oxidative stress and exerting a protective effect on renal injury (38).

GPX3 affects signaling pathways. Modifications in GPX3 play a role in the regulation of various signaling pathways in

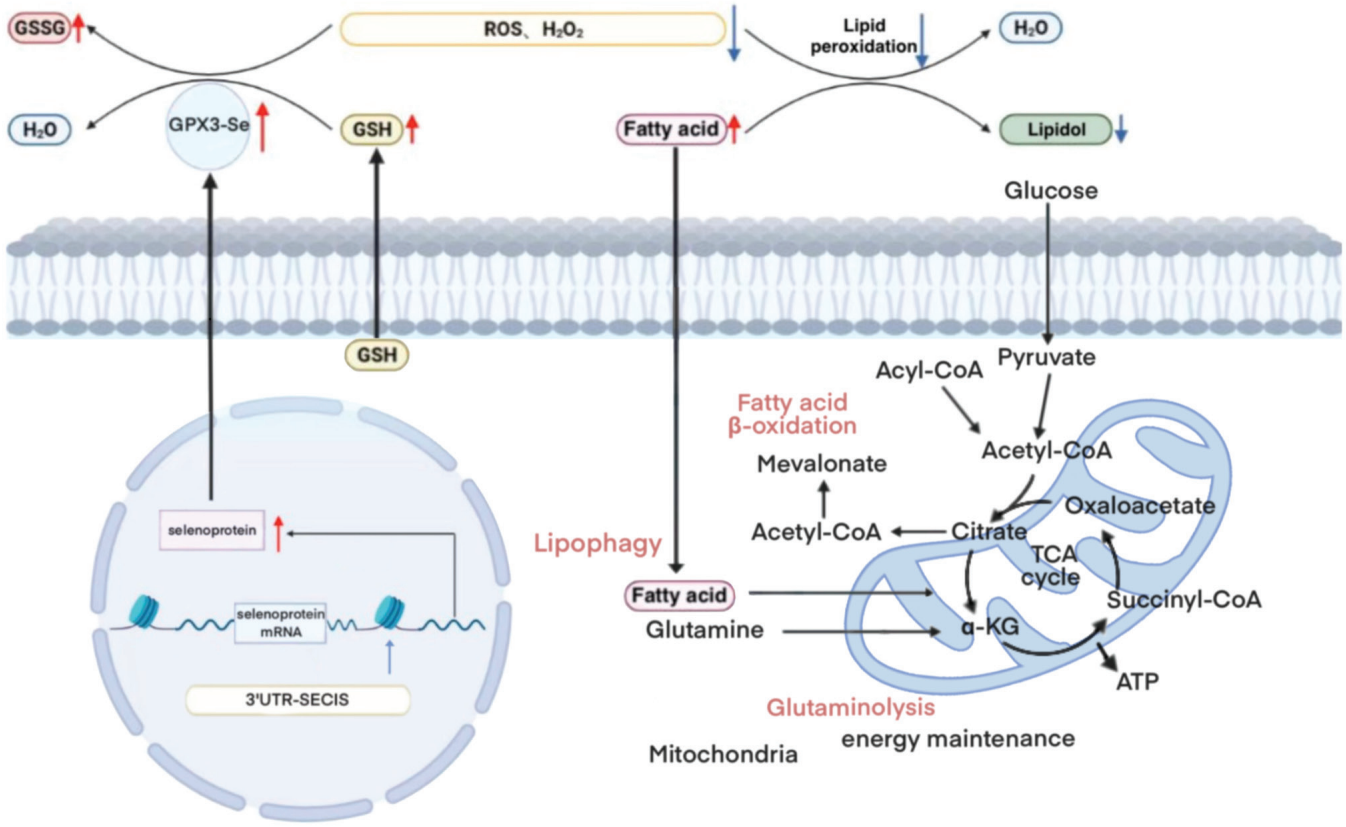

Figure 1. Model diagram of the mechanism of action of GPX3 involved in the scavenging of extracellular ROS and influencing the remodeling of lipid metabolism in promoting the maintenance of stemness in ovarian cancer cells. The 3'UTR of selenoprotein mRNA possesses a specific sequence, the SECIS element. The SECIS element plays a crucial role in recognizing the UGA codon as a signal for selenocysteine incorporation, thereby facilitating the activation of extracellular GPX3. The activated GPX3 enzyme is responsible for catalyzing GSH reduction to generate GSSG. This enzymatic reaction helps in consuming extracellular ROS and ultimately protects OCSCs from ROS-induced cellular damage. Similarly, OCSCs can uptake and utilize extracellular fatty acids, exogenous glucose and glutamine-derived citrate for the purpose of participating in lipogenesis and meeting their energy metabolism requirements. 3'UTR, 3'untranslated region; mRNA, messenger RNA; GPX3-Se, glutathione peroxidase 3 includes selenoprotein; SECIS, insertion sequence element; GSH, glutathione; GSSG, oxidized glutathione; ROS, reactive oxygen species; TCA cycle, tricarboxylic acid cycle; ATP, adenosine triphosphate; acyl-CoA, organic compound-coenzyme A ester; acetyl-CoA, acetyl coenzyme A; succinyl-CoA, succinyl coenzyme A; α-KG, α-ketoglutaric acid.

cancer, including nuclear factor κ-B (NF-κB), Wnt/β-catenin and JNK signaling. In lung cancer cells, GPX3 acts as an inhibitor of proliferation, migration and invasion of tumor cells by suppressing ROS-mediated NF-κB signaling (27,39). The expression of GPX3 can inhibit the activation of NF-κB through the Erk pathway, leading to the suppression of the cell cycle proteins B1 and G2/M and the inhibition of epithelial-mesenchymal transition (EMT) by downregulating the Erk-NF-κ B-SIP 1 signaling axis (40). Additionally, a study by Liu *et al* (41) demonstrated that miR-196a promotes the development of non-small cell lung cancer by downregulating the expression of GPX3 and activating the JNK pathway, thereby enhancing the proliferation, differentiation, self-renewal ability and invasiveness of cancer stem cells (CSCs) (41). These findings suggest that GPX3 and the JNK pathway could serve as potential therapeutic targets for non-small cell lung cancer (5). GPX3 can inhibit the migration and invasion of gastric cancer cells and selectively inhibit the NF-κB/Wnt5a/JNK signaling pathway (42).

