Role of solute carrier transporters in ovarian cancer (Review)

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Abstract. Solute carrier (SLC) transporters are involved in various biological processes associated with metabolic reprogramming and cancer, supporting the increased requirement of nutrients and energy. Over the past decade, there have been significant advancements in understanding the expression and function of SLCs in ovarian cancer (OC). This gynecological condition has a high mortality rate and limited treatment options; thus, early diagnosis remains a target clinically. OC exhibits complexity and heterogeneity, resulting in different clinical characteristics, resistance to chemotherapy drugs and poor prognosis. Additionally, SLCs have a different expression pattern between healthy and tumor tissue, and consequently, their inhibition or activation could modify signaling pathways involved in the tumor growth process, such as cell proliferation, apoptosis and drug accumulation. The present review aims to consolidate current data to provide a comprehensive understanding of the potential importance of SLCs in OC. Additionally, it seeks to offer guidance for further research on utilizing SLCs as prognostic biomarkers and therapeutic targets.

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1. Introduction

Transporters are membrane proteins that facilitate the movement of various substances such as nutrients, neurotransmitters, ions, metabolites and drugs, and are involved in important biological processes including the regulation of cell signaling and the organization of cellular organelles (1). Originally, these membrane proteins were categorized as ATP-independent transporter proteins, but in 2004 they were classified into two major superfamilies: The ATP-binding cassette (ABC) and solute carrier (SLC) families (2-4).

Membrane transporters SLCs, which are more numerous than ABCs, play a crucial role in facilitating communication between the cell and its environment. Genetic variants in the SLC family have been associated with various diseases, including neurological or metabolic disorders and cancer (5,6). Despite their biological importance, SLCs are among the most understudied class of proteins, with >455 membrane-bound proteins classified into 66 families, for this reason, numerous aspects of their biology remain unknown (7).

There have been significant advances in the structural biology of membrane proteins, which have greatly improved the understanding of molecular-level transport (6). SLC transporters are an extremely diverse family of membrane proteins. The most common structural classes in human SLCs are the LeuT-like fold leucine transporter (such as SLC6) and the Major Facilitator Superfamily (such as SLC2) (7-10). The diversity of SLC proteins is determined by the specificity of the substrate, as well as the different regulatory properties and tissue- and cell-type-specific metabolic requirements (11-13).

Ovarian cancer (OC) is a gynecological pathology with a high mortality rate, often diagnosed at an advanced stage, leading to a poor prognosis (14). The main response at the onset of the disease is instrumental screening followed by surgical ablation. However, therapeutic options are limited, especially in relapses, which often become resistant to chemotherapy drugs (15,16). The complexity and heterogeneity of OC can result from the uncontrolled proliferation of epithelial, germ or stromal cells, leading to the development of malignant tumors with differences in epidemiology, clinical characteristics, response to chemotherapy and prognosis (16).

In recent decades, it has been widely demonstrated that hereditary or acquired genetic alterations have an important role in the etiology of OC. For instance, *BRCA1* and *BRCA2* mutations have long been associated with an increased risk of developing breast cancer or OC (16-18). Additionally, genetic variants in other genes such as *RAD51C*, *RAD51D* and *PALB2*,

as well as in *MLH1*, *MSH2* and *MSH6* genes, have been identified in 15-20% of OC cases (19,20). This knowledge allows us to identify and screen individuals with a greater probability of developing certain tumor syndromes and to activate counseling and tumor surveillance, particularly when the risk assessment is correlated with a previous family history (15).

Recent studies have shown that changes in gene expression levels can significantly impact patient survival and their response to chemotherapy. Additionally, identifying the molecular pathways and biomarkers involved in tumor growth, proliferation and migration in OC is crucial in fighting this type of tumor. Transcription factors that modulate regulatory genes involved in epithelial-mesenchymal transition (EMT) have been recently identified (21-23). Chen *et al* (23) demonstrated that upregulation of RUNX family transcription factor 1 (RUNX1) is linked to tumor progression and overall survival (OS), while its knockdown showed a significant decrease in the capacity for proliferation and invasion in OC cell lines. Additionally, RUNX1 knockdown reduces EMT through the EGFR/AKT/STAT3 pathway and promotes apoptosis via the FOXO1-Bcl2 axis in OC cell lines. Furthermore, lower expression of RUNX1 improves sensitivity to chemotherapeutics in patients, as observed in short hairpin-RUNX1 ovarian cell lines, suggesting a synergistic effect (23). Moreover, not only genes but also mutation types can play a role in different sensitivities to chemotherapy treatments, as shown by certain studies reporting a different sensitivity to PARP inhibitors, depending on the type and location of *BRCA1/2* mutations or in other genes (24).

An increasing body of information has been obtained regarding the role played by ABC and SLC transporters in the development of multidrug resistance (MDR). This information has been gathered from gene expression analysis in OC cell lines and human primary tumors using microarray techniques (25,26). These analyses have highlighted changes in the expression patterns of transporters and their involvement in tumor progression and the development of resistance to chemotherapy drugs (27). Teng *et al* (28) have demonstrated that ABCC1 or ABCG2 overexpression compromised the drug response in OC cell lines, decreasing their cytotoxic capacity. It was also observed that the knockout of the singular genes or competition by specific inhibitors reversed the resistance process since they significantly reduced the efflux of the anticancer drug from the cells (28).

