Calcium signals and potential therapy targets in ovarian cancer (Review)

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Abstract. Ovarian cancer (OC) is a deadly disease. The poor prognosis and high lethality of OC are attributed to its high degrees of aggressiveness, resistance to chemotherapy and recurrence rates. Calcium ion (Ca^{2+}) signaling has received attention in recent years, as it appears to form an essential part of various aspects of cancer pathophysiology and is a potential therapeutic target for OC treatment. Disruption of normal Ca^{2+} signaling pathways can induce changes in cell cycle progression, apoptosis, proliferation and migration and invasion, leading to the development of the malignant phenotype of tumors. In the present review, the main roles of ion channel/receptor/pump-triggered Ca^{2+} signaling pathways located at the plasma membrane and organelle Ca^{2+} transport in OC are summarized. In addition, the potential of Ca^{2+} signaling as a novel target for the development of effective treatment strategies for OC was discussed. Furthering the understanding into the role of Ca^{2+} signaling in OC is expected to facilitated the identification of novel therapeutic targets and improved clinical outcomes for patients.

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1. Introduction

Ovarian cancer (OC) is considered to be the most lethal of the three major types of gynecological cancer known, which also include cervical and endometrial cancer (1). Different histological subtypes of OC can be distinguished by their unique combination of risk factors, cellular origins, molecular profile, clinical characteristics and response to treatment. Epithelial ovarian cancer (EOC) accounts for 90% of all ovarian tumors, which can then be further subdivided into the following four subtypes: Plasmacytoma, endometrioid carcinoma, clear cell carcinoma and mucinous carcinoma. In total, ~10% ovarian malignancies are classified as non-epithelial, which includes germ cell tumors, gonadal mesenchymal tumors and metastatic tumors (2,3). As the principal female reproductive organ, the ovaries are in charge of oogenesis, female sex hormone production and secretion. Previous research indicates that OC originates in the fallopian tubes rather than the ovary, as previously thought (4,5). Ovarian malignancies are difficult to detect in the early stages due to their position in the peritoneal cavity and being shielded and they are frequently discovered in the late stages. However, detecting early atypical OC remains difficult due to molecular similarities between cells in the fallopian tubes, ovaries and peritoneum (4). Ovarian cancer is exceedingly common, second only to breast cancer in terms of incidence and it has the greatest mortality rate among the three primary gynecologic malignancies, posing a substantial threat to women. OC is a very aggressive cancer that is resistant to treatment, has a high recurrence rate and has a low 5-year survival rate (6-9). In comparison to other gynecological cancers, research in this field is wanting and needs more attention and exploration. As a result, identifying early diagnostic markers and developing further focused therapy options for this cancer is critical.

Calcium ion (Ca^{2+}) is an essential second messenger that participates in a wide range of critical physiological processes (10). Signal transduction involving Ca^{2+} is essential for a wide variety of biological functions, including proliferation, differentiation, growth and apoptosis. Ca^{2+} flow through intracellular Ca^{2+} ($[Ca^{2+}]i$) channels are necessary for the transition from the G_1/S phase to mitosis in the cell cycle. By contrast, Ca^{2+} deficiency can halt cell cycle at the G_0/G_1 and S phases (11). A number of ovarian pathologies, such as OC, typically result from the dysregulation of plasma membrane-based and organelle-based Ca^{2+} signaling mechanisms (12). Ca^{2+} levels have a profound effect on the physiology of the female reproductive system, especially the ovary. $[Ca^{2+}]i$ concentrations can regulate almost every cellular process currently known, from energy production and cellular metabolism to phenotypic development. In particular, novel ideas of ovarian oncogenesis involving altered Ca^{2+} signaling have been steadily proposed over the past decade (12). Variations in $[Ca^{2+}]i$ concentrations can translate through the cell to effect distant regions, to modulate Ca^{2+} signaling pathways that can regulate cell cycle progression, apoptosis, proliferation and metastasis. This contributes to the promotion of more malignant tumor phenotypes (13-16). The present review summarized the current knowledge on the role of Ca^{2+} channels and Ca^{2+} signaling dysfunction in OC development. In addition, how plasma membrane Ca^{2+} channels, $[Ca^{2+}]i$ channels, Ca^{2+} transport proteins, mitochondrial Ca^{2+} transport, the S100 family and extracellular factors can regulate OC development and progression are comprehensively reviewed. The potential roles of these ion channels as therapeutic targets for the diagnosis and treatment of OC are also discussed. The present review not only discussed the most recent findings in the field, but also aimed to swiftly propose entry points for developing treatment methods and future research avenues.

2. Plasma membrane Ca^{2+} channels

Transient receptor potential (TRP) channels. TRP channels form a group of non-selective cation channels that allow Ca^{2+} to permeate. These channels can be categorized into seven groups based on the similarity of their amino acid sequences: TRP canonical (C), TRP vanilloid (V), TRP mestatin (M), TR polycystic protein (PP), TRP mucin (ML), TRP anchor protein (A) and TRP no mechanoreceptor potential C (N) (17). Studies have shown that mutations in the TRP gene can affect the spatial and temporal distribution of Ca^{2+}, which can in turn promote the proliferation and spread of cancer cells (18-22). In OC, the TRPC, TRPM and TRPV families of TRP channels have received the most attention.

TRPC is a subfamily of TRP channels that can be activated by hormones and growth factors, which can mediate Ca^{2+} transport (19). TRPC1, which is widely expressed, is involved in various physiological processes, including cancer development (20), cell proliferation, differentiation, migration, membrane permeability, fluid secretion and apoptosis (21). In OC, the mRNA expression levels of TRPC1 have been reported to be significantly decreased, especially in drug-resistant cases. In addition, this decrease may be associated with higher histological tumor grades and drug resistance (22).

TRPC3 is an important member of the TRPC family and has been shown to be involved in tumor proliferation, metastasis and invasion in OC (23). The protein levels of TRPC3 are considerably higher in human OC samples compared with those in normal ovarian tissue (23-26). Relapse, metastasis and a poor prognosis in human OC have all been associated with high TRPC3 expression (24-26). Downregulating TRPC3 expression in human OC cells leads to a reduction in cell proliferation through the suppression of epidermal growth factor-induced Ca^{2+} influx, dephosphorylation of cell division cycle 2 and Ca^{2+}/calmodulin (CaM)-dependent protein kinase IIα, in addition to prolonged M phase progression (23). By contrast, follicle-stimulating hormone (FSH), estrogen and long chain noncoding RNA (lncRNA) small nucleolar RNA host gene (SNHG)3 can upregulate TRPC3 expression, which contributes to the progression of human OC (24-26). Additionally, phospholipase A2-activated protein has been found to inhibit OC cell invasion and tumor metastasis via decreasing the levels of m6A-modified TRPC3 mRNA by inhibiting methyltransferase-like 3 expressions (27). Therefore, TRPC3 probably serves a significant role in the progression of human OC, rendering it a potential diagnostic and therapeutic target for this malignancy. In particular, TRPC3 downregulation in aging fibroblasts has been documented to increase endoplasmic-reticulum (ER)-mitochondrial Ca^{2+} transfer, which enhances oxidative phosphorylation in mitochondria and promotes the release of tumor-promoting molecules such as interleukin-8 and matrix metalloproteinase 1 (28). However, it remains unclear whether this mechanism would have a counteracting effect on the downregulation of TRPC3 in the treatment pathway for OC, for which further research is required.