Single nucleotide polymorphisms (SNPs) in the GPX3 gene. SNPs are primarily located in the non-coding region of the GPX3 gene and exhibit a positive association with the susceptibility to cancer development (43). Research has demonstrated that the presence of the GPX3 rs736775 C allele is linked to the survival outcomes of patients with colorectal cancer (44). In gastric cancer, the effect of two introns of the GPX3 gene, namely rs3805435 and rs3828599, on gene expression and disease susceptibility has been demonstrated (26). Furthermore, the expression of GPX3 rs736775 in patients undergoing adjuvant chemotherapy with platinum and fluorouracil has been associated with enhanced overall survival (45). Consequently, GPX3 rs736775 can be regarded as a potential prognostic marker. The presence of SNPs influences the downregulation of GPX3 mRNA, resulting in a reduction of GPX3 expression. This reduction in GPX3 expression leads to an imbalance in extracellular redox homeostasis, ultimately promoting cancer development (46).

GPX3 and intra and extracellular redox imbalance. ROS can alter the energy metabolic pathways in tumor cells, promoting glycolysis and facilitating glucose transport through direct regulation of glucose transporter proteins (47). Additionally, ROS can react with unsaturated fatty acids on lipid membranes, leading to the production of free radicals and inducing fatty acid peroxidation, resulting in the

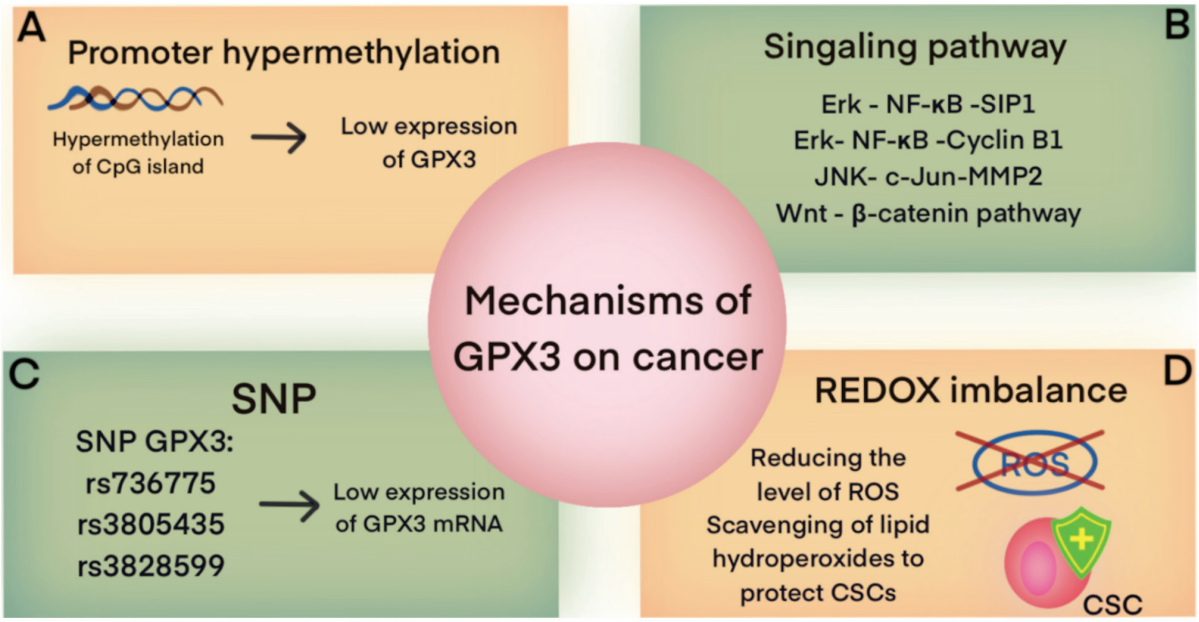

Figure 2. Mechanisms of action for the presence of GPX3 in cancer. (A) Hypermethylation of the CpG island of the GPX3 promoter results in decreased GPX3 expression, leading to the proliferation of tumor cells. (B) Modifications in GPX3 play a crucial role in the regulation of various signaling pathways in tumors, including NF-κB, Wnt-β connexin, and JNK signaling. (C) SNPs are predominantly located in the non-coding region of the GPX3 gene and have been shown to have a positive association with cancer risk. GPX3 rs3805435 and rs3828599 have been linked to the development of gastric cancer, and GPX3 rs736775 may serve as a prognostic marker. (D) GPX3 can actively scavenge ROS within the TME, thereby enhancing the removal of soluble lipid hydroperoxides present in the extracellular tumor environment. This process protects the tumor cells. GPX3, glutathione peroxidase 3; CpG, cytosine, and guanine; mRNA, messenger RNA; Erk, extracellular regulated protein kinases; NF-κB, nuclear factor-κB; Wnt, Wingless; SIP1, Smad interacting protein 1; JNK, c-Jun N-terminal kinase; MMP2, matrix metalloproteinase 2; SNP, single nucleotide polymorphism; ROS, reactive oxygen species; CSC, cancer stem cell; TME, tumor microenvironment.

generation of fatty acid-ROS (48). This process disrupts biological membranes, depletes antioxidants and ultimately increases oxidative stress (40). The function of GPX3 is to reduce ROS levels (49). GPX3 exhibits a dual role in cancer, and these seemingly contradictory results may be closely related to ROS. In early-stage cancer and precancerous lesions, decreased expression of GPX3 and increased ROS production promote cancer development. In melanoma, the upregulation of GPX3 plays a role in regulating ROS levels by inhibiting the expression of HIF-1α and -2α (50). HIF-1 is upregulated in various human cancers and plays a key role in driving tumor growth, invasion and metastasis. It induces changes in lipid metabolism through both HIF-dependent and -independent mechanisms. Under hypoxic conditions, mitochondria produce more ROS. GPX3 can suppress the expression of HIF-1α by regulating ROS, affecting tumor cell energy metabolism, and inhibiting the growth of melanoma cells (51). However, GPX3 also serves to protect tumor cells from exogenous oxidant damage by enhancing the removal of hydrogen and soluble lipid hydroperoxides from the extracellular tumor environment (52). Consequently, GPX3 promotes tumor invasiveness and chemoresistance. Increased expression of GPX3 has been associated with unfavorable patient prognosis in OC, stem cells and certain colorectal cancers (44,52).