In cancer, including OC, SLC transporters are dysregulated. This allows tumors to obtain more energy and nutrients giving them an advantage in supporting their metabolic needs (29,30). Additionally, some SLCs can contribute to drug resistance by interfering with the cell death processes and various signaling pathways that influence proliferative capacity and tumor progression (3,31). Therefore, the present review aims to summarize the current knowledge regarding the involvement of SLCs in OC and how they may impact the pharmacological response.

2. SLCs expressed in OC

SLC transporters are differentially expressed in various cell types and tissues. Dysregulation of these transporters is linked to metabolic diseases and tumorigenesis. While a number of studies have explored the role of SLCs in different types of tumors, there has been insufficient research focusing on their involvement in OC (4-6). The SLCs associated with this form of cancer exhibit different transport mechanisms (Fig. 1). The localization and further information on the transporters reported in the present review are listed in Table I.

SLC1A5. The expression levels of SLC proteins differ between healthy and cancer cells. Amino acid transporters, such as SLC1A5 (also known as ASCT2), play a crucial role in cancer metabolism by supporting the increased energy demand for rapid cellular growth. SLC1A5 is involved in the uptake of amino acids (Ala, Ser, Cys and Gln), and downregulation of Gln metabolism has been found to inhibit cell proliferation in various tumors, including OC (3,32,33). In OC tissues, SLC1A5 is significantly upregulated and has been linked to clinical factors and prognosis (32,33). In epithelial OC (EOC), high expression of both SLC1A5 and phosphorylated (p-)mTOR has been observed, and the mTOR signaling pathway is known to promote tumor cell proliferation through Gln metabolism. Furthermore, the co-expression of SLC1A5 and p-mTOR has been associated with poor OS, indicating a synergistic effect on the growth and development of EOC (33). Recent studies have also identified specific microRNAs (miRNAs) that can modulate *SLC1A5* gene expression in OC. For instance, upregulation of miR-122-5p has been shown to regulate SLC1A5 expression by downregulating circular RNA (circ)_0072995, thereby affecting cell growth, apoptosis and invasion. This study reported the role of the cir_0072995/miR-122-5p/SLC1A5 axis in OC tumorigenesis (34). Another study highlighted a similar mechanism of SLC1A5 regulation through the circ_0025033/hsa_miR-370-3p axis (35). Additionally, a new axis has been identified between claudin-4, SLC1A5 and SLC7A5. *Claudin-4* is a gene that encodes a tight junctional protein involved in modulating genomic instability and is associated with worse patient outcomes in OC (36). This axis plays a critical role in amino acid transport through the plasma membrane, contributing to increased OC aggressiveness (36).

SLC3A2. The *SLC3A2* gene, also known as 4F2hc or CD98, encodes for a type II transmembrane glycoprotein that can bind to SLC7A5, SLC7A6, SLC7A7, SLC7A8, SLC7A10 and SLC7A11, forming heterodimeric transporters expressed in different tissues (37,38). In particular, the interaction between SLC3A2 and SLC7A11 (also known as xCT) or SLC7A5 [also known as L-type amino acid transporter (LAT) 1] is involved in an exchange that imports Cystine and essential amino acids (EAAs) and exports Glu and Gln, respectively (37). In addition to the cell membrane, the heterodimeric complex formed by SLC3A2 and SLC7A5 is present in the lysosomal membrane, where SLC3A2/SLC7A5 binds to lysosome associated protein transmembrane 4B (LAPTM4b) promoting Leu and other EAAs to influx into lysosomes, which is required for mTORC1 activation via V-ATPase (38).

Several studies have demonstrated that SLC3A2 expression and its partners are dysregulated in a number of cancer types, where this protein is involved in different stages of tumor development (39-41). In OC, SLC3A2 upregulation supports chemotherapy treatment and decreases tumor masses (40,41). A recent bioinformatics analysis study demonstrated the

Table I. Transport type and location of SLCs in ovarian cancer.

SLCs	Alias	RefSeq ID	Transport type	Subcellular location	(Refs.)
SLC1A5	ASCT2, AAT	NM_005628	Na^+/neutral AA cotransporter	Plasma membrane	(32,33)
SLC3A2	4F2hc, CD98	NM_001012662.3	AA exchanger (Cys/Gln), uptake Leu	Plasma and lysosomal membrane	(37)
SLC4A11	BTR1, NaBC1	NM_001174090.2	Na^+/OH^- and $NH4^+$ transporter	Plasma membrane	(43)
SLC7A1	ATRC1, CAT-1	NM_003045.5	CAT-facilitated transporter	Plasma membrane	(3,49)
SLC7A2	ATRC2, CAT-2	NM_003046.6	CAT-facilitated transporter	Plasma membrane	(3)
SLC7A5	LAT1	NM_003486	Uptake Leu	Plasma and lysosomal membrane	(38)
SLC7A6	LAT2	NM_001076785.3	LAT transporter	Plasma membrane	(3)
SLC7A11	xCT	NM_014331.4	Cystine/Glu antiporter	Plasma membrane	(54)
SLC9A1	NHE-1	NM_003047.5	Na^+/H^+ exchanger-1	Plasma membrane	(81,83)
SLC12A5	KCC2	NM_001134771.2	K^+/Cl^- cotransporter	Plasma membrane	(89)
SLC16A3	MCT4	NM_001206950.2	Lactic acid, ketone bodies and pyruvate transport	Plasma membrane	(59,90)
SLC31A1	CTR1	NM_001859.4	Copper transporter	Plasma membrane	(98)
SLC34A2	NaPi2b	NM_006424.3	Na^+/Pi cotransporter	Plasma membrane	(101)
SLC39A4	ZIP4	NM_017767.3	Uptake Zn	Plasma membrane	(111)
SLC39A13	ZIP13	NM_001128225.3	Zn transporter	Golgi apparatus	(113)
SLC53A1	XPR1	NM_004736.4	Pi transporter	Plasma membrane	(102)