TRPV1 is a non-selective cation channel that belongs to the TRP channels family. It is particularly sensitive to capsaicin, heat, protons, lipids, phorbols and phosphorylation (29,30). Aberrant expression of TRPV1 has been associated with malignant tumors in the female reproductive system, including breast, ovarian and cervical cancer (31-33). During the development and progression of OC, Han *et al* (33) previously found that high TRPV1 expression was present in the tissues of ovarian malignancies, particularly in the plasma-type EOC. Therefore, it was proposed that high TRPV1 expression can be applied as an independent prognostic factor for the overall survival of patients with OC. In addition, Han *et al* (33) found that the expression of PTEN, a dual-lipoprotein phosphatase, was negatively correlated with that of TRPV1 expression in late-stage OC, whereby high TRPV1/low PTEN was confirmed by Cox regression analysis to be a significant predictor of prognosis in patients with OC. Subsequent *in vitro* functional studies revealed that inhibiting TRPV1 can prevent the development of OC cells (33). In another previous study, Wang *et al* (34) found that the TRPV1 antagonist DWP05195 significantly suppressed the proliferation of five human OC cell lines A2780, SKOV3, OVCAR3, TOV-21G and Hey8A by inducing C/EBP homologous protein expression, ER stress and apoptosis through the accumulation of reactive oxygen species (ROS). Cisplatin, which is used to treat OC, is known to increase the risk of cytotoxicity. Ursolic acid treatment has been reported to effectively prevent the development of cytotoxicity by inhibiting the TRPV1/-Ca^{2+}/calpain signaling

pathway in the cochlea (35). At present, TRPV1 is one of the most extensively researched TRP channels. However, the mechanism underlying its involvement in the development of OC requires further study. These promising findings provide a path for the future investigation of TRPV1 as a possible therapeutic target for OC.

TRPV2 is typically found inside the cell membrane and has been shown to regulate a number of pathological processes, including cancer, through a signaling route that occurs outside the membrane (36). TRPV2 activation has been found to promote cell migration and cell invasiveness, while the absence or modification of TRPV2-mediated signaling can lead to uncontrolled proliferation and apoptotic (37). Cannabidiol (CBD) has been shown to bind to the TRPV2 channel and has been associated with the dysregulation of proliferation, cell differentiation and invasion in a variety of cancer cell lines and animal models (36). CBD treatment of endometrial cancer has been reported to reverse the cytotoxic effects of chemotherapeutic agents, which is also enhanced by TRPV2 overexpression. Antitumor effects of CBD on OC have been previously observed, both as a potential monotherapy and in combination with conventional chemotherapeutic agents (36). Using PLGA-microparticles as carriers of CBD in combination with paclitaxel, the therapeutic efficacy for OC was increased without any worsening of paclitaxel-related side effects (38). However, whether CBD can improve chemotherapy prognosis for patients with OC by targeting TRPV2 remains to be elucidated. Additionally, TRPV2 also been proposed to be a novel marker for type II EOC, especially for the plasmacytic subtypes and high-grade tumors (39). Further research is required to fully establish the role of TRPV2 in OC.

TRPV4 is a non-selective mechanosensitive transmembrane Ca^{2+}-permeable cation channel (40). Increased expression of TRPV4 in OC has been associated with poorer overall survival, disease-specific survival, disease-free interval and progression-free interval (41). Furthermore, patients with OC who express higher levels of TRPV4 may be more resistant to the chemotherapeutic drugs cisplatin and oxaliplatin. Zhang *et al* (42) previously reported that screened high TRPV4 expression was associated with poor prognosis in patients with ovarian serous cystadenocarcinoma and also demonstrated by Cox regression analysis that TRPV4 was the most probable therapeutic target for ovarian serous cystadenocarcinoma. The role of TRPV4 in the dysregulation of cell migration and adhesion may be crucial for the poor prognosis in OC. This is because it has been known to physiologically regulate endothelial vasodilatation and shear stress sensing, cell migration and skin adhesion junctions (43).

TRPV6 is a highly selective Ca^{2+} channel with its own spontaneous activity that depends on intracellular and extracellular Ca^{2+} concentration (44,45). Its overexpression has been observed in several types of cancer, including prostate, breast and ovarian cancers, and is strongly associated with tumorigenesis, metastasis and prognosis (46,47). Clear cell carcinoma, endometrioid carcinoma, high-grade plasmacytoma, low-grade plasmacytoma and mucinous carcinoma all possess higher TRPV6 mRNA and protein expression levels compared with those in normal tissue, suggesting that targeting TRPV6 channels may inhibit the growth of tumor cells in OC xenograft models and that TRPV6 is a viable target for OC therapy (48). Lidocaine, an anesthetic at concentrations below clinical levels, has been shown to reduce TRPV6 expression in OC cells, to prevent cell invasion and migration (49). By contrast, lapatinib has been observed to suppress TRPV6 mRNA expression in breast and lung adenocarcinoma cells, but has not been studied in OC cells (50).

TRPM2 is a cation channel that allows the passage of Na^+, K^+ and Ca^{2+}, which are in turn regulated by $[Ca^{2+}]i$ in a manner that is dependent on the CaM-binding IQ-like motif (51). TRPM2-antisense (AS) is a lncRNA that acts as an antisense RNA for TRPM2 (52). It has been discovered that TRPM2-AS expression is increased in OC tissues and cells, where it may serve a role in cell proliferation, colony formation, cell migration and invasion *in vitro*. By primarily activating syndecan 3 expression by sponging microRNA (miR-)138-5p, TRPM2-AS was documented to promote tumor growth by OC cells and increase resistance to cisplatin (53). As a novel treatment target for OC, focusing on TRPM2 may prove fruitful.

TRPM7 is a channel that allows the passage of Ca^{2+} and magnesium ions, where it has been found to be abnormally expressed in various types of cancer, including OC (54,55). It probably serves an important role in the carcinogenic process and is strongly associated with tumorigenesis, metastasis and prognosis in patients with OC (56,57). Previous studies have shown that downregulating TRPM7 activity with inhibitors of 5-lipoxygenase and $[Ca^{2+}]i$ chelators can inhibit OC epithelial-mesenchymal (EMT) transition and metastasis by inhibiting the Ca^{2+}-related PI3k/AKT activation (58,59). Therefore, TRPM7 is considered as a potential therapeutic target for the intervention of OC.

The present section discussed the TRP channels that are most likely associated with OC, including TRPC1, TRPC3, TRPV1, TRPV2, TRPV4, TRPV6, TRPM2 and TRPM7. While these channels have been associated with various physiological processes, such as cell proliferation, apoptosis, migration and invasion, in addition to $[Ca^{2+}]i$ regulation, the precise mechanisms underlying their roles in OC development remain to be elucidated. Additionally, there are other TRP channels associated with cancer, but their links to OC have not been confirmed. Therefore, further research is required to fully understand the role and mechanism of TRP channels in the development and therapeutic intervention of OC. Fig. 1 and Table I summarize the TRP channels discussed and their possible associations with OC.

Voltage-gated Ca^{2+}Channels (VGCCs). VGCCs, including T-type Ca^{2+} channels (TTCC) and L-type Ca^{2+} channels (LTCC), play a significant role in regulating the physiological activities of cells (60). Studies highlight that the TTCC-mediated influx of Ca^{2+} regulates cell proliferation, which has been associated with different types of cancer, including OC (61,62). Blocking TTCC expression with NNC 550396, mibefradil or TTCC subunits (Cav3.1/3.2) downregulation impairs the proliferation of OC cells, increases G_0/G_1 phase distribution and slows down OC formation in nude mice (61). TTCC inhibitors, such as mibefradil and related 3,4-dihydroquinazoline derivatives, alter the normal progression of cells through the cell cycle, leading to a similar decline in OC cell proliferation (62). Survivin is an antiapoptotic protein encoded by the BIRC5

Table I. TRP channels in ovarian cancer.