3. OC and OCSCs

OC. According to the 2014 World Health Organization criteria, there are five main types of epithelioid OC tissue, among which, epithelial OC is the most prevalent, constituting ~90% of all cases. OC is a complex disease that can be classified into five main subtypes: HGSOC, low-grade serous OC, serous, clear cell and mucinous (52). Among these subtypes, HGSOC is the most prevalent in clinical settings, accounting for 70-80% of OC-related deaths (53). Recent studies have revealed that precancerous lesions of HGSOC are primarily located in the fallopian tube epithelium and are driven by TP53 mutations (7,26,54). However, in certain cases, plasmacytoid tubal intraepithelial carcinoma can also serve as a metastatic counterpart to HGSOC (55).

The primary characteristics of HGSOC include TP53 mutations and frequent mutations in BRCA1 and 2 (56). Additionally, specific cases of HGSOC exhibit overexpression of proto-oncogenes such as AKT and ERRB2; this leads to increased genetic instability and heightened activity of DNA repair mechanisms, such as overexpression of poly (ADP-ribose) polymerase. Additionally, epigenetic traits, including DNA hypomethylation and gene-specific hypermethylation, are observed (57). Specifically, hypermethylation of CpG sites at gene promoters affects specific tumor suppressor genes such as SLIT2, PTEN, OPCML, RASSF1A, p16, MLH1, E-calmodulin and APC (58). The poor prognosis and high susceptibility to recurrence in patients with tumors such as HGSOC can be attributed to the genetic instability of these tumors.

OCSCs and markers. CSCs are a subset of aberrant cells that possess the unique capacity for self-renewal and differentiation, playing a crucial role in tumor initiation, progression and metastasis throughout the tumorigenesis process (59). Makino

Table I. Mechanisms of GPX3 in different cancers.

First author(s), year	Cancer type	Expression of GPX3	Causes of expression	Regulation of pathway	Outcome	(Refs.)
Cai *et al*, 2019 He *et al*, 2023	Gastric	Downregulated	Promoter hypermethylation, DNA copy number losses	Inhibit epithelial-mesenchymal transition (EMT) and NF-κB/ Wnt 5a/JNK	Cancer progression and metastasis	(5,6)
Lou *et al*, 2020	Breast	Downregulated	Promoter hypermethylation, release of hsa-miR-324-5p inhibition	-	Cancer progression	(17)
Wang *et al*, 2022	Lung	Downregulated	GPX3 promoter hypermethylation,	NF-κB/Wnt/JNK pathway, Erk-NF-κ B-SIP 1	Cancer progression and metastasis	(27)
Cai *et al*, 2019 Liu *et al*, 2019	NSCLC	Downregulated	miR-196a	Induce JNK pathway	Cancer progression	(5,41)
Falck *et al*, 2010	Endometrial	Downregulated	GPX3 promoter hypermethylation	- poor prognosis	Cancer proliferation and	(29)
Zhang *et al*, 2014	Cervical	Downregulated	GPX3 promoter hypermethylation	-	Cancer progression, metastasis and poor prognosis	(30)
Rizzo *et al*, 2022	Prostate	Downregulated	GPX3 promoter hypermethylation	c-Met signaling and p53-induced gene 3 to induce apoptosis	Cancer proliferation and poor prognosis	(31)
Krzysztof, 2019	Head and neck	Downregulated	GPX3 promoter hypermethylation	-	Chemoresistance and cancer progression	(32)
Yi *et al*, 2019	Melanoma	Downregulated	GPX3 promoter hypermethylation	Inhibit expression of HIF-1α and -2α	Poor prognosis	(50)
Chen *et al*, 2011	Barrett's disease	Downregulated	GPX3 promoter hypermethylation	Epigenetic inactivation of the glutathione pathway	Cancer progression	(21)
Zhao *et al*, 2015 Zhang *et al*, 2023	Thyroid	Downregulated	GPX3 promoter hypermethylation	Wnt/β-catenin signaling negative effect of miR-146b-5p on the 3'-UTR of GPX3 mRNA	Cancer progression and metastasis	(36,37)
Chen *et al*, 2011 Fan *et al*, 2022	Esophageal	Downregulated	GPX3 promoter hypermethylation	Suppress expression of matrix metalloproteinase 9 by deactivating the FAK/AKT pathway	Cancer progression and metastasis	(21,22)

'-', the regulation of pathway is not clear. GPX3, glutathione peroxidase 3; NF-κB, nuclear factor-κB; Erk, extracellular regulated protein kinases; SIP1, Smad interacting protein 1; JNK, c-Jun N-terminal kinase; Wnt, Wingless; c-Met, cellular-mesenchymal epithelial transition factor; HIF, hypoxia inducible factor; FAK, focal adhesion kinase; AKT, threonine protein kinase; 3'UTR, 3'untranslated region; miR, microRNA.

initially proposed the concept of CSCs in 1959 (60). In 2005, Bapat *et al* (61) made a substantial breakthrough by isolating and culturing suspended cell spheres with CSC characteristics from ascites obtained from patients with advanced OC. This discovery confirmed the existence of OCSCs. Further research revealed that during regular ovulation in women, ovarian epithelial cells undergo continuous repair damage, leading to the continuous proliferation and differentiation of OCSCs (62). Additionally, if OCSCs are exposed to inflammatory mediators, undergo mesenchymal endothelial transformation, or experience dysregulation of the redox balance in the tumor microenvironment (TME), they may stimulate the continuous proliferation of OCSCs, potentially leading to OC development (63). Moreover, the unlimited proliferation and immune evasion properties of CSCs contribute to drug resistance and tumor recurrence in patients with OC, making OCSCs a major factor in these clinical challenges (64). Table II presents the various markers of OCSCs, and the names and mechanisms of drugs that have been or will be discovered for their treatment.