AA, amino acid; CAT, cationic amino acid; LAT, L-type amino acid transporter; SLC, solute carrier.

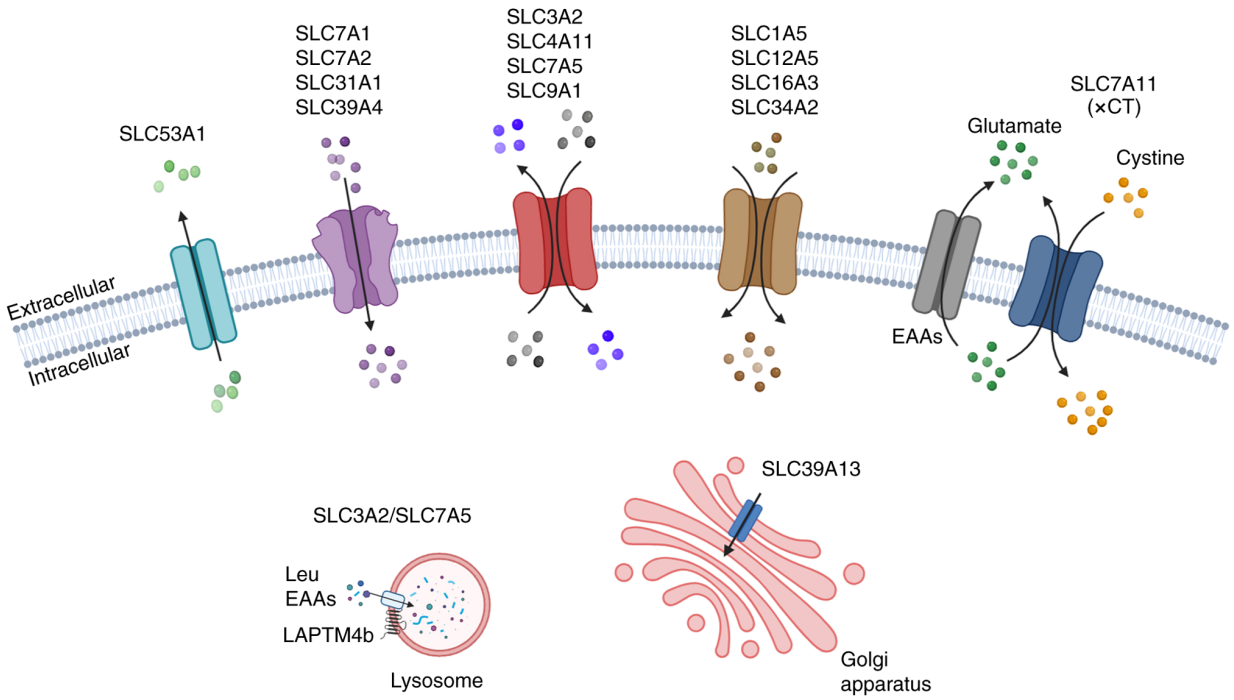

Figure 1. Schematic representation of SLCs responsible for transporting various substances across the cell membrane in OC. The figure illustrates examples of SLCs demonstrating the transporter types and their specific localization in OC. Uniporters: SLC53A1 (efflux); SLC7A1, SLC7A2, SLC31A1, SLC39A4, SLC32A2/SLC7A5 and SLC39A13 (influx). Antiporters: SLC3A2, SLC4A11, SLC7A and SLC9A1. Symporters: SLC1A5, SLC12A5, SLC16A3 and SLC34A2. The xCT system involving SLC7A11 in the exchange of L-Cystine/L-Glu across the plasma membrane. EAAs, essential amino acids; LAPTM4b, lysosome associated protein transmembrane 4B; SLC, solute carrier. Created with BioRender software.

association of the SLC3A2-CD147 complex as a potential risk factor in patients with OC (42).

SLC4A11. The SLC4 family includes 10 proteins involved in the homeostasis control of intracellular pH (pHi) that mediate

Cl^-/HCO_3^- and Na^+/HCO_3^- membrane cotransport. A divergent role has been shown for the SLC4A11 protein that instead mediates the Na^+/OH^- and $NH4^+$ exchange (43). In OC cells, the metabolic changes typical of the neoplastic environment induce upregulation of H^+ transporters with consequent extracellular acidification, supporting tumor invasion and metastasis (43-46). It has been demonstrated that SLC4A11 upregulation is more evident in OC tissues than in normal tissues, particularly in patients with metastasis vs. those without metastasis. Moreover, higher SLC4A11 expression has been linked to poor OS. Dataset analysis of the *SLC4A11* gene regulation highlighted that regulation depends on methylation and DNA amplification processes (43).