TRP channels	Expression	Effects	(Refs.)
TRPC1	Decreased	Lower TRPC1 expression may be associated with drug resistance and a high histological tumor grade.	(22)
TRPC3	Increased	Higher TRPC3 expression levels are correlated with early relapse, metastasis and worse prognosis.	(23)
TRPV1	Increased	Higher TRPV1 expression are correlated with a poor overall survival.	(33)
TRPV4	Increased	High expression of TRPV4 is associated with poor overall survival, disease specific survival, disease-free and progression free intervals, and increases drug resistance.	(42,43)
TRPV6	Increased	There is a strong relationship between tumorigenesis, metastasis, and prognosis.	(50)
TRPM2	Increased	TRPM2-AS promotes cell proliferation, colony formation, Cell migration and cell invasion *in vitro*.	(55)
TRPM7	Increased	Promotes pelvic metastasis of ovarian cancer cells, resulting in a poor prognosis.	(59,60)

TRP, transient receptor potential; TRPM2-AS, TRPM2 antisense RNA.

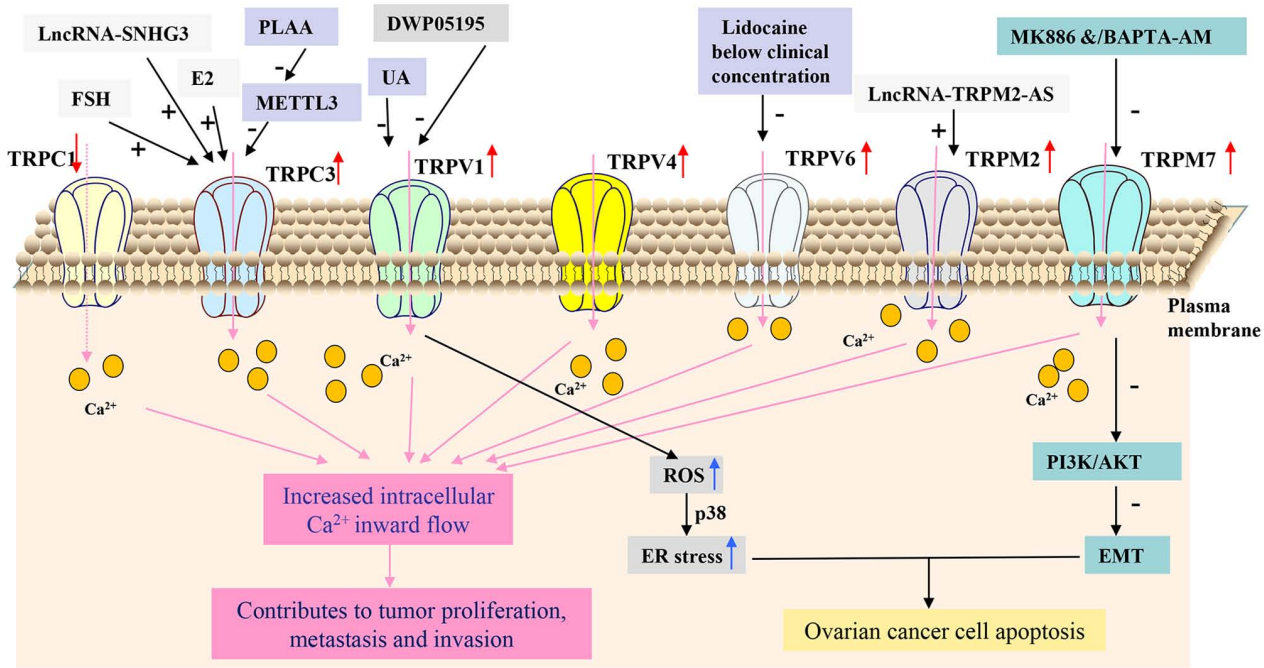

Figure 1. TRP channels in OC cells. Abnormal expressions of TRPC1, TRPC3, TRPV1, TRPV4□TRPV6, TRPM2 and TRPM7 contributes to OC cell proliferate, metastasize and invade. Lower TRPC1 expression may be associated with drug resistance and a high histological tumor grade. The expression of TRPC3 was induced by FSH, E2 and lncRNA-SNHG3 and downregulated by PLAA via METTL3 inhibition. Cell apoptosis was triggered by DWP05195 because it inhibited TRPV1 expression, increased ROS accumulation and p38 activation and triggered endoplasmic reticulum stress. TRPM2-AS is upregulated in OC tissues and cells. *In vitro*, TRPM2-AS also contributes to cell proliferation, migration and invasion. Reduced [Ca^{2+}]i levels and attenuated PI3K/AKT activation after treatment with MK886 and/or BAPTA-AM inhibited EMT by downregulating TRPM7 in OC cells. TRP, transient receptor potential; OC, ovarian cancer; TRPC, TRP canonical; TRPV, TRP vanilloid; FSH, follicle-stimulating hormone; E2, estrogen 2; lncRNA, long non-coding RNA; PLAA, phospholipase A2 activating protein; METTL3, methyltransferase-like 3; UA, ursolic acid; DWP05195, TRPV1 antagonist; ROS, reactive oxygen species; lncRNA TRPM2-AS, antisense RNA of TRPM2; MK886, 5-Lipoxygenase inhibitor; BAPTA-AM, Intracellular calcium chelator; EMT, epithelial-mesenchymal transition. +, Promote; -, Inhibit.

gene and is also downregulated during this process (63). Inhibiting TTCC in OC cells not only suppresses growth and increases apoptosis but also downregulates the expression of BIRC5 (63). Additionally, the effectiveness of platinum agents in treating OC can be improved by inhibiting Survivin (63). TTCC blocker and platinum treatment, in combination,

Table II. Alterations in Ca^{2+} signaling in ovarian cancers.

Calcium signals		Expression	Effects	(Refs.)
VGCCs	TTCC	Increased	Plays a reinforcing role in ovarian cancer cell proliferation, cell cycle progression, and apoptosis evasion.	(63)
	LTCC	Increased	Increases ovarian cancer cell proliferation and metastasis.	(68)
CRAC	Orai & STIM	Increased	Stimulates tumor growth and metastasis and enhances tumor drug resistance.	(75)
BKCa	KCNMA1	Increased	Is associated with the malignancy and poor prognosis of the cancer.	(83)
	KCNMA1	Decreased	Enhances the drug resistance of ovarian cancer.	(84)
IP3Rs	IP3R1	Increased	Possesses pro-proliferative and anti-apoptotic effects.	(104)
	IP3R2	Increased	Promotes development and progression of ovarian cancer.	(112)
RyRs	RyR1	Increased	Is involved in the onset and development of ovarian cancer.	(112)
	RyR2	Decreased	Promotes tumorigenesis and development.	
Ca^{2+}-ATPase	SERCA	Increased	Involved in the progression of ovarian cancer.	(121)
	PMCA	Increased	Disrupts calcium homeostasis and contributes to the progression of drug-resistant cancer cells.	(126)
MCU	MICU1	Increased	MICU1 overexpression correlates with poor overall survival and resistance to chemotherapy.	(132)

VGCC, Voltage-gated Calcium Channel; TTCC, T-type Ca^{2+} channel; LTCC, L-type Ca^{2+} channel; CRAC, Ca^{2+} Release-Activated Ca^{2+} Channel; STIM, stromal interaction molecule; BKCa, large conductance Ca^{2+}-activated K^{+}; KCNMA1, Ca^{2+}-activated potassium channel subunit α-1; IP3R, inositol 1,4,5-trisphosphate receptor; RyR, lysine receptor; SERCA, sarco/endoplasmic reticulum; PMCA, plasma membrane; MCU, mitochondrial Ca^{2+} uniporter; MICU1, mitochondrial Ca^{2+} uniporter regulator 1.

promote apoptosis of OC cells and reduce ectopic metastasis of platinum-resistant tumors in mice, providing a model to investigate OC metastasis in humans (63,64). In the study by Fornaro *et al* (65), it was found that the expression of TTCC genes (three isoforms: CACNA-1G, CACNA-1H and CACNA-1I) were correlated with overall survival in patients with tumors, especially in gastric cancer. The correlation between the expression of all CACNA genes and overall survival when considering staging was also significant in OC, demonstrating that altered CACNA gene expression correlates with tumor prognosis and promising for further evaluation in OC.