$CD133^+$ is a glycosylated membrane protein that was initially discovered in murine neuroepithelial stem cells and is identified as a marker for CSCs in brain tumors (65). A study by Liou (65) revealed that CD133 can modulate cell cycle progression by affecting Wnt signaling and promoting the invasiveness of tumor cells (64-67). CD117 is a tyrosine kinase receptor, and peritoneal fluid obtained from patients with OC having $CD117^+$ cells can form tumors with the same self-renewal and differentiation capacity as cells derived from the tumor (68). CD44, which serves as the primary receptor for hyaluronic acid, can influence tumor proliferation and metastasis through the STAT3/AKT/NF-κB/IL-8 signaling pathways (69). Additionally, the interaction between NANOG, a gene associated with stem cells, and STAT3 increases MDR1 expression and the efflux of chemotherapeutic drugs, leading to chemoresistance development (70). Studies have shown that APC transporter proteins play a role in protecting tumor cells by actively transporting intracellular toxic substances or drugs to the extracellular compartment, thereby contributing to chemoresistance (70,71). The glycoprotein CD24, which is attached to the cell surface via glycosylphosphatidylinositol, has been implicated in tumorigenesis through the JAK2-STAT3 signaling pathway. Additionally, ALDH1, an intracellular aldehyde dehydrogenase, serves as a marker for OCSCs (72). OCs that exhibit elevated levels of ALDH1 expression possess increased tumorigenicity. Additionally, the isoform ALDH1A1 promotes the maintenance of stemness in OCSCs (72).

Drug resistance in OC. The phenotype of tumor stem cells exhibits dynamic characteristics rather than being a static attribute of tumor cells (73). Signal transduction, redox homeostasis, cell-to-cell contact and secreted factors present in the TME can prompt differentiated tumor cells to reacquire stem cell-like characteristics. Mounting evidence indicates that conventional therapies alone are inadequate in eradicating tumor stem cells. Furthermore, residual individual CSCs can trigger tumor recurrence (74).

In OC development, the involvement of β-catenin in the Wnt/β-catenin signaling pathway has been observed in stem cell proliferation and differentiation, as well as in drug resistance in OCSCs. Chen *et al* (75) reported that the Notch signaling pathway contributes to the survival of ovarian stem cells and their resistance to platinum-based chemotherapeutic drugs. Additionally, the expression of Notch3 is associated with a poor prognosis in patients with OC. Furthermore, endothelial cells in the TME activate the expression of the Notch1 receptor (N1ICD) and facilitate peritoneal metastasis. Studies have demonstrated that the lifespan of mice with OC is considerably reduced owing to the continuous activity of N1ICD, which leads to the aging of endothelial cells, increased expression of chemokines and the adhesion molecule VCAM1, and facilitates recruitment of neutrophils and invasion of tumors (70,74). Additionally, CD117 is expressed at high levels in OCSCs and plays a role in tumor initiation and resistance to cisplatin/paclitaxel by activating the Wnt/β-catenin-ABCG 2 pathway (76).

ROS is a known inducer of cell proliferation (73). Elevated ROS levels are associated with migration, invasion and metastasis. Currently, platinum-based chemotherapy in OC treatment increases intracellular ROS levels, leading to damage to macromolecules such as nucleic acids and proteins, ultimately resulting in cell death. It has been reported that GPX3 is expressed at high levels in OC cells and is associated with platinum resistance (73,74). The IC50 is commonly used in clinical practice to reflect the sensitivity of cells to drugs. The higher the IC50, the greater the amount of drug required to kill cancer cells, indicating lower sensitivity to chemotherapy (42). Hu *et al* (42) showed that the expression level of GPX3 is positively associated with the IC50 of numerous drugs, including paclitaxel, 5-fluorouracil, carboplatin, etoposide, cisplatin and doxorubicin. Higher expression levels of GPX3 were associated with an increase in the IC50 of drugs, indicating reduced sensitivity of cells to drugs. In clear cell OC, overexpression of GPX3 lead to resistance to cisplatin (42). When GPX3 is inhibited by RNA interference, the sensitivity of clear cell adenocarcinoma cells to cisplatin increases. Following GPX3 inhibition, tumor cells may proliferate, enhancing drug accumulation within the cells (73,77).

Recently, the interest among researchers in the role of non-coding RNAs in the regulation of tumorigenesis and development is growing. Wang *et al* (77) conducted a study that focused on the small nuclear kernel RNA host gene 16 (SNHG16)/Enhancer binding protein β(CEBPB)/GATA3 axis and its influence on precursor mRNA processing factor 6 (PRPF6) and GATA3 expression. The findings of their study revealed that PRPF6 promotes the expression of GATA3 by inducing SNHG16 (77). SNHG16 specifically interacts with CEBPB to upregulate the transcriptional activity of GATA3. This upregulation of GATA3 promotes OC cell migration and invasion, enhances resistance to paclitaxel drugs and ultimately affects the prognosis of patients with advanced OC (77). Liu *et al* (78) conducted a study that revealed the regulatory role of the non-coding cyclic RNA circ-0000231 in the proliferation, differentiation and invasion of OC cells. They discovered that circ-0000231 acts through the circ-0000231/miR-140/RAP1B axis, leading to increased expression of E-cadherin in paclitaxel-resistant tumor cells. This discovery highlighted circ-0000231 as a potential target for the precision treatment of OC.

Table II. Therapeutic targeting of molecules in OCSCs.

First author(s), year	Target molecule	Inhibitor	Mechanism of action	Outcome	(Refs.)
Liou, 2019	CD133	Amcasertib	Chemokine pathway and Wnt signaling	Inhibit cell cycle	(65)
Pei *et al*, 2023 Abdellateif *et al*, 2023	CD117 (c-kit)	Imatinib	Increase expression levels of stem cell-related genes such as SOX2, OCT4 and NANOG in OCSCs	Inhibit cell proliferation, apoptosis and cell signal transduction	(64,68)
Jiang *et al*, 2020	CD44	Hyaluronic acid nanodelivery system	STAT3/AKT/NF-κB/IL-8 signaling	Inhibit metastasis of OCSCs	(69)
Robinson *et al*, 2021	CD24	CD24-shRNA	Decrease microvascular density	Inhibit proliferation of OCSCs	(70)
Fan, 2023	CD47	-	Combine chemotherapy drugs and photodynamic therapy drugs with anti-CD47 antibody Fab	Improve drug sensitivity	(71)
Robinson *et al*, 2021	CD326 (EpCAM)	-	Regulate homophilic adhesion interactions	Inhibit metastatic invasion	(70)
Jiang *et al*, 2020	ALDH	All-trans retinoic acid	ALDH/Nrf 2 pathway	Weaken the CSC-like properties of ALDH cells	(69)
Kaipio *et al*, 2020	ALDH1 A1	CM37	Promote the accumulation of intracellular ROS	Damage DNA to induce apoptosis of OCSCs	(72)

