Mitochondrial-associated endoplasmic reticulum membrane interference in ovarian cancer (Review)

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Abstract. The mitochondria-associated endoplasmic reticulum (ER) membrane (MAM), serving as a vital link between the mitochondria and ER, holds a pivotal role in maintaining the physiological function of these two organelles. Its specific functions encompass the participation in the biosynthesis and functional regulation of the mitochondria, calcium ion transport, lipid metabolism, oxidative stress and autophagy among numerous other facets. Scientific exploration has revealed that MAMs hold potential as effective therapeutic targets influencing the mitochondria and ER within the context of cancer therapy. The present review focused on elucidating the related pathways of mitochondrial autophagy and ER stress and their practical application in ovarian cancer, aiming to identify commonalities existing between MAMs and these pathways, thereby extending to related applications of MAMs in ovarian cancer treatment. This endeavor aimed at exploring new potential for MAMs in clinically managing ovarian cancer.

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1. Introduction

Ovarian cancer, a malignant tumor frequently present in the reproductive system of women, can be classified based on its primitive tissue type into epithelial ovarian cancer, germ cell tumors and stromal tumors. However, the pathogenesis of ovarian cancer has yet to be fully elucidated. The currently favored hypotheses include BRCA1 and BRCA2 gene mutations (1), sexual hormone imbalance and prolonged chronic inflammation stimulation. Concurrently, epidemiologic studies indicated that the disease prevalence significantly correlates with ethnicity and country (1). Due to its inconspicuous symptoms at early stages, it is challenging to identify promptly; although it can be managed at advanced stages with surgery and treatments such as chemotherapy and radiotherapy, the outcome remains unsatisfactory. This, together with the extraordinary incidence and mortality rate, poses an alarming threat to women's health, compelling immediate exploration of innovative therapies.

In recent years, mitochondria-associated endoplasmic reticulum (ER) membrane (MAM), a unique cellular membrane structure existing between the outer mitochondrial membrane and the ER, has become implicated in a range of physiological functions such as mitochondrial biogenesis, function regulation, calcium ion carriage, lipid metabolism, oxidative stress and autophagy through this unique position. More importantly, mounting evidence indicates that MAMs may act as a potential therapeutic target influencing mitochondria and ER, two vital organelles in the cancer field. Hence, elucidating the MAMs could potentially provide a novel strategy for tackling diseases including ovarian cancer in the future.

However, despite the relatively modest research conducted on MAMs till date, it is evident from all empirical findings that MAMs bear a relationship with various disorders including cancers and neurodegenerative diseases. Regardless of whether it is basic or clinical research, reports on MAMs are comparatively scarce. Given its exceptional physiological structure and distribution, it is conceivable that MAMs hold substantial research value. Therefore, the impact of MAMs on physiological function was primarily discussed in the present review and fresh perspectives on the practical application of MAMs in ovarian cancer treatment were provided via examining proteins existing on MAMs, combined with their implementation in the management of ovarian cancer.

2. Mitochondrial inner membrane association with cellular physiological processes

In the appraisal of the profound correlation between ER and mitochondria, it was found that the dynamic adjustments of mitochondria and ER directly influence their physiological role and structure. These phenomena imply the existence of MAMs. Employing electron microscopy technology, the gap between mitochondria and ER was observed to be ~10-30 nanometers-an incredibly diminutive distance facilitating a plethora of protein interactions within this ambit, thereby constructing the biological grounding to affect the functions of mitochondria and ER (2). Despite the prevalent perception that the functions of mitochondria and ER have distinct differences, they can reciprocally influence each other via MAMs.

While it was previously proposed that MAMs are an illusion (2), more recent investigation utilizing cutting-edge scientific tools confirmed: MAMs indeed exist. Notably, MAMs are not static; their distance often varies with the presence of ribosomes. For instance, on a smooth ER (SER), the distance of MAMs is usually 10-15 nanometers, whereas on a rough ER (RER) it expands to 20-30 nanometers. More crucially, MAMs serve as pivotal in maintaining cell calcium homeostasis (3,4), lipid homeostasis (5), mitochondrial dynamic equilibrium (6) and the stability of organelles, among other physiological functions, which are critical for the survival of the organism.

Calcium homoeostasis. Calcium ions (Ca^{2+}) serve as the secondary messengers within cells, regulating a myriad of cellular processes. MAMs, significant bridges for Ca^{2+} transport, finely tune Ca^{2+} signal transmission ensuring precise and flawless execution of cell biological functions. At present, two primary types of Ca^{2+} release channels have been well-understood in MAMs, namely: IP3Rs and RyRs.