In addition, when the LTCC is affected by adverse factors, such as serum gonadotropins and lysophosphatidic acid (LPA), resulting in its abnormal activation of Ca^{2+} inward flow, it is strongly associated with the proliferation and metastasis of OC cells (66,67). Nifedipine (a LTCC blocker) could inhibit LPA-induced OC cell migration and adhesion (67). OC stem cells are a major contributor to drug resistance in OC patients. LTCC blockers (manidipine, lacidipine, benidipine and lomepizine) and trimebutine maleate could inhibit the viability and proliferation of OC stem cells by downregulating the expression of the LTCC gene, thereby inducing apoptosis (68,69). CACNA1C, as an important type of LTCC ion transmembrane channel, plays regulatory roles in the development and progress of multiple tumors. Chang and Dong (70) revealed that CACNA1C could be a prognostic predictor of overall survival in OC and it was closely related to immunity. In conclusion, the current research indicates that TTCC and LTCC play an important role in OC cell proliferation, cell cycle progression and metastasis and is also linked to OC prognosis (Table II).

Ca^{2+} release-activated Ca^{2+} channel (CRAC). The CRAC channel, composed of Ca^{2+} release-activated Ca^{2+} channel protein 1 (Orai1) and stromal interaction molecule (STIM), serves a vital role in regulating Ca^{2+} signaling and gene expression in cells by activating store-operated Ca^{2+}-entry (71). Previous studies suggest that targeting this channel can be a potential therapeutic strategy for treating cancer. Khan *et al* (72) reported that blocking the CRAC channel, which is overexpressed in various cancer cells and tissues, may benefit patients with cancer. Hypoxia inducible factor (HIF)-1α has been found to promote tumor growth and metastasis by elevating expression the levels of Orai1 and STIM1 in OC cells after exposure to placental growth factor (73). In addition, Schmidt *et al* (74) found that Orai1 and STIM1 expression levels were slightly higher in drug-resistant OC cells, suggesting the potential involvement of CRAC channel in supporting the survival of OC cells. Other studies have demonstrated that upregulated Orai1 expression in OC cells could lead to increased cell proliferation and metastasis; meanwhile, silencing Orai1 expression was demonstrated to inhibit these aforementioned effects (75,76). Therefore, currently available evidence suggests that CRAC channel likely serves a role in the initiation and progression of OC, contributing to poorer patient outcomes (Table II). Although there is limited data on other subtypes of Orai/STIM and few clinical trials have used CRAC channel blockers, targeting this channel may be a promising approach for developing OC therapies.

Table III. Alterations in Ca^{2+} exchange proteins in ovarian cancer.

Calcium signals		Expression	Effects	(Refs.)
GPCRs	CaR	Decreased	Causes changes in the physiology of tumor cells and acceleratestumor progression.	(88)
	GPER	Increased	Induces metastasis and invasion of tumor cells, with a poor prognosis.	(91-94)
S100 family	S100A1/2/ 4/5/6/7/10/ 11/13/14/16	Increased	Correlated with lymph node metastasis, FIGO staging and tumor grade.	(155,157,178)
	S100B/ S100P	Increased	Upregulation linked to tumor growth, survival, prognosis and resistance to cancer drugs.	(174,176)
TROP	TROP2	Increased	Enhances the ability of ovarian cancer cells to proliferate, invade and migrate.	(177)
CaMKK	CaMKK2	Increased	Enhances the ability of ovarian cancer cells to proliferate, invade and migrate.	(181)

GPCR, G-protein-coupled receptor; CaR, Ca^{2+}-sensing receptor; GPER, G protein-coupled estrogen receptor; FIGO, International Federation of Gynecology and Obstetrics; TROP, tumor-associated calcium signal transducer; CaMKK, Ca^{2+}/calmodulin-dependent protein kinase.

Large conductance Ca^{2+}-activated K^+ (BKCa) channel. The BKCa channel has been implicated in human cancer development, including OC, by contributing to cell cycle disruption, proliferation and migration (77,78). The BKCa channel opener NS1619 has been found to reduce proliferation while inducing apoptosis in OC cells by upregulating death-inducing proteins (such as P53, P21 and Bax) (79). The α-subunit of BKCa channel is encoded by the Ca^{2+}-activated potassium channel subunit α-1 (KCNMA1) gene, which has been shown to serve a role in the formation of macromolecular signaling complexes through the action of local Ca^{2+} introductory channels (80). The BKCa channel subunit KCNMA1 contributes to macromolecular signaling complexes, whereby KCNMA1 amplification is associated with higher proliferation rates and higher degrees of malignancy in ovarian, endometrial and breast cancers (81,82). However, a study reported that knocking out KCNMA1 expression increases cisplatin resistance in OC cells (68). A recent study found that trimebutine maleate inhibits the viability of OC stem cells by targeting the BKCa channel and can prevent drug resistance and recurrence in OC (69). Further investigation into the precise mechanism of BKCa channel-regulated proliferation, apoptosis and resistance in OC cells is necessary to determine their potential as biomarkers or therapeutic targets for OC (Table II).

G-protein-coupled receptors (GPCRs). GPCRs form a class of receptor proteins that can activate G proteins to elicit cascade reactions affecting a wide range of biological functions including cancer progression (83,84). GPCRs can exert different types of effects on OC (Table III). The Ca^{2+}-sensing receptor (CaR) is a GPCR that mediates Ca^{2+} signaling and disrupts normal epidermal differentiation by sensing extracellular Ca^{2+} (85). The CaR rs17251221 G allele has reported protective effects, reducing the risk of OC development (86,87). By contrast, lysophosphatidylglycerol-induced proliferation and migration of human OC cells are mediated by pertussis toxin-sensitive GPCRs (88). Previous studies have highlighted the role of G protein-coupled estrogen receptor (GPER) in OC pathogenesis, where its high expression is associated with malignant OC, tumor cell invasion and poorer patient survival (89,90). GPER activation may be involved in OC initiation and progression, although GPER has also been reported as possessing anti-cancer properties (91,92). Notably, OC cells treated with GPER-specific agonist G_1 exhibited increased levels of apoptosis and impeded cancer progression (93). GPCRs are primarily stimulated by most neurotransmitters and inflammation-related ligands, which can in turn promote OC proliferation, metastasis and invasion, as reviewed by Predescu *et al* (94). Despite the scarcity of animal models and clinically relevant data, GPCRs have emerged as promising therapeutic targets for OC (94). It is reported that 2-thioureidothiophene-3-carboxylates (TUTPs), a novel class of antagonists for the GPCR C-X-C chemokine receptor type 2, effectively inhibits C-X-C motif ligand 8-mediated cell migration while exhibiting a synergistic effect with doxorubicin on OC cells (95). These findings suggest that TUTPs hold promise as potential anticancer agent for OC treatment, highlighting the potential of GPCR-based approaches for OC therapy.

3. Intracellular Ca^{2+} channels and transporters

Inositol 1,4,5-triphosphate receptor (IP3R) and ryanodine receptors (RyR) channels. IP3Rs are a family of Ca^{2+}-releasing channels located in the ER membrane (96). There are three main isoforms of IP3Rs: IP3R type 1 (IP3R1), InsP3R type 2 (IP3R2) and IP3R type 3 (IP3R3). They serve a crucial role in the regulation of Ca^{2+} release from the ER and sarcoplasmic reticulum and are expressed to varying degrees in different mammalian tissues (97-99). When activated, IP3Rs regulate the release of Ca^{2+} from the ER to either the mitochondria and/or cytoplasm, where they serve an essential role in regulating

cellular metabolism and survival (100). All three isoforms of IP3R can be detected in ovarian tissue sections from normal experimental animals and OC A2780 cells and some studies suggest that IP3R is emerging as a key locus for the regulation of pro- and anti-apoptotic factors (101,102). Hypoxia has been shown to control the intensity of Ca^{2+} signaling in cancer cells through IP3Rs (103). In addition, Lencesova *et al* (104) previously demonstrated that hydrogen sulfide causes ER stress and apoptosis under hypoxic conditions, suggesting that IP3Rs are closely associated with apoptosis in OC cells. Additionally, stable TAT-fused IP3R1-derived peptides can increase cisplatin-induced Ca^{2+} flux from the ER into the cytosol and mitochondria, sensitizing OC cells to cisplatin by targeting the BH4 structural domain of Bcl-2 (Table II) (105,106).