STAT3, signal transducer and activator of transcription 3; AKT, threonine protein kinase; NF-κB, nuclear factor-κB; IL-8, interleukin-8; Nrf 2, NF-E2-related factor 2; EpCAM, epithelial cell adhesion molecule; ALDH, acetaldehyde dehydrogenase; ALDH1 A1, recombinant aldehyde dehydrogenase 1 family, member A1; CM37, inhibitor of ALDH A1; OCSCs, ovarian cancer stem cells; shRNA, short-hairpin RNA; ROS, reactive oxygen species; CSC, cancer stem cell.

4. Association of GPX3 with OC

Altered expression of GPX3 in OC. Several studies have demonstrated an aberrant expression of GPX3 in various malignant cells, and this aberration plays a dual role in different tumors (18). In OC, advanced papillary plasmacytoid OC is associated with low GPX3 levels in the serum (28). However, in plasmacytoid OC cells, patients with increased expression of GPX3 had a reduced median survival of 9.3 months (79). High expression of GPX3 in OC has been potentially linked to the more prevalent subtype HGSOC. Additionally, advanced tumors tend to exhibit higher levels of GPX3 expression. This is particularly important as patients with high GPX3 expression and advanced-stage tumors often experience poor survival rates. This finding may be attributed to the presence of considerable amounts of ascites, which creates a favorable environment for the survival of tumor cells (80). Furthermore, several findings have indicated an upregulation of GPX3 expression in less common subtypes of ovarian clear cell carcinoma, which has been linked to chemoresistance development (73).

GPX3 and the TME of OC. The TME refers to the specific location where tumor cells develop, proliferate and spread. It encompasses the structural and functional aspects of the cellular surroundings, but also the presence of metabolites such as glucose, amino acids and lipids within the TME, as well as environmental factors such as hypoxia and acidity (81). CSCs can consume metabolites within the TME. Additionally, CSCs actively contribute to the remodeling of the TME by secreting various metabolites, thereby creating a favorable ecological environment for tumor initiation and progression (74). GPX3 can clear ROS through various signaling pathways, protecting cancer cells from damage caused by exogenous oxidants while also utilizing exogenous fatty acids provided in the TME to help OCSCs to survive in the complex TME. Additionally, the high expression of GPX3 may be related to the immunosuppressive state of the TME, with its expression positively associated with plasma cells and M0 macrophages and negatively associated with monocytes and M1 and M2 macrophages (Fig. 3) (63).

GPX3 is involved in ROS scavenging in the TME. ROS is a broad term that includes oxygen radical and non-radical compounds, such as H_2O_2, hydroxyl radicals, lipid radicals and (phospho)lipid hydroperoxides (82). Elevated ROS levels have been observed in various cancers and have been linked to the activation of signaling pathways involved in cancer initiation and progression, including the mitogen-activated protein kinase/Erk, phosphatidylinositol-3-kinase (PI3K)/Akt, and IκB kinase/NF-κB pathways (83). Furthermore, ROS accumulation over time leads to irreversible damage, and Harman's (84) theory provides further insight into the role of extracellular ROS in triggering age-related cancer progression (85). Transformation, alterations in metabolism and heightened ROS production contribute to elevated levels of oxidative damage in tumor cells compared with normal counterparts (80). The elevation of ROS within tumor cells has been associated with several detrimental effects, including enhanced cell proliferation, facilitation of mutations and heightened genetic instability (86).

The inhibition of the GPX3 gene leads to a decrease in the ability of tumor cells to survive without anchorage and a reduced capacity to respond to external oxidative stress. These findings suggest that GPX3 may play a crucial role in the reduction of extracellular ROS. Additionally, Worley *et al* (4) determined whether GPX3 is essential for OC cells to respond to extracellular oxidants. The results showed that cells with suppressed GPX3 expression were more susceptible to cell death induced by ascorbate, indicating that GPX3 expression is crucial for scavenging excessive extracellular H_2O_2. Another study demonstrated that GPX3 protects OC cells from damage caused by external oxidants by scavenging H_2O_2 (74).

GPX3 affects tumor cell metastasis in TME. In OC, the process of EMT is necessary for tumor metastasis. EMT is a critical biological process through which malignant tumor cells derived from epithelial cells acquire migratory and invasive capabilities. Through EMT, epithelial cells lose cell polarity, connections to the basement membrane and other epithelial phenotypes, and gain mesenchymal phenotypes such as increased migratory and invasive abilities, anti-apoptotic features and the capacity to degrade the extracellular matrix (79). This process confers the tumor cells the ability to invade and metastasize. The tissue factors Snail and Slug, involved in EMT, promote the inactivation of cancer-generated and p53-mediated apoptotic programs (35). Additionally, Shishido *et al* (80) demonstrated that the adhesion of OC cells to the peritoneal mesothelium is facilitated by the interaction between the OCSC markers CD44 and integrin-β1, which are recognized by hyaluronic acid receptors on the mesothelial cell membrane (80). These findings indicate that mesothelial cells can enhance the stem cell-like characteristics of OC spheres. This implies that the adhesion and stemness of OCSCs establish a mutually reinforcing positive feedback loop (87). Furthermore, Hu *et al* (42) discovered that the downregulation of the GPX3 gene resulted in a decrease in the wound healing capacity and transmembrane migration rate of OC and colorectal cancer cells. Moreover, the expression level of GPX3 was found to be closely associated with tumor metastasis. In early-stage cancer and precancerous lesions, decreased expression of GPX3 and increased ROS production stimulate oxidative stress in TME, promoting the progression of EMT and cancer development. In advanced cancer, the high expression of GPX3 clears excess ROS in the extracellular environment, maintaining the redox homeostasis in the TME, protecting tumor cells and enhancing drug resistance (88).