SLC7 family. The *SLC7* family genes mediate amino acid transport, and their dysregulation is linked to a number of human diseases, different stages of tumor development and the drug resistance of different cancer types (47,48). The SLC7 family is divided into two subfamilies, namely the cationic amino acid (CAT) and LAT transporter families. The human CAT subfamily includes SLC7A1, SLC7A2, SLC7A3 and SLC7A4, while the LAT family comprises six proteins, SLC7A5, SLC7A6, SLC7A7, SLC7A8, SLC7A10 and SLC7A11 (3,49). To date, few studies have examined the role of SLCs in OC. However, some proteins of the SLC7 family, SLC7A2, SLC7A5 and SLC7A11, have been recognized to play critical roles in OC (38,47,50-54).

Different expression of SLC7 members was revealed in OC compared with normal tissue using the GEPIA dataset, which showed the upregulation of SLC7A1, SLC7A4 and SLC7A7, and the downregulation of SLC7A2 and SLC7A8 (47). A recent study by Gong *et al* (47) showed that SLC7A1 upregulation was correlated with poor OS in OC, as was reported in different tumor types where high SLC7A1 expression was also involved in the tumor-infiltrating immune microenvironment (48). In addition, patients with OC and high SLC7A1 levels develop drug resistance and a higher probability of recurrence (47,49). Another recent study by Circle-seq revealed that some upregulated genes, including *SLC7A1*, were associated with OC prognosis and were able to influence the cell adhesion and extracellular matrix-receptor interaction pathways (55).

Unlike SLC7A1, SLC7A2 is downregulated in various tumor types and induces tumor proliferation and resistance to chemotherapy drugs (48). Moreover, in an OC datasets analysis, Sun *et al* (50) observed that the SLC7A2 expression levels were significantly lower in younger individuals compared with patients ≥60 years old. In addition, this study also demonstrated the role of SLC7A2 in tumor progression by functional experiments in cancer cell lines. The results highlighted that SLC7A2 interferes with apoptosis, signaling pathways and drug resistance. Further SLC7A2 knockdown experiments showed an increased capacity for cell invasion and migration as well as elevated levels of EMT protein markers, such as N-cadherin and vimentin, in OC cell lines (50).

Numerous studies have shown that SLC7A5, also known as LAT1, is upregulated in several OC cell lines and primary tumors. In patients with OC, elevated levels of LAT1 have been correlated with tumor growth, angiogenesis and poor survival rates (32,56-58). A recent study using immunohistochemical analysis demonstrated that SLC7A5 upregulation is associated with certain histological subtypes, such as ovarian clear cell carcinoma (OCCC) (59). It was also previously shown that high SLC7A5 expression is correlated with chemoresistance only in CCC histological sub-types (58). SLC7A5 interacts with SLC3A2 to form a heterodimeric amino acid transporter and is involved in Leu uptake into lysosomes, mediating the interaction with LAPTM4b to activate the mTORC1 complex, as aforementioned (38). A recent study of OCCC demonstrated that inhibiting SLC7A5, which suppresses Leu entry, reduced cellular growth via the mTOR pathway (60). As aforementioned, the claudin-4/SLC1A5/SLC7A5 axis plays a critical role in decreasing patient survival, contributing to increased tumor aggressiveness (36).

The role of SLC7A6 has been investigated in the A2780 and A2780/cisplatin (CDDP) EOC cell lines using dataset analysis. This analysis highlighted an increased expression of CircSLC7A6 in A2780/CDDP cells, which was correlated with SLC7A6 upregulation and miR-2682-5p downregulation. Moreover, the CircSLC7A6/miR-26825p/SLC7A6 axis has been confirmed through CircSLC7A6 silencing experiments, revealing a direct decrease of SLC7A6 and an increased expression of miR-2682-5p (61). In addition, Li *et al* (61) reported a synergistic anti-proliferative and pro-apoptotic capacity of CDDP and baicalein when CircSLC7A6 was knocked down in A2780/CDDP cells.

SLC7A11 is the functional subunit of the Xc-system, which targets the exchange of L-Cystine and L-Glu across the plasma membrane (48). Numerous studies have highlighted the role of SLC7A11 in cancer biology (48,62-64). Altered expression of the *SLC7A11* gene can regulate cell apoptosis, ferroptosis and autophagy in different types of cancer (54,65,66). The Cystine/Glu transport mediated by SLC7A11 promotes glutathione (GSH) biosynthesis, decreases reactive oxygen species (ROS) levels and protects cells from lipid peroxidation, as well as playing a role in metabolism, cell proliferation and drug resistance (67). In OC, the regulation of SLC7A11 has been the subject of much research and has sparked some controversy. One study indicated that high levels of SLC7A11 in patients with OC were linked to a favorable prognosis, while another study suggested that SLC7A11 was a poor prognostic factor and a potential therapeutic target associated with platinum resistance (53,68). Additionally, low expression of SLC7A11 inhibited the process of disulfidptosis and was associated with a poor prognosis. In this research, database analysis was conducted on a cohort of patients divided into two groups (worse and improved prognosis) and it was found that high expression of a gene set, which included *SLC7A11*, was correlated with the group showing improved prognosis (69). Previous dataset analyses have reported that the downregulation of SLC7A11 in drug-resistant OC tissues and paclitaxel-resistant cell lines negatively modulated autophagy genes (*STX17*, *UVRAG* and *RAB33B*) through competing endogenous RNA interactions (54,70,71).