Compared with IP3R1, IP3R3 has been shown to exert both pro-proliferative and anti-apoptotic effects on cancer cells. Elevated IP3R3 expression levels have been observed to enhance the migratory and invasive properties of cancer cells by increasing mitochondrial metabolism and driving anabolic pathways (107,108). By contrast, a recent study found that OC cells become more resistant to chemotherapy-induced apoptosis after IP3R3-mediated Ca^{2+} flux to mitochondria was blocked (109). Therefore, further research is necessary to elucidate the function of IP3R3 in OC cells. By comparison, IP3R2 has received less attention. Nonetheless, increased expression of the IP3R2 gene was observed in iron-treated epithelial OC cells and cisplatin-resistant cells of the same cell line, indicating its probable role in the development and progression of OC (110).

RyRs are also members of the Ca^{2+}-releasing channels family located on the ER membrane, of which three known isoforms (RyR1, RyR2 and RyR3) exist. RyRs are widely expressed and mediate Ca^{2+} release from intracellular membrane compartments, leading to transient and reversible alterations in cytoplasmic and ER Ca^{2+} levels (111). RyRs have been found to be useful in determining the severity of malignant diseases and their prognosis, as they may serve a role in the onset and progression of prostate, breast and head and neck cancers (112-114). In OC cells, RyRs can interfere with the estrogen receptor α (ERα-)/PLCγ-/IP3R pathway by altering the activity of ERα biomodulators (115). Furthermore, RyRs have been reported to regulate the activation of the unfolded protein response in OC cells and in turn their sensitivity to paclitaxel and adriamycin (116). A previous study found that both epithelial OC cells (MDAH-2774) and cisplatin-resistant OC cells of the same cell line (MDAH-2774/DDP) showed increased RyR1 gene expression after iron treatment, while only EOC cells (MDAH-2774) showed decreased RyR2 mRNA levels (110). This suggests that RyRs can affect the progression of OC by regulating Ca^{2+} levels in OC cells through multiple mechanisms (Table II).

IP3Rs and RyRs are considered to serve central roles in $[Ca^{2+}]i$ movement and have an important and complex role in the development of types of cancer. However, the role and mechanism of IP3Rs and RyRs in OC remain poorly understood. Further studies are therefore necessary to gain an in-depth understanding into the occurrence, development and prognosis of OC. Information from these studies are likely to provide novel insights into possible therapeutic approaches for OC by targeting the ER-related Ca^{2+}-releasing channels.

Ca^{2+}-ATPases. Ca^{2+}-ATPases or Ca^{2+} pumps regulate Ca^{2+} homeostasis and are essential for reproduction. However, their dysregulation can interfere with the production of sex hormones and disrupt normal ovarian physiology (117,118). To date, three major families of Ca^{2+}-ATPases have been identified: Those located on the sarco/endoplasmic reticulum (SERCA); on the plasma membrane (PMCA); and on the secretory pathway (SPCA) (118). In OC tissues, aberrant SERCA expression has been observed, the inhibition of which has been revealed to increases cytoplasmic Ca^{2+} concentration, resulting in OC cell apoptosis. This suggests that SERCA serves a role in OC progression (119,120). Seo *et al* (120) found that curcumin inhibits SERCA activity to disrupt $[Ca^{2+}]i$ homeostasis, which promotes apoptosis in OC cells. Transmembrane and coiled-coil domains 1 (TMCO1), which is essential for ovarian follicle development and female fertility in granulosa cells, is regulated by SERCA (121). The disruption of TMCO1 was demonstrated to cause Ca^{2+} overload in the ER and increased ROS levels in granulosa cells, which ultimately caused follicular dysgenesis. These phenomena have been associated with various ovarian-associated pathological conditions, such as OC (121,122).

Ovarian granulosa cells rely on PMCA to regulate their $[Ca^{2+}]i$ concentrations in response to basic fibroblast growth factor (bFGF), which suggests that bFGF regulates PMCA as part of an anti-apoptotic mechanism in ovarian granulosa cells (123,124). Iron treatment was found to upregulate the mRNA expression of both PMCA1 and PMCA3 in cisplatin-resistant epithelial OC cells, suggesting that PMCA is an independent pathway of drug resistance in OC cells (110). Additionally, the mRNA expression profiles of Ca^{2+} homeostasis-associated genes (SERCA1/2/3, PMCA1/2/3/4) were decreased in a cisplatin-resistant cell line compared with those in their parental cell lines (Table II) (125). Currently, there is a lack of research focusing on the role of Ca^{2+}-ATPases in OC, which should be explored as a starting point for future investigations into expanding the understanding of Ca^{2+}-ATPases and their potential as therapeutic targets.

4. Mitochondrial Ca^{2+} transport

Mitochondria serve as a central hub of $[Ca^{2+}]i$ regulation and mediate Ca^{2+} uptake through the mitochondrial Ca^{2+} uniporter (MCU) channel, which regulates $[Ca^{2+}]i$. MCU transports Ca^{2+} within the mitochondrial lumen, using the negative charge of the inner mitochondrial membrane to sustain the Ca^{2+} levels (126). The MCU complex consists of endosomal channel-dependent MCU proteins and their regulators, including the MCU-dominant negative b subunit (MCUb) and MCU-related regulatory proteins, such as the mitochondrial Ca^{2+} uptake (MICU) family (MICU1, MICU2 and MICU3), MCU regulator 1 (MCUR1) and essential MCU regulator (EMRE) (127). The activity of the MCU channel is regulated by MICU1 and MICU2, which form 95 kDa dimers through disulfide bonds. At higher Ca^{2+} levels, Ca^{2+}-dependent MICU1 activation and MICU2 inhibition ensure a rapid mitochondrial response to Ca^{2+} signals generated in the cytoplasm (128,129). In OC, it has been discovered that mitochondrial Ca^{2+} uptake by the gatekeeper mitochondrial calcium uptake 1 (MICU1/CBARA1) drives aerobic glycolysis. MICU1 is

Table IV. Summary of drugs/compounds targeting Ca^{2+} signaling for ovarian cancer treatment.

Calcium signals		Drugs/Compounds	Mechanism	(Refs.)
TRP	TRPC3	PLAA	Inhibitor	(27)
	TRPV1	DWP05195, Ursolic acid	Antagonist	(34,35)
	TRPM7	MK886, BAPTA-AM	Inhibitor	(61)
VGCCs	TTCC	Mibedil, 3,4-dihydroquinazoline derivatives	Blocker	(64)
	LTCC	Nifedipine	Blocker	(69)
	TTCC& LTCC	CCBs	Blocker	(70,71)
BKCa	-	NS1619	Activator	(81)
	-	Trimebutine Maleate	Inhibitor	(71)
GPCRs	-	TUTP	Antagonist	(97)
MCU	-	Gentisyl Alcohol, β-Sitosterol, Campesterol, Stigmasterol, Osthole, Fucosterol, Laminarin, Chrysophanol, Chrysin, Epothilone B	Inhibitor	(136-145)
	-	ABT-737, GRP75	Activator	(150,151)
Others	-	Saikosaponin D	Calcium mobilizer	(182)

TRP, transient receptor potential; PLAA, phospholipase A2 activating protein; MK886, 5-Lipoxygenase inhibitor; BAPTA-AM, Intracellular calcium chelator; VGCC, Voltage-gated Calcium Channel; TTCC, T-type Ca^{2+} channel; LTCC, L-type Ca^{2+} channel; CCBs, calcium channel blockers; BKCa, large conductance Ca^{2+}-activated K^+; NS1619, the BKCa channel opener; GPCR, G-protein-coupled receptor; TUTP, 2-thioureidothiophene-3-carboxylate; MCU, mitochondrial Ca^{2+} uniporter; ABT-737, a small-molecule Bcl-2 inhibitor; GRP75, glucose-regulated protein 75.

overexpressed in a panel of OC cell lines (CP20 and OV90) and its overexpression is associated with decreased overall survival (130). *In vitro* silencing of MICU1 increases oxygen consumption, decreases lactate production and inhibits clonal growth, migration and invasion of OC cells, while *in vivo* silencing inhibits tumor growth and enhances cisplatin efficacy and overall survival (Table II) (130).