GPX3 affects lipid metabolism. Lipids, such as triglycerides, play a crucial role in supporting oncogenic signals and meeting the energy demands of rapidly dividing cancer cells. Compared with differentiated tumor cells, CSCs rely heavily on lipid metabolism to maintain their stemness and fulfill intracellular biosynthesis and energy metabolism requirements (89). In patients with OC, the omentum and peritoneum contain a substantial number of adipocytes. These adipocytes can transform into cancer-associated adipocytes through interaction with OC cells. These disease-associated adipocytes release lipids, hormones, adipokines and tumor-promoting factors that facilitate tumor growth and metastatic progression (90).

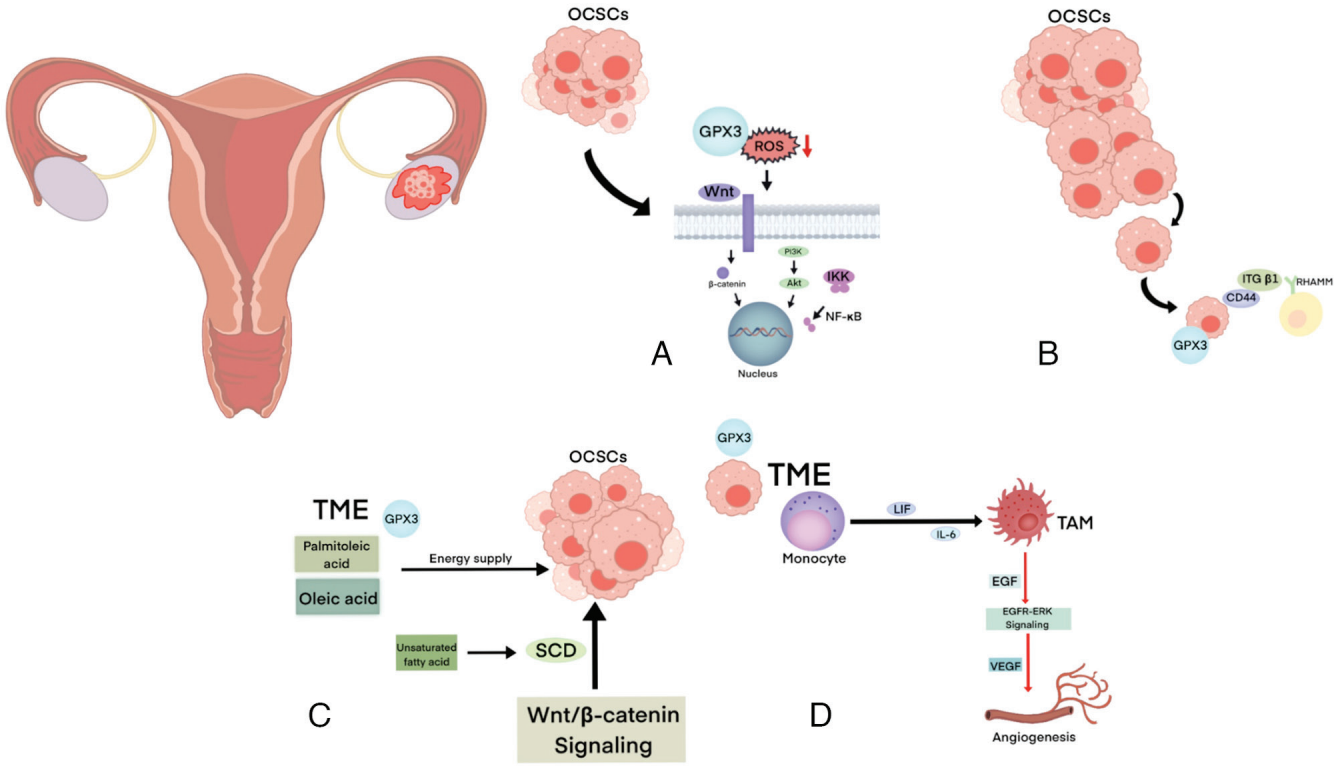

Figure 3. Schematic diagram of the mechanism by which GPX3 is involved in maintaining the stemness of OCSCs in the TME. (A) GPX3 is implicated in signaling pathways that are pertinent to the initiation and progression of cancer. Additionally, GPX3 plays a protective role in ovarian cancer cells by mitigating the detrimental effects of exogenous oxidant damage through the scavenging of ROS. (B) Ovarian cancer cells establish interactions with the peritoneal mesothelium by means of specific markers, which are recognized by HA receptors located on the mesothelial membrane. This recognition leads to the adhesion of the cancer cells to the mesothelium, promoting tumor cell metastasis. (C) GPX3 can support the survival of OCSCs within the intricate TME by protecting them from cell death induced by iron transport through the provision of exogenous fatty acids such as palmitoleic and oleic acids. Additionally, the self-renewal capacity of OCSCs is influenced by the degree of unsaturated fatty acids, which modulate their stemness via the Wnt/β-catenin signaling pathway. (D) Ascites from patients with ovarian cancer induce the differentiation of monocytes into TAMs through the action of LIF and IL-6 factors, which stimulate the release of EGF, which in turn activates the EGFR-ERK pathway. Activation of this pathway leads to the upregulation of VEGF, which promotes angiogenesis and maintains the stemness of OCSCs. ROS, reactive oxygen species; mRNA, messenger RNA; GPX3, glutathione peroxidase 3; NF-κB, nuclear factor-κB; Wnt, Wingless; PI3K, phosphatidylinositol 3-kinase; Akt, protein kinase B; CD44, membrane adhesion glycoprotein; ITGβ1, recombinant integrin β1; RHAMM, hyaluronic acid receptor; OCSC, ovarian cancer stem cell; SCD, stearoyl CoA desaturase; TME, tumor microenvironment; TAM, tumor-associated macrophage; LIF, leukemia inhibitory factor; IL-6, interleukin-6; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; ERK, extracellular regulated protein kinase; VEGF, vascular endothelial growth factor.

Additionally, the high expression of the fatty acid chaperone FABP4 by adipocytes in OC during proliferation and differentiation is positively associated with tumor recurrence following surgery (91). This phenomenon can be attributed to the upregulation of FABP4 by Notch1, which subsequently enhances tumor growth and angiogenesis in ovarian tumor xenografts (91).