The IP3Rs, voltage-dependent anion channels that dominate Ca^{2+} release above MAMs, collaborate with GRP75 and VDAC to take on this formidable task. The tripartite protein complex assists calcium ions in traversing from mitochondria to ER.

Another primal ER protein SEPN1, abundant in this type of MAMs, can replenish calcium ions on the ER when it is depleted, thus circumventing ER stress. Besides protecting IP3R from oxidative harm by Ero1a, SEPN1 also upholds calcium ion equilibrium between MAMs, mitochondria and ER (6).

Existing in the same form as a protein complex are Sig-78 and immunoglobulin. When calcium ions are depleted in the ER, Sig-78 dissociates from the complex and interacts with IP3Rs, substantially enhancing Ca^{2+} influx into mitochondria. Moreover, Ero1a, an oxidase residing in MAMs, prompts calcium ion flux towards mitochondria when faced with ER stress by oxidative binding to IP3R, thereby activating IP3R (7,8).

Lastly, glutathione peroxidase 8 (GXP8), a bipolar transmembrane protein present in MAMs, can lower calcium level on the ER by suppressing the activity of SERCA when overexpressed. Also acting similar to GXP8 is the redox enzyme TMX1 located on the ER, again by preventing the action of SERCA. SERCA plays a core role in the transportation process of calcium ions. It regulates the content of intracellular Ca^{2+} ions and profoundly influences the flow of calcium ions in MAMs. When the pressure on the ER becomes excessive, the activity of SERCA1 dramatically escalates, thereby propelling calcium ions from the ER to mitochondria, culminating in mitochondrial apoptosis (7,8).

Moreover, mitochondria demonstrate their unique role during the transport of calcium ions over a short time period. Upon the transfer of calcium ions from the ER to MAMs (7,8), high calcium concentration regions often emerge macroscopically. Under this state, the speed at which mitochondria absorb calcium ions markedly accelerates. By contrast, when calcium ion concentration is low, the efficiency of mitochondria in absorbing calcium ions noticeably decreases. Therefore, the regulation of calcium ion concentration is indeed heavily influenced by a profound impact led by MAMs. Besides, existing research has unveiled that mitofusin 2 (Mfn 2) is a pivotal target for regulating calcium ion concentration in MAMs; however, some studies have yielded contrary experimental conclusions (9). Thus, there still remains considerable research exploration space in terms of how MAMs affect the degree of influence on the flow of calcium ions between mitochondria and ER.

Lipid homeostasis. There is robust correlation between MAMs and lipid homeostasis. Since other organelles lack the capacity to synthesize phospholipids from their precursor, and the ER is a pivotal site for regulating cell intrinsic lipid balance, lipids must diffuse from the ER into other organelles. It has been previously reported that MAMs are a cholesterol enriched membrane system, predominantly composed of caveolin proteins, serving an essential function, contributing towards enriching the related elements of MAMs' lipid metabolism, thereby underscoring the indispensable role of MAMs in preserving lipid homeostasis. Phosphatidyl serines (PS), as the predominant enzyme system generated within the ER, is primarily localized on MAMs. Subsequently, it translocates to mitochondria to be converted into phosphatidyl ethanolamines (PE) (10). Some of the PE, upon return to the ER, transforms into phosphatidyl cholines, which is further distributed to various other organelles. In this process, the pro-phospholipid acid of PS is synthesized in the ER, but necessitates storage in MAMs.

In addition to phospholipid synthesis, MAMs also perform another crucial element of cholesterol metabolism. The newly synthesized cholesterol within the ER must be transported to mitochondria to convert into pregnenolone, the primary substance of sex steroids. In the rate-limiting step of this process, MAMs serve a pivotal role. Furthermore, research indicates the abundant presence of MAMs in cholesterol acyltransferase 1 (ACAT1), an enzyme responsible for the conversion of free cholesterol into cholesterol esters (CEs). Such CEs are commonly stored in fat droplets. Hence, it is feasible to indirectly evaluate the activity of MAMs by measuring the activity of ACAT1 (11). As such, MAMs have gradually emerged as the primary activator of mitochondrial steroid synthesis. Subsequently, MAMs also participate in the generation of ceramide, regulating cell growth, inflammation response, differentiation and apoptosis (12,13).

Mitochondrial dynamics. Significantly, it has been previously elucidated that MAMs are the initial locations of mitochondrial division (14). For instance, mitochondrial division proteins 1, mitochondrial division factors, and mitochondrial dynamics proteins are all sequestered at the MAMs site and completed prior to mitochondrial division (15). Additionally, processes such as mtDNA replication, mitochondrial transport and mitochondrial self-division, all revolve around the MAMs.