It is known that the electron transport chain (ETC) drives physiological mitochondrial Ca^{2+} uptake. However, ETC overload and partial ETC inhibition can cause ROS production, leading to oxidative damage to the mitochondrial membrane. This in turn results in cell death and ROS-dependent tumor cell metastasis and invasion (131-133). Several studies have shown that modifying the Ca^{2+} concentration in mitochondria can be a potential treatment method for OC (134-136). Gentisyl alcohol, which has antibacterial, antifungal, antiviral and anticancer properties, is observed to inhibit cell proliferation while inducing apoptosis in human OC cells through DNA fragmentation (134). In addition, β-Sitosterol (135), Campesterol (136), Stigmasterol (137), Osthole (138), Fucosterol (139), Laminarin (140), Chrysophanol (141), Chrysin (142) and Epothilone B (143) have all been shown to increase ROS production by dose-dependently elevating Ca^{2+} concentrations in the cytoplasm and mitochondria of OC cells, leading to oxidative stress through the endogenous pathway and initiate apoptotic signaling (Table IV). Mitochondrial Ca^{2+} overload activates the unfolded protein response and the ER/mitochondrial axis, which then disrupt $[Ca^{2+}]i$ homeostasis, initiate apoptosis and inhibit cell proliferation (144). Treatment of cells with β-Sitosterol or Campesterol impairs mitochondrial membrane function, leading to the loss of membrane potential and disruption of Ca^{2+} homeostasis (135,136). Furthermore, laminarin suppresses the expression of the ER mitochondrial coupling protein glucose-regulated protein 75 (GRP75) in OC cells (140), where the lack of GRP75 expression has been associated with Ca^{2+} overload (145).

The high mortality rate of OC is largely attributed to its resistance to currently available chemotherapeutic drugs (7). Cisplatin is commonly used for the treatment of malignant OC, but acquired resistance limits its application. The inability to upregulate $[Ca^{2+}]i$ in OC cells results in cisplatin resistance by reducing oxidative stress (146). Bcl-2, a key regulator of survival and apoptosis, is known to block cisplatin-induced apoptosis by regulating Ca^{2+} signaling in various cancer cell lines. Bcl-2 overexpression inhibits ER mitochondrial Ca^{2+} signaling and increases cisplatin resistance in OC cells (147). ABT-737, a small-molecule Bcl-2 inhibitor, has been shown to increase free Ca^{2+} levels in the mitochondria in combination with cisplatin treatment of cisplatin-resistant OC cells, thereby enhancing mitochondria-mediated cell apoptosis (148). Increased mitochondrial Ca^{2+} may induce apoptosis in cisplatin-resistant OC cells, where the enrichment of GRP75 in the mitochondria-associated ER membranes may be responsible for this effect (149). In paclitaxel-resistant OC cells, lncRNA-RNA component of mitochondrial RNA processing endoribonuclease (RMRP) has been shown to increase MICU1 expression through miR-580-3p aggregation. By contrast, targeting lncRNA-RMRP was found to inhibit the miR-580-3p/MICU1 axis to increase paclitaxel sensitivity (150). Overall, mitochondrial Ca^{2+} alterations probably

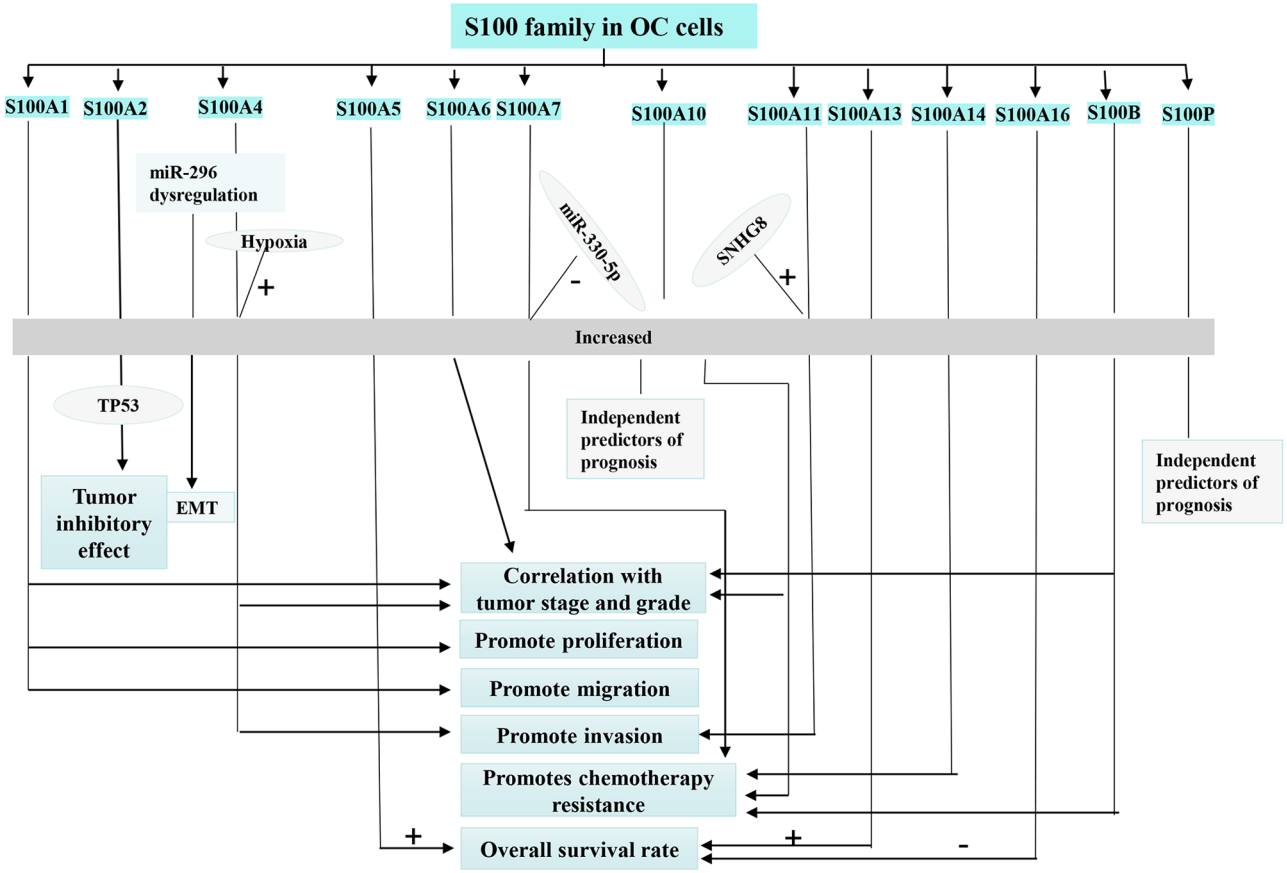

Figure 2. Effects of the S100 family on ovarian cancer cells. The abnormal expression of S100A1, S100A2, S100A4, S100A5, S100A6, S100A7, S100A10, S100A11, S100A13, S100A14, S100A16, S100B and S100P mainly contributed to the tumor progression. EMT, epithelial-mesenchymal transition; SNHG8, long non-coding RNA SNHG8; miR, microRNA; +, Promote; -, Inhibit.

serve a significant role in the treatment of OC. Further in-depth studies into MCU channels can aid in understanding their roles in the occurrence, development and prognosis of OC. These are expected to facilitate the development of novel therapeutic targets and search for new therapeutic methods.