The experimental findings presented by Wang *et al* (35) indicate a strong association between OCSCs and the TME. It has been demonstrated that OCSCs have a higher demand for mono-unsaturated fatty acids compared with non-OCSCs. This indicates that lipid desaturation could serve as a potential biomarker for identifying OCSCs (93). The regulation of fatty acids and cholesterols in the TME is closely associated with the formation and maintenance of OCSCs (89). Signaling pathways that regulate lipid metabolism play a crucial role in normal cellular and embryonic development. However, in CSCs, these pathways become dysregulated, leading to abnormal fatty acid and cholesterol metabolism (94). This abnormal lipid metabolism affects cellular signaling and influences CSCs. In the case of OCSCs, the enzyme stearoyl coenzyme A desaturase (SCD1) plays a critical role. SCD1 inhibits the production of fatty acids and lipids, which in turn triggers iron-transport-induced cell death in OCSCs (89). The provision of exogenous fatty acids in the TME, such as palmitoleic and oleic acids, can spare OCSCs from iron-transport-induced cell death (95). Furthermore, SCD1 activity is dependent on the level of unsaturated fatty acids. SCD1 regulates the stemness of CSCs through the Wnt/β-catenin pathway. This highlights the intricate relationship between lipid metabolism, cellular signaling and the maintenance of CSC properties. Overall, understanding the signaling pathways and metabolic alterations in CSCs is crucial for developing targeted therapies that can effectively disrupt CSC function and improve cancer treatment outcomes. Previous studies have demonstrated that GPX3 plays a crucial role in promoting cell survival within the complex TME and *in vitro* culture of ascites extracted from patients with OC. These findings indicate that GPX3 is essential for the clonal survival of OCSCs (96,97). Furthermore, a bioinformatics analysis revealed that GPX3 is highly enriched in fatty acid metabolism and adipogenesis

in the ovary. This suggests that GPX3 may contribute to the maintenance of stem cell properties of OCSCs within the TME by influencing lipid metabolism in tumor cells (97).

Interaction of GPX3 with immune cells in the TME. Immune cells have been observed to infiltrate the TME in OC. Among these cells, some function as tumor-associated immune cells, including immature/tolerogenic dendritic cells (DCs), M2 macrophages, regulatory T cells and myeloid-derived suppressor cells (98). These cells play a role in maintaining immune tolerance and suppressing anti-tumor immunity, ultimately leading to drug resistance in the ovary (12). By contrast, mature DCs, M1 macrophages and natural killer cells can directly inhibit tumor growth or enhance susceptibility to OC-targeted therapies (99). Within the TME, immunosuppressive cells, such as myeloid DCs and $CD4^+$ Th1- and Th2-type T cells, have been positively associated with the expression of GPX3 (100). This suggests that the high expression of GPX3 may be linked to the immunosuppressive state of the TME. Pei *et al* (64) revealed a close relationship between pathological injury of renal tissues following renal ischemia-reperfusion, increased GPX3 expression (a marker of oxidative stress) and various processes (including GSH metabolism, oxidative stress pathways and regulation of T-cell activation). The expression of GPX3 was positively associated with plasma cells and M0 macrophages, whereas it exhibited a negative association with monocytes and M1 and M2 macrophages.

Tumor-associated macrophages (TAMs) are found at high concentrations in the ascites of patients with OC due to the induction of monocyte differentiation into TAM by factors such as leukemia inhibitory factor and IL-6 (98). TAMs are responsible for the release of epidermal growth factor (EGF) in OC, which directly activates the EGF receptor (R)-ERK pathway (101). This activation, in turn, upregulates the vascular endothelial growth factor and promotes angiogenesis (102). Additionally, glutamine is recognized as a crucial metabolite in cancer cells and is emerging as having a major role in TAM metabolism (84). Data indicate that OC cells release N-acetyl aspartate, which in conjunction with IL-10, synergistically induces the transformation of macrophages into M2-type TAMs that overexpress glutamine synthetase (103). Hartwell *et al* (104) observed that $CD8^+$ tumor-infiltrating T cells, under hypoglycemic and hypoxic conditions, alter the metabolic profile of tumor cells from glycolysis to fatty acid catabolism, thereby sustaining the energy supply and stemness characteristics of tumor cells.

GPX3 provides new ideas for OC treatment

Traditional treatments for OC. The current primary treatment approach for patients diagnosed with OC involves performing a surgical procedure to achieve complete tumor reduction. Tumor reduction surgery encompasses procedures such as hysterectomy, omentectomy, and the potential excision of other affected tissue. Despite achieving complete remission following a combination of subtractive surgery and first-line chemotherapy, a substantial proportion of patients (range, 70-80%) experience recurrence within 2-5 years. This recurrence is attributed to the presence of residual tumor tissue and tumor stem cells which serve as the origin for future recurrences (105). At present, the primary approach to inhibit DNA synthesis in actively

Table III. Therapeutic targeting of lipid metabolism in different types of cancers.

First author(s), year	Cancer type	Targeted cell	Inhibitor	Mechanism of action	(Refs.)
Li *et al*, 2022	Gastric Cancer	Gastric cancer stem cells	Resveratrol	Regulate PTEN/AKT Signaling to inhibit epithelial-mesenchymal transition	(63)
Yao *et al*, 2021	Breast Cancer	BCSCs	Resveratrol	Reduce lipogenesis to suppress fatty acid synthase	(47)
Lou *et al*, 2020			Atorvastatin	Inhibit mevalonate pathway to inhibit proliferation of BCSCs	(17,28)
Saelee *et al*, 2020					
Mukherjee *et al*, 2021	Ovarian Cancer	Ovarian cancer stem cells	Orlistat	Inhibit fatty acid synthase	(90)
Luis *et al*, 2023	Colon Cancer	Colon cancer stem cells	Orlistat + Oxaliplatin	Inhibit lipogenesis	(91)
Wang *et al*, 2022 Tesfay *et al*, 2020	Lung Cancer	Lung cancer stem cells	Pterostilbene	Reduce fatty acid synthesis	(27,89)
Noci *et al*, 2016 Bhardwaj *et al*, 2023	Pancreatic Cancer	Pancreatic cancer stem cells	Orlistat	Inhibit fatty acid synthase	(44,92)
Bhardwaj *et al*, 2023	AML	Leukemic stem cells	Sulfosuccinimidyl oleate	Prevent lipid uptake to inhibit the proliferation of $CD36^+/CD34^+$ leukemic stem cells	(92,93)
Szczuko *et al*, 2019					

PTEN, phosphatase and tensin homolog deleted on chromosome ten; AKT, threonine protein kinase; AML, acute myelocytic leukemia; BCSCs, breast cancer stem cells.

proliferating tumor cells in patients with OC is achieved by using platinum- and paclitaxel-dependent chemotherapy (106). However, the development of drug resistance to these treatments affects the prognosis of patients with OC.