Mitochondrial fusion and division, a highly dynamic network system, maintains a steady state equilibrium of fusion and division under normal physiological conditions to ensure optimal cell functioning. Certainly, appropriate stimulation is paramount for maintaining a high quality of mitochondria. Among key constituents of the mitochondrial fusion mechanism, Mfn1, Mfn2 and optic atrophy 1 (OPA1) play pivotal roles. Notably, Mfn1, acting as a requisite GTPase for outer membrane fusion, primarily restricts mitochondrial function through its interaction with Mfn1 on the MAMs (16). In concert with Mfn1 and Mfn2 on the MAMs, Mfn2 helps form the mitochondrial outer membrane and acquires specific morphology (17). Given the heightened degree of Mfn2 enrichment on the MAMs, it is conjectured that the MAMs hold great significance during mitochondrial fusion, particularly when post-MITOL/MARCH5 ubiquitination machinery causes alterations in the intersection between the ER and mitochondria (18).

Acting as a cytosolic protein, Dlp1 dynamically congregates to the mitochondrial membrane and substantially enhances membrane contraction velocity via a GTP-dependent oligomerization pathway. Under hypoxic circumstances, the accumulation of the OMM protein FUNDC1 induces ectopic Dlp1 accumulation in the MAMs (19). Furthermore, as an integral component of the apoptotic process, Fis1 can bind to BAP31 in the MAMs, transmitting the mitochondrial apoptotic signals to the ER. BAP31, a critical escort protein on the ER membrane, participates in the degradation of misfolded protein and apoptotic signaling within the endoplasmic reticulum stress pathway. When Fis1 unites with BAP31, it cleaves BAP31 into p20 BAP31; as an apoptosis-promoting protein, p20 BAP31 activates procaspase-8 to convert it into a functional form, which can cleave Bid and initiate cell apoptosis (20,21). Activation of p20 BAP31 also facilitates Ca^{2+} translocation from the ER to the mitochondria, indicating the ability of cellular apoptotic signals to feedback to the mitochondria (22,23). The stability of calcium ions similarly directly or indirectly influences the dynamics of the mitochondria (24).

Apoptosis. The relationship between calcium homeostasis and tissue structural integrity is exceedingly significant. With the excessive metabolism of Ca^{2+}, it can induce the opening of the mitochondrial permeability transition pore, escalating the permeability of the inner mitochondrial membrane. The mitochondrion then undergoes depolarization, subsequently impeding ATP synthesis, leading to an expansion in the mitochondria's molecular form and ultimately causing the rupture of the outer membrane, thereby releasing a substantial amount of cytochrome c, culminating in apoptosis. Noteworthy, previous studies have also elucidated that apoptotic signaling exists within MAMs (25-27). The majority of apoptotic signals from the ER converge on the mitochondria autophagy pathway. This further suggests that the ER stress situation will directly influence the physiological alterations of the mitochondria, and the most pivotal factor among these is the BH3 protein (25), which is uniquely activated by the ER and transmits autophagy signaling to the mitochondria (26). However, presently, it remains elusive whether this protein can be concurrently activated by all forms of ER damage, or is activated only during specific pathological processes where the ER is specifically damaged. It is conceivable that it may emerge as a potential therapeutic drug target for diseases in the future (27).

Moreover, the mitochondrial division factor Fis1 aids in maintaining the junctions between the ER and mitochondria through its interaction with Bap31 (28). When procaspase-8 is recruited, the cleavage of Bap31 will lead to an increase in mitochondrial permeability and instigate apoptosis (29,30). In the ordinary state, ceramide is synthesized via the ceramide synthase pathway. However, under stress conditions (for example, heat shock, TNF-α, Fas, chemotherapy drugs, toxins, radiation and other factors), ceramide can be rapidly synthesized in sphingomyelinase from sphingomyelinase. The accumulation of ceramide not only modulates various molecules involved in apoptotic signaling transductions but can interact with them, such as protein phosphatase 1A/2A, protein kinase C, NF-κB and Ras. A substantial accumulation of ceramide can lead to the formation of pores on the external mitochondrial membrane, induce the release of pro-apoptotic substances (such as cytochrome C) in the mitochondrial membrane gap, and propagate stress signals from the ER to the mitochondria (31). Whereas suppressing the activity of ACS1/4 can reduce the synthesis of ceramide and deter the occurrence of cell apoptosis (32). Nevertheless, given the intricate nature and cross-domain relationships of apoptosis itself, markedly more profound and meticulous discussions are needed to delve deeper into this complex matter.