Numerous studies have shown that SLC7A11 is regulated by various factors and is involved in cell death processes, making it a therapeutic target in tumor progression (54,65). The high expression levels of SLC7A11, determined through CCAAT enhancer binding protein γ (CEBPG)-mediated transcriptional control, inhibited ferroptosis and promoted ovarian tumor growth in *in vivo* experiments. These results

were confirmed by CEBPG knockdown, which reduced ovarian tumor cell proliferation both *in vitro* and *in vivo*. Additionally, upregulation of CEBPG and SLC7A11 is associated with poor outcomes in patients with OC (54,72). Similarly, Ogiwara *et al* (73) demonstrated that, in AT-rich interaction domain 1A-deficient OC cell lines, decreased SLC7A11 protein expression led to low GSH levels, inducing cell vulnerability to drugs targeting glutamate-cysteine ligase synthetase catalytic subunit (GCLC). The inhibition of GSH/GCLC leads to apoptosis by increasing ROS levels (73). SLC7A11 is also involved in ferroptosis through silencing STEAP3, which reduces the expression levels of this Cystine/Glu transporter and inhibits the tumor growth of OC cells via the p53/SLC7A11 pathway (74). Another study showed that SNAI family transcriptional repressor 2 binds to the *SLC7A11* gene promoter, decreasing its expression and inhibiting cell apoptosis and ferroptosis in OC cell lines (54,75). Additionally, the interaction between HRD1 and SLC7A11 induces the degradation of the transporter and suppresses tumorigenesis, promoting ferroptosis in OC (76).

Long non-coding (lnc)RNA and miRNA are important regulators of gene expression (77). Evidence indicates their involvement in both promoting and suppressing cancer in different tumor types, including OC. A recent study highlighted that lncRNA ADAMTS9-AS1 was upregulated in OC cells. Knocking down this lncRNA promoted ferroptosis, inhibiting cancer cell proliferation and migration. These effects were achieved via the miR587/SLC7A11 axis, suggesting that lncRNA ADAMTS9-AS1 plays a critical role in SLC7A11 expression (78).

In recent years, SLC7A11 has been identified as a biomarker involved in the mechanism of ferroptosis and in the alteration of a series of signaling pathways that can influence proliferative capacity and tumor progression (79,80). Moreover, bioinformatics analyses have been conducted to explore the tumor expression of SLC7A11 and evaluate its association with patient prognosis and survival in OC. This indicates SLC7A11 as an important factor in prognostic assessment (48,53,54,69).

SLC9A1. SLC9A1, also known as Na^+/H^+ exchanger 1 (NHE1), is a ubiquitous membrane protein involved in pHi control. In tumor cells, the metabolic switch leads to a decrease in pHi due to lactate production, which releases H^+ ions in anaerobic conditions (46). Thus, to prevent hyper-acidification in the OC cell environment, transporters excluding protons from across the plasma membrane are upregulated to regulate the cellular pH (81,82). Increased NHE1 levels have been observed in EOC cell lines and tissues. Moreover, NHE1 upregulation has been correlated with shorter OS compared with individuals with lower NHE1 levels in patients with EOC (83). Through *in vivo* experiments, Szadvari *et al* (82) have reported that overexpression of the NHE1-Na^+/Ca^{2+} exchanger 1 complex leads to alkalinization of pHi and prevents intracellular Na^+ overload. However, alterations in NHE1 function, such as internalization or inhibition, result in cell hyper-acidification that induces apoptosis, which plays a critical role in cancer growth (46,82).

SLC12A5. The *SLC12A5* gene, which encodes a potassium chloride cotransporter, is significantly expressed in various human cancer types and promotes the progression of prostate, bladder urothelial, hepatocellular and colorectal carcinoma (84-87), as well as other tumor types. There is an association between SLC12A5 and methyltransferases or DNA repair proteins (88). Research conducted by Yang *et al* (89) demonstrated the prognostic value of *SLC12A5* in OC, where increased expression was associated with poor prognosis and survival. The authors also found a positive correlation between SLC12A5 protein upregulation and a more aggressive or invasive tumor phenotype. Gene amplification of *SLC12A5* was detected in ~10.3% of OC cases, while no upregulation was observed in normal ovarian tissues.