5. S100 family and other Ca^{2+} signaling pathways

S100 family. There are 21 members in the S100 family known to date, all of which are found in human tissues and are acidic Ca^{2+}-binding proteins. These proteins are highly homologous both in terms of sequence and structure, can switch roles within a given biological process and are involved in a wide variety of cellular events, such as proliferation, apoptosis, migration, inflammation and differentiation (151). The proteins that make up the S100 family can serve as both Ca^{2+} sensors on the inside of cells and as extracellular factors promoting proliferation from the outside. Therefore, aberrant expression of S100 proteins has been proposed to be another factor in tumor development and progression (152,153). In a previous review, Bresnick *et al* (151) discussed the importance of S100 family members in diagnosing and treating cancer, how S100 signaling can affects the growth of tumors and how S100 inhibitors were found to treat cancer. With the progression of the disease, multi-drug resistance to tumor therapy remains to be a problem. Hua *et al* (154) found that the dysregulation of different S100 proteins can contribute to the development of tumor drug resistance, which worsens the prognosis of patients with cancer. A summary was also provided of how S100 family members can affect tumor resistance to therapy, pointing out that inhibition of S100 proteins can mediate the response of tumors to therapy. Accumulating evidence suggests multiple members of the S100 family are involved in OC development and progression (Fig. 2 and Table III) (153).

Compared with fallopian tube and normal ovarian epithelial tissues, S100A1 expression tends to be significantly higher in OC tissues, which is also associated with lymph node metastasis, International Federation of Gynecology and Obstetrics (FIGO) staging and tumor grade (155). S100A2 has also been hypothesized to be a tumor suppressor that aids in the stabilization and response to the transcription of mutant p53, thereby controlling cell proliferation (156). Higher expression levels of S100A2 have been shown to predict superior overall survival in patients with OC expressing wild-type TP53, but had no prognostic value in patients with mutant p53 OC. This suggests that the interaction between S100A2 and TP53 may mediate the tumor suppressive effects of S100A2 (153). The function of S100A3 in OC remains to be elucidated. Kikuchi *et al* (157) found that S100A4 is highly expressed in the nucleus in OC tissues; OC patients with stronger nuclear S100A4 expression showed a significantly shorter survival time compared those without. Subsequent treatment with the recombinant S100A4 resulted in the translocation of S100A4 into the nucleus, the enhancement of which enhanced OC cell invasiveness. These

findings suggest that the nuclear expression of S100A4 is involved in the aggressive behavior of OC. Furthermore, nuclear expression of S100A4 in combination with the nuclear HIF-1α protein under hypoxic conditions has been demonstrated to induce hypoxia response element-free methylation of the S100A4 gene and promote OC aggressiveness (158). In addition, miR-296 is an important upstream regulator of S100A4 and aberrant regulation of the miR-296/S100A4 axis has been reported to promote the EMT process and hasten OC progression (159). It was first proposed by Link *et al* (160) that high levels of circulating metastasis-associated in colon cancer 1 and S100A4 transcripts could predict the prognosis of patients with OC, because they were associated with advanced FIGO staging. Another previous study has shown that the insulin-like growth factor 1 receptor 6-/integrin-/S100A4 molecular network can regulate the organ-specific metastasis of chemoresistant epithelial OC cells. Genetic and pharmacological inhibition of S100A4 was found to significantly reduce distant metastasis and completely eliminated lung invasion by advanced chemoresistant epithelial OC cells (161). S100A5 is a novel member of the S100 protein family that can interact with Ca^{2+}, Zn^{2+} and Cu^{2+} (162). High S100A5 expression was previously reported to predict overall survival in all patients with EOC (153).

S100A6 expression has been documented in cancer xenografts and OC tissues. Wei *et al* (163) found that serum S100A6 concentrations are higher in patients with advanced OC compared with those with early OC. This suggests that S100A6 concentrations are associated with experimental tumor load and clinical disease stage, making S100A6 a useful biomarker for detecting and/or monitoring OC (163). In addition, in a previous study by Bai *et al* (153), a positive association between S100A6 mRNA expression levels and overall survival was identified in stage II patients but a negative association was found with stage IV patients. This suggests that S100A6 may serve different roles in patients with early and advanced OC. It is necessary to be able to independently reproduce these results followed by a deeper investigation into the associated underlying mechanism. S100A7 has been shown to promote tumor cell proliferation, migration, invasion and tumor metastasis. Metastasis and chemoresistance in OC cells have been shown to be controlled by S100A7 through the MAPK signaling pathway. miR-330-5p can target the 3'-untranslated region of S100A7, thereby reducing the activity of the protein and then the proliferation of OC cells (164). S100A10 is found in the plasma membrane, where it associates with Annexin A2 to form a heterotetramer (165). S100A10 expression in OC tissues has been associated with decreased overall survival and progression-free survival (165). In addition, a high S100A10 expression was found to be an independent predictor of OC prognosis, increasing the risk of progression and mortality from OC (166). Supporting this, OC cells were rendered more sensitive to carboplatin when the expression of S100A10 was downregulated (167).

High expression of S100A11 in the serum of patients with OC and increased proliferation, migration and invasion of OC cells are attributed to the lncRNA SNHG8, which regulates OC progression by targeting miR-1270 and S100A11 (168,169). Patients with grade II, stage I+II and p53 mutant OC had a longer overall survival if S100A13 levels were elevated (153). Serum S100A14 levels was found to be consistently higher in patients with OC, where a link was also found between elevated S100A14 and resistance to platinum-based chemotherapy (170). Higher levels of S100A16, a member of the S100 family isolated from astrocytomas (171), have also been associated with worse prognosis in patients with OC, particularly those with grade II, III and stage III EOC (153). S100B protein is overexpressed in OC tissues compared with that in normal ovaries and is in turn associated with advanced tumor stage, decreased differentiation and shorter overall survival (172). In addition, S100B has been documented to mediate chemotherapy resistance in OC cells through p53 (173) and controls the stemness of OC stem cell-like cells (172). Although high S100P expression is associated with a worse prognosis in OC patients in terms of overall survival and progression free survival, S100P has been shown to increase chemosensitivity of OC cells to carboplatin and paclitaxel *in vitro* (174,175). Overall, a comprehensive understanding of the function of S100 family members is clinically instructive for the diagnosis and prognosis of OC patients. According to results from a previous survey, S100 protein mRNA expression is strongly associated with overall survival in patients with OC, with high levels of S100 family members S100A10, S100A11, S100A16, S100B and S100P predicting worse overall survival, while S100A1, S100A2, S100A5, S100A6 and S100A13 were associated with longer overall survival, depending in part on OC subtype and clinicopathological features (153,176).

Several promising approaches are currently proposed and make use of current knowledge to assess S100 proteins as potential therapeutic targets of cancer therapy, as evidenced by the aforementioned studies. However, additional research is required to firmly establish S100 proteins as reliable biomarkers for OC therapy and to further characterize their roles in OC pathophysiology. Although these initial findings show promise, the true extent of the function of S100 proteins in OC remains unknown, which requires unravelling it can be fully exploited in the clinic.