Targeted therapy for OC. Several recent studies have shown that targeted therapy against OC cells and OCSCs will provide a new strategy for the treatment or even cure of OC (106,107).

Levamisole, a therapeutic agent that specifically targets CD133, a recognized marker of OCSCs, has been developed (67). CM37, an inhibitor of ALDH1A1, has been shown to induce the intracellular accumulation of ROS in OCSCs, leading to DNA damage (72). Additionally, imatinib, a targeted agent for CD117, inhibits the expression of genes associated with OCSC. Furthermore, novel therapeutic approaches have been developed to target signaling pathways in OCSCs (108). For instance, the combination of inhibitors targeting the PI3K/Akt pathway with paclitaxel drugs has been shown to enhance the sensitivity of paclitaxel (109). Alwosaibai *et al* (110) investigated the relationship between programmed death-ligand 1 (PD-L1) expression, tumor infiltrating lymphocyte expression and tumor stem cell markers in OC (110). The researchers discovered that inhibiting PD-L1 using immune checkpoint inhibitors resulted in a reduction in the number of stem cells associated with cancer recurrence (111). Additionally, Zhou *et al* (112) examined the effect of miR-1307 on the cell cycle and chemosensitivity of OCSCs. They discovered that miR-1307 influenced the transcriptional effectors of the capicua transcriptional repressor gene and receptor tyrosine kinase signaling in OC cells. Furthermore, miR-1307 was found to be a reliable predictor of chemotherapy effectiveness in patients, providing valuable guidance for individualized treatment plans in clinical settings. Moreover, the expression level of miR-1307 can be utilized for more accurate and sensitive detection of OC.

With the progressive advancement of therapeutic investigations on drug-resistant OC, clinical interventions have increasingly emphasized targeting molecular markers associated with OC in conjunction with conventional chemotherapy. For instance, a recent study demonstrated that 3-hydroxy-3-methyl glutaryl coenzyme A reductase can act as a prognostic indicator for statin treatment (96). The concurrent administration of statins and adriamycin enhances the DNA-damaging effect and effectively suppresses P-glycoprotein, thereby reducing drug resistance in patients with OC. Statins are cost-effective, have minimal adverse effects and require comprehensive investigation as potential alternative treatments for OC (113). Recent developments in targeted therapeutic agents for lipid metabolism in various CSCs have been documented and summarized in Table III (107). Based on these findings, it was hypothesized that GPX3 may play a role in the regulation of redox homeostasis and lipid metabolism molecules within the TME. This hypothesis aims to identify potential therapeutic targets for OCSCs. Multidrug-resistant proteins, which are commonly upregulated in cancers, can also transport GSH (114). This finding implies that the enhanced release of GSH into the extracellular space may play a role in the upregulation of GPX3 activity within the TME. Consequently, amino acid precursors involved in GSH synthesis and substances like N-acetylcysteine could enhance the effectiveness of GPX3 (44). In OC, the dysregulation of signaling pathways that control lipid metabolism disrupts the normal processing of fatty acids and cholesterol in OCSCs. Further investigation is required to elucidate the specific role of GPX3 in lipid metabolism within OCSCs (115).

With the advancement of research in the field of OC, the interest in using immunotherapy and bioengineering techniques in clinical settings is on the increase. Carboplatin and paclitaxel have been found to induce an inflammatory state through the upregulation of IFN-γ (116). By contrast, the administration of carboplatin and gemcitabine creates an immunosuppressive milieu. Platinum agents have been demonstrated to enhance IL-6 and PGE2 production in OC cell lines. This is followed by the activation of the STAT3 pathway and the induction of M2 polarization, accompanied by upregulation of IL-10 (117). Platinum agents may have an immunosuppressive effect on the TME by promoting M2 TAM polarization (118). Chen *et al* (119) used high levels of GSH reductase in the TME and showed that the disulfide bond (-SS-) in SSBPEI-DOX could be specifically reduced, allowing it to bind to the conventional chemotherapeutic drug DOX and induce apoptosis or necrosis of CSCs. The researchers developed a novel nanoparticle system (SSBPEI-DOX@siRNAs/iRGD-PEG-HA) that was dual-targeted and GSH-responsive. This system efficiently and specifically delivered a combination of adriamycin and small interfering RNAs to OCSCs (119).

The function of GPX3 as an extracellular antioxidant enzyme in the cytosol and mitochondria can affect the fatty acid metabolism of tumor stem cells, and the levels of GSH and unsaturated fatty acids in the TME (120). These factors can influence the maintenance of stemness of tumor stem cells. Additionally, the measurement of GPX3 levels in plasma holds potential as a valuable prognostic and diagnostic biomarker (121).

5. Conclusion and prospects

OC is a prevalent malignancy affecting the female reproductive system, and its etiology is complex, involving a combination of genetic, environmental and hormonal factors (122). Due to the limited availability of early diagnostic techniques and the prevalence of chemotherapy resistance, the overall survival rate for individuals with advanced OC remains considerably low. Extensive research has indicated that GPX3 is significantly downregulated in OC, and patients with elevated expression levels of this gene in their tumors are more likely to experience a poor prognosis. Moreover, the upregulation of GPX3 expression may confer protection to tumor stem cells against exogenous oxidative stress injury, thereby facilitating the maintenance of stemness characteristics in OCSCs. This phenomenon, in turn, can promote OC recurrence and chemoresistance development. However, this association is purely observational, and further research is required to establish a causal relationship (122).

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Authors' contributions

MW and DG conceived and designed the study. DG wrote the manuscript. YZ and MW revised the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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