SLC16A3. The *SLC16A* gene family consists of transporter proteins termed monocarboxylate transporters (MCTs), which are involved in metabolic processes and pH balance. This family includes *SLCA16A1* (MCT1), *SLCA16A7* (MCT2), *SLCA16A8* (MCT3) and *SLCA16A3* (MCT4) (90). Metabolic reprogramming and epigenetic modifications are well-known hallmarks of cancer, and they play a significant role in the uncontrolled growth and proliferation of tumor cells (91,92). Upregulation of SLC16A1 and SLC16A3 has been well-documented in the context of the tumor environment, due to their role in maximizing the capacity of lactate exporters, which helps prevent intracellular hyper-acidosis (93-95). RNA-sequencing (RNA-Seq) analysis revealed that *SLC16A1* and *SLC16A3* are upregulated in OC tissues compared with normal tissues. Additionally, SLC16A3 expression was found to be elevated in metastatic tissue and correlated with poor prognosis, suggesting it could be a potential therapeutic target (95).

In a previous study, it was found that certain SLC proteins, such as SLC16A3, can impact how cells respond to chemotherapy in both OC cell lines and tissues. These proteins can interfere with the movement of drugs across cell membranes. High expression of SLC16A3 was positively correlated with the MDR1 marker (96).

Furthermore, an analysis using Affymetrix Human Genome U219 microarrays in OC cell lines revealed the dysregulated expression of 32 SLCs. Specifically, 17 genes showed increased expression (such as *SLC16A3*, *SLC2A9*, *SLC16A14*, *SLC38A4* and *SLC39A8*), while 15 genes showed decreased expression (such as *SLC2A14*, *SLC6A15*, *SLC8A1* and *SLC27A2*). The study demonstrated that the significant upregulation of SLC16A3 contributed to drug resistance in cancer cells (97).

SLC31A1. SLC31A1, also known as CTR1, regulates copper homeostasis and acts as a transporter for platinum-based drugs (98). Regarding drug delivery, a study has linked SLC31A1 to the development of CDDP resistance in patients with OC (99). Various mechanisms including epigenetic changes, protein expression and post-translational modifications can influence drug resistance (25). Specifically, the transcriptional regulation of SLC31A1 in patients with CDDP-resistant EOC has been studied (100). Researchers using a CRISPR CAPTURE approach followed by mass spectrometry demonstrated that the transcription factor, ZNF711, targets the *SCL31A1* promoter and recruits the demethylase, JHDM2A, in OC cell lines. This mechanism leads to increased activation of SLC31A1 transcription by removing

the repressive transcriptional marker, H3K9me2. Additionally, the downregulation of this transcription factor has been linked to enhanced resistance to CDDP in patients with EOC by suppressing *SLC31A1* transcription (100).

SLC34A2. The sodium-dependent phosphate transporter type 2b (NaPi2b; also known as SLC34A2 and NPT2) is a member of the SLC34 family, which also includes secondary transporters (such as NaPi2a and NaPi2c). The *SLC34A2* gene encodes a protein involved in uptake control and in maintaining inorganic phosphate balance and is typically expressed in tissues under physiological conditions. However, upregulation of this protein has been observed in certain tumors, such as OC, leading to toxic accumulation of intracellular phosphate (101). Genome-scale CRISPR/Cas9 loss-of-function analysis in human cancer cell lines has revealed that inhibiting xenotropic and polytropic retrovirus receptor 1 (XPR1)-dependent phosphate efflux in SLC34A2-overexpressing cell lines can induce cancer cell death by disrupting inorganic phosphate balance (102). Analysis of datasets has shown high SLC34A2 expression in ovarian tumor tissues, which is correlated with reduced life expectancy (103).

SLC39 family. The availability of Zn^{2+} in cells depends on various physiological factors, including uptake and efflux facilitated by specific transporters with different tissue localizations. Changes in transporter expression and Zn availability are considered to be linked to certain diseases and can pose an additional risk factor for tumor development. The transporter families, SLC39 (ZIP) and SLC30 (ZnT), are responsible for the uptake and excretion of zinc ions, respectively. The storage of this ion is regulated by metallothioneins. ZIP transporters consist of four subfamilies with 14 different isoforms (ZIP1-14), characterized by 8 highly conserved transmembrane domains (104,105). ZnT transporters are divided into four groups with 6 transmembrane helices and a conserved zinc-binding site between helices II and V, where specific amino acids play a crucial role in determining metal specificity (105). Several studies have demonstrated an aberrant expression of SLC39A4 (ZIP4) in various types of tumors, including breast, pancreatic, ovarian carcinoma and hepatocarcinoma (106-109). RNA-seq data analyses have confirmed upregulation of *ZIP4* in EOC tissues compared with normal tissues. This zinc transporter, activated by the lysophosphatic acid (LPA)/PPARγ axis, is upregulated in mice with more aggressive EOC, leading to spheroid formation and promoting cancer stem cell (CSC) activity and drug resistance to commonly used drugs such as CDDP or doxorubicin (DOX) (110). In high-grade serous ovary carcinoma, ZIP4 is upregulated compared with normal human tissues (111). Upregulation of this transporter mediates CSC-related cellular functions including tumor-forming capacity, the ability to increase cancer proliferation and invasion as well as conferring resistance to CDDP and DOX. ZIP4 is particularly associated with increased expression of CSC markers, such as aldehyde dehydrogenase 1 family member A1, SOX9, OCT4 and NOTCH3 (108). SLC39A13 (ZIP13) is involved in Zn release from the Golgi apparatus and vesicles, and its dysfunction is correlated with connective tissue disorders (104). Dataset analysis has shown a significant correlation between ZIP13 expression and poor OS and progression-free Survival (PFS) in human OC. Additionally, ZIP13 knockdown significantly reduced the migratory and invasive abilities of OC cells *in vitro* (112). In a metastasis model using BALB/c nude mice, OC cells with depleted ZIP13 via CRISPR/Cas9 technology, showed significantly decreased metastasis both in terms of tumor number and size compared with the control groups. This reduction in metastasis is considered to be due to the inhibition of the Src/focal adhesion kinase (FAK) signaling pathway (112).