Other Ca^{2+} signaling pathways. Ca^{2+} signaling is also associated with other molecules such as tumor-associated calcium signal transducer 2 (TROP2), calcium/calmodulin-dependent protein kinase (CaMKK) and saikosaponin-D (SSD) in OC (Table III) (177-179). TROP2 is a newly identified marker that plays a vital role in the proliferation and invasion of various tumors by transducing $[Ca^{2+}]i$ signaling (177). Wu *et al* (177) found that suppressing TROP2 expression in OC cells significantly slows cell proliferation, invasion and migration. CaMKK-β-mediated AMPK activity is required for regulating autophagy induction in OC spheroids and supporting cell viability, at least in part (180). Elevated $[Ca^{2+}]i$ activates the expression of CaMKK2, which mediates epidermal growth factor signaling through Akt signaling and is used by cancer cells as a signal for growth and survival (178). Chen *et al* (181) reported that CaMKK2 promotes the progression of ovarian carcinoma through the PI3K/PDK1/Akt Axis. SSD, a major bioactive component of Radix Bupleuri, exhibits anti-inflammatory, anti-tumor, anti-oxidant and anti-viral effects (179). Tsuyoshi *et al* (182) found that SSD may be a new adjuvant for the treatment of

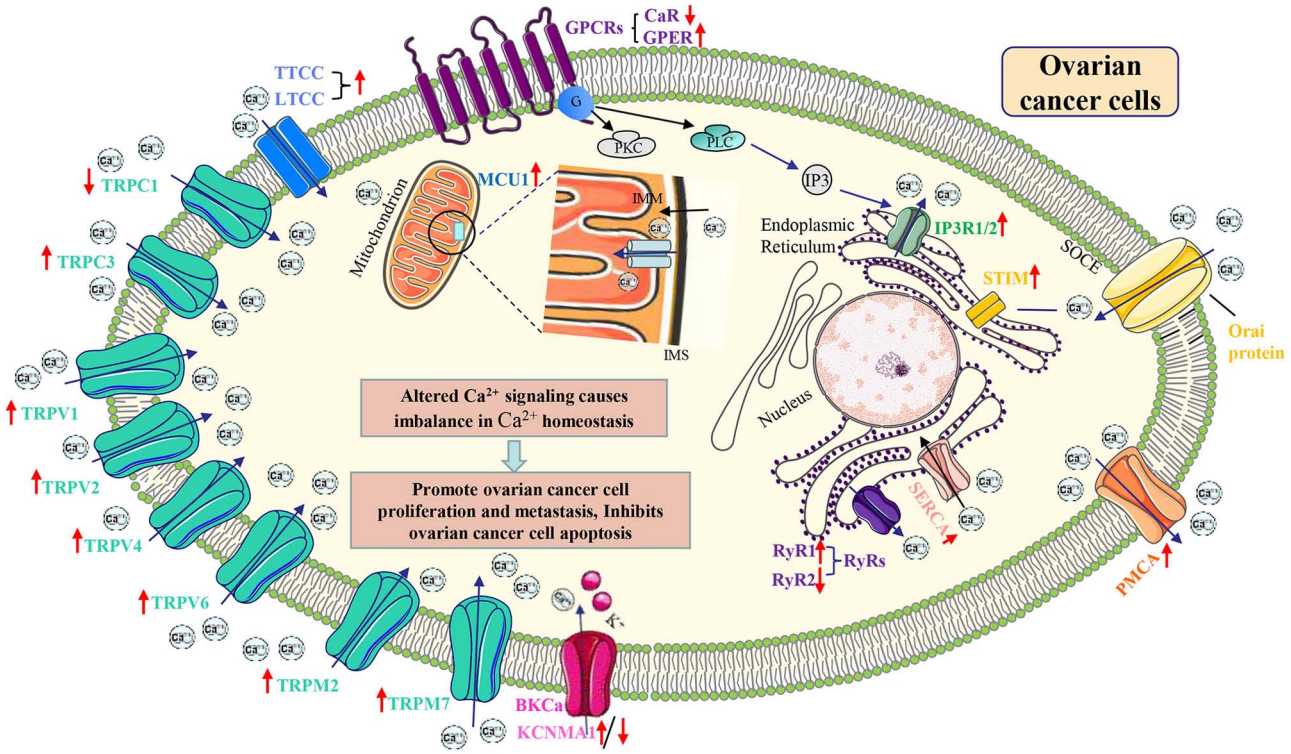

Figure 3. Altered intracellular Ca^{2+} signaling in ovarian cancer cells. Different Ca^{2+} channels, transporter proteins and pumps mediate the regulation of cytoplasmic Ca^{2+} concentration. In the PM, TRP channels, VGCC, BKCa channels, CRAC channels, PMCA pumps and GPCRs regulate intracellular and extracellular Ca^{2+} transport. IP3R, RyR and SERCA pump control Ca^{2+} storage in the endoplasmic reticulum. Members of the mitochondrial Ca^{2+} monotransport protein family are needed to regulate the amount of Ca^{2+} taken up by the mitochondria. All of the above alterations in Ca^{2+} signaling cause an imbalance in Ca^{2+} homeostasis in ovarian cancer cells and promote the development and progression of ovarian cancer. PM, plasma membrane; TRP, transient receptor potential; VGCC, voltage-gated Ca^{2+} channels; BKCa, large conductance Ca^{2+}-activated K^+; CRAC, Ca^{2+}-release-activated Ca^{2+}; PMCA, PM Ca^{2+}-ATPase; GPCR, G protein-coupled receptors; IP3R, inositol 1,4,5-trisphosphate receptor; RyR, ryanodine receptor; SERCA, sarcoplasmic reticulum Ca^{2+}-ATPase; TTCC, T-type Ca^{2+} channel; LTCC, L-type Ca^{2+} channel; TRPC, TRP canonical; TRPV, TRP vanilloid.

chemoresistant OC because it acts as a Ca^{2+} mobilizer and sensitizes OC cells to cisplatin by promoting mitochondrial division and G_2/M blockade through multiple signaling pathways. These findings suggest that TROP2, CaMKK2 and SSD are critical molecules in OC cell proliferation and point to a promising direction for future research.

6. Conclusion and outlook

Healthy and malignant cells both rely on cytosolic Ca^{2+} signaling for the regulation of their intracellular cellular processes. However, alterations in Ca^{2+} fluxes can overlap with crucial stages of the life cycle of types of cancer. Changes in the expression of Ca^{2+} channels, pumps and exchange proteins in OC tissues all suggest that Ca^{2+} plays an important role in regulating OC cell proliferation, migration and invasion (Fig. 3). In addition, drug-resistant OC cells have lower levels of Ca^{2+} and key genes involved in Ca^{2+} homeostasis, supporting the hypothesis that alterations in Ca^{2+} regulation contribute to tumorigenesis, metastasis, prognosis and drug resistance. The currently proposed inhibitors or activators targeting Ca^{2+} channels for the treatment of OC are summarized in Table IV.

Although recent advancements in Ca^{2+} channel research have provided promising insights, further investigations are required to establish effective combinatorial methods of targeted medications and chemotherapy to boost the survival rate of patients with OC. Understanding the biological processes that govern the modulation of Ca^{2+} signaling pathways in OC cells is urgently required. Ca^{2+} signaling appears to be a valid target for anticancer therapy in patients with OC and is supported by a substantial body of preclinical and clinical evidence. However, gaps in knowledge remain in our understanding of the role of Ca^{2+} signaling in types of cancer which is required to uncover the mechanisms of Ca^{2+} signaling in OC pathogenesis and facilitate the creation of novel therapeutic strategies. In conclusion, alterations in Ca^{2+} fluxes can influence malignant transformation, tumor progression and response to therapy in patients with OC by affecting a complex network of OC cell-intrinsic and extrinsic functions. Further research is necessary to disentangle its molecular and functional complexity.

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Availability of data and materials

Data sharing is not applicable to this article, as no data sets were generated or analyzed during the current study.

Ethics approval and consent to participate

Not applicable.

Authors' contributions

QG and FD wrote the original draft of the manuscript. QG, YZ, JL, MF, CZ and BJ reviewed and edited the manuscript. QG, FD, YZ, HD and TX supervised the present study. QG, JQ, JC, FD, JL, MF and JQ performed project administration: Data authentication is not applicable. All authors have read and agreed to the published version of the manuscript.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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