SLC53A1. SLC53A1, also known as XPR1, is a gene involved in the efflux of inorganic phosphate. XPR1 variants determine the intracellular phosphate accumulation, leading to the formation of calcium phosphate precipitates (102). Recent research has shown high expression of XPR1 in OCCC cell lines. Experiments conducted *in vitro* and in mouse xenograft models using small interfering RNA-mediated knockdown of XPR1 in EOC cell lines have revealed its significant role in cellular proliferation and tumorigenicity in OC (113). Furthermore, as aforementioned, XPR1 plays a role in controlling phosphate homeostasis. Experiments in SLC34A2-overexpressing cell lines have shown that the loss of the XPR1 phosphate exporter inhibits cancer cell viability (102).

3. Therapeutic drugs and target genes

OC treatment options are determined by the stage of the disease. A number of studies have aimed to understand how to overcome drug resistance mechanisms (25,114). Various biological processes, including epigenetic changes, modifications in plasma membrane transport with drug accumulation and dysregulation of signaling pathways can lead to chemotherapeutic drugs resistance in OC (25). Recently, SLC transporters have gained recognition for their role in maintaining substrate availability and facilitating the influx or efflux of drugs across plasma membrane. Increasing knowledge underscores the importance of SLC transporters, such as SLC3A2 and the SLC7A family, in anticancer drug resistance (Table II) (38,41,49,50,60,61).

Most chemotherapeutic drugs function by inducing apoptotic processes in tumor cells. SLC7A11 is involved in various molecular pathways that are key in treating drug resistance in several tumors, including OC. A number of studies have suggested that the involvement of SLC7A11 can restore sensitivity to drugs and overcome chemoresistance to different antineoplastic molecules (54). Recent studies have shown that SLC7A11 can influence either cell proliferation or tumor progression (79,80). Treatment with the morpholine derivative, N-(4-morpholinomethylene) ethanesulfonamide (MESA), or the quinoline derivative Pt(II)-based complex, PtQ, in OC cells induced ferroptosis and inhibited the SLC7A11/glutathione peroxidase 4 (GPX4) signaling pathway. Specifically, treatment with MESA in OC cell lines led to cell death by increasing nuclear factor erythroid 2-related factor 2 (NRF2) expression and affecting ferroptosis-related signaling pathways (79,80).

Current advances in drugs design have introduced new inhibitory molecules representing a valid approach for regulating target genes. SLC9A1 plays a critical role in cancer growth, and a previous study in OC cells have

Table II. Pharmaceuticals targeting SLCs and signaling pathways in ovarian cancer.

SLCs	Expression	Pharmaceuticals	Targets	Effect	(Refs.)
SLC1A5	↑	-	↑p-mTOR	↑Tumorigenesis	(33)
	↓	-	↑miR122-5p/↓circ_0072995	↓Tumorigenesis	(34)
	↓	-	↑miR370-3p/↓circ_0025033	↓Tumorigenesis	(35)
	↑	-	↑claudin-4/SLC7A5	↑Tumorigenesis	(36)
SLC3A2	↑	CDDP	↑ZEB1	↑Drug sensitivity	(41)
	↑		↑mTORC1	↑Cancer proliferation	(38)
SLC7A1	↑	CDDP	-	↓Drug sensitivity	(49)
SLC7A2	↓	CDDP	↑EMT markers	↑Tumorigenesis	(50)
SLC7A5	↑	Chemotherapy drugs	↑mTORC1	↑Tumorigenesis	(38,58)
	↑		↑claudin4/SLC1A5	↑Tumorigenesis	(36)
	↑		↑mTORC1	↑Cancer proliferation	(38)
	↓		↑mTOR	↓Tumorigenesis	(60)
SLC7A6	↓	Cisplatin-baicalein	↓CircSLC7A6/↑miR-26825p	↓Tumor growth/↑Apoptosis	(61)
SLC7A11	↓	-	↓Disulfide bonds	↓Disulfidptosis/↑Poor prognosis	(69)
	↓	-	↓STEAP3 via p53	↓Tumor growth	(74)
	↓	MESA	↑NRF2 ↓SLC7A11/GPX4	↑Ferroptosis	(79)
	↓	PtQ	↓SLC7A11/GPX4	↑Ferroptosis	(80)
SLC9A1	↑	Zoniporide	-	↓Cancer proliferation	(46)
	↑	HMA	-	↓Cancer proliferation	
SLC31A1	↑	CDDP	↑ZNF711/↑JHDM2A	↑Drug sensitivity	(100)
	↑	BIX-01294	↓H3K9me2	↑Drug sensitivity	
SLC34A2	↓	LIFA	-	↑PFS, ↑OS	(101)
	↓	UpRi	-	↑PFS, ↑OS	(101,105)
SLC39A4	↑	CDDP-DOX	↑LPA/PPARγ	↑Tumorigenesis	(111)
	↑	CDDP-DOX	↑ALDH1, ↑SOX9, ↑OCT4, ↑NOTCH3	↑Tumorigenesis	(109)
SLC39A13	↓	-	↓Src/FAK	↓Tumorigenesis	(113)

SLC, solute carrier; CDDP, cisplatin; EMT, epithelial-mesenchymal transition; MESA, N-(4-morpholinomethylene) ethanesulfonamide; PtQ, quinoline derivative based Pt(II) complex; HMA, 5-N,N-hexamethylene amiloride; BIX-01294, diazepin-quinazolinamine derivative; LIFA, lifastuzumab vedotin; UpRi, Upifitamab rilsodotin; DOX, doxorubicin; PFS, progression-free survival; OS, overall survival; miR, microRNA; circ, circular (RNA); p-, phosphorylated; ZEB1, zinc finger E-box-binding homeobox 1; NRF2, nuclear factor erythroid 2-related factor 2; GPX4, glutathione peroxidase 4; LPA, lysophosphatic acid; ALDH1, aldehyde dehydrogenase 1 family member A1; FAK, focal adhesion kinase.

shown that SLC9A1 inhibitors (such as Zoniporide and 5-N,N-hexamethylene amiloride) could support chemotherapeutic treatment to reduce proliferative capacity (46). As aforementioned, drug delivery experiments have shown that suppressing SLC31A1 expression impaired CDDP resistance in patients with EOC. Treatment with BIX-01294 (a diazepin-quinazolinamine derivative), a histone methyltransferase inhibitor, has been shown to increase the sensitivity of EOC cells to CDDP by removing the repressive transcriptional effects of SLC31A1 mediated by ZNF711 transcription factor and the demethylase, JHDM2A (100).

Targeted therapies have revolutionized the landscape of OC using highly selective monoclonal antibodies, and studies with a specific antibody-drug conjugates (ADCs) are underway (115). SLC34A2-targeting ADCs, LIFA (lifastuzumab vedotin) or UpRi (Upifitamab rilsodotin), have been used as a treatment for gynecological tumors. This approach combines the tumor-targeting ability of monoclonal antibodies with chemotherapy agents. Promising trials are underway in OC to improve health-related quality of life and treatment efficacy, particularly in terms of PFS, OS and other measures (101,116).

Altered expression of Zn transporters and their availability have been linked to various solid tumors and represent an additional risk factor for disease progression (104,105). Research has shown that upregulation of SLC39A4 is activated by the LPA/PPARγ axis, inducing resistance to drugs such as CDDP or DOX (110). SLC39A13 knockdown reduces migratory and invasive abilities of OC cells. In a BALB/c nude mice model injected with ZIP13-depleted OC cells, significantly decreased tumorigenesis through inhibition of the Src/FAK signaling pathway was observed (112). Table II reports the expression of known SLCs in OC correlated to target genes associated with cancer proliferation, survival and resistance to chemotherapy. Therefore, studying the different ways in which SLC transporters impact cancer cells and assessing the activation

or inhibition of signaling pathways could be a crucial step in expediting the development of drugs to treat OC.

4. Conclusions

The present review discussed the involvement of SLC transporter proteins in OC and summarized the existing evidence regarding their role. While a number of SLCs are extensively studied in various types of cancer, their role in OC has not yet been fully explored. Various SLCs play a crucial role in tumor cells by supporting rapid growth and modifying the cellular microenvironment. Recent bioinformatics analysis of ovarian tumor tissues has revealed different expression levels of SLCs, highlighting their involvement in cancer progression and modifying drug sensitivity. The heterogeneity of SLC expression in various diseases and tumors including OC, and their dysregulation is also associated with tumor progression. However, as aforementioned, numerous SLCs in OC are still uncharacterized and poorly understood, leading to limited options for improving cancer cell response to chemotherapy drugs. Furthermore, early-stage OC diagnosis requires the identification of new potential biomarkers to predict response to chemotherapy drugs and improve the OC prognosis. Moreover, it is important to consider the long-term impact on the quality of life, as it may influence therapeutic treatment.

New strategies targeting SLCs through innovative immunotherapy may increase the therapeutic opportunities and improve the response to chemotherapeutic drugs for treating OC. In the last decade, multi-omics data analysis has provided valuable information that can support the understanding of clinical aspects (such as PFS and OS) and the expression of SLCs. Therefore, more focused studies are needed to identify a subset of genes, including SLC transporters, that are prognostically relevant. This is crucial to bridge the information gap between the dysregulation of molecular pathways, immunotherapy response and drug resistance linked to poor outcomes in OC.

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Authors' contributions

BQ, MCF and MM conceived and designed the review. SS was responsible for acquisition and interpretation of the data. BQ, SS, MCF and MM drafted and edited the manuscript for publication and reviewed the literature. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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