3. Proteins contributing to the function of MAMs

The unique attributes of MAMs encompass their protein composition and structure, underscoring their pivotal roles in numerous physiological processes. Research on MAM proteins has unveiled a broad spectrum of physiological functions; however, comprehensive understanding remains to be achieved due to the intricate diversity present in the richly diverse MAM proteome. For example, the GTPase Mfn1/Mfn2, which plays an essential role in mitophagy during mitotic spindle formation, was identified with seemingly contradictory functional features (33); also present on the surface of MAMs are the calcium release channels IP3R and VDAC (35), responsible for regulating mitochondrial calcium homeostasis. Lastly, Grp75 holds a significant influence on the organizational structure of MAMs (38). The interactions among these proteins remain unexplored and hint at the need for further research.

FUNDC1. Research signifies that FUNDC1 is a ubiquitous protein within organisms (46). This protein is composed of 155 amino acids, encompassing three membrane spanning regions. Notably, its N terminus harbors the LTR motif, which aids in interaction with LC3 to regulate autophagy in mitochondria (41,42). The regulation of this activity is notably prominent

under low oxygen environments; the study predominantly focused on the effects of decreased Src kinase activity and weaning tyrosine 18 phosphorylation levels, thereby reinforcing the mutual interplay between LC3 and FUNDC1 (46).

FUNDC1 can also play a pivotal role in calcium transfer through interaction with IP3R2. Under hyperglycemic conditions, the activation of FUNDC1 can stimulate the binding of CREB to the FIS1 promoter, thereby promoting MAM formation. This indicates that FUNDC1 plays a critical part in the entire process of MAM formation. Additionally, FUNDC1 also participates in regulating mitochondrial dynamics, forming a synergistic relationship with OPA1. It has been discovered that incorporating change in lysine 10 in FUNDC1 significantly induces mitochondrial aggregation, reflecting the importance of FUNDC1 in regulating mitochondrial dynamics (47). NRF1, as a transcription factor, can stimulate its expression by binding to the FUNDC1 promoter 186/176 (48).

In HeLa cells, experiments have revealed that suppressing expression of FUNDC1 propels mitochondrial fusion, whereas augmenting its expression retards it, probably by inducing DRP1 to drive mitochondrial proliferation (49). This process also encompasses phosphorylation at site S13, which attenuates the interplay between FUNDC1 and Drp1 while amplifying the interaction with OPA1. These observations signify that alterations in FUNDC1 structure may guide distinct pathways that culminate in corresponding alterations in mitochondrial structure. Research along the path of FUNDC1 upstream regulation and its influence on structural alteration is projected to be a vital direction of future studies. Within the unique structure of MAMs, FUNDC1 plays a pivotal role in the evolution of various pathologies.

Experimental evidence has confirmed that suppression of FUNDC1 expression fosters the generation of extensive MAMs in diabetes-induced cardiomyopathy. This morphological and functional reconfiguration of MAMs initiates cell apoptosis and the disintegration of abnormal mitochondria, ultimately resulting in reduced synthesis and disruption of the respiratory chain function of mitochondria. In both patients afflicted with heart failure and murine cardiac muscle cells, a decrease was observed in the FUNDC1 protein level (49). Additional research uncovered that FUNDC1 mainly impairs mitochondrial function, causing harm to cardiac muscle cells, and the disruption of MAMs is intricately linked to mitochondrial dysfunction (50). Similarly, magnesium oxide and α-lipoic acid can diminish the phenotypic characteristics of cardiac muscle cells through interaction with FUNDC1 (51). Besides these diseases, FUNDC1 can also instigate mitochondrial autophagy, promptly triggering cell apoptosis and myocardial infarction (52). These instances not only underscore the significance of FUNDC1 but also spotlight the pivotal position of MAMs within cellular processes.

PACS-2. The PACS family is composed of the two proteins PACS-1 and PACS-2, which share a similar structure but exhibit distinct functions. Both proteins contain a furin binding region (FBR), an intrinsically disordered mid-region (MR), and a C-terminal region (CTR) (52). Specifically, the MR domain encompasses a native nuclear localization signal (NLS) domain and an Akt phosphorylation site, although the precise function of the CTR domain remains undefined (53). The prevailing consensus in academia suggests that the FBR domain plays a crucial role in recognizing and adhering to cargo proteins.

In 1998, Werneburg *et al* (54) identified the crucial role of PACS-1 in directing trafficking across the Golgi network (TGN) for the first time. Subsequently, in 2005, Köttgen *et al* (55) postulated that both PACS-1 and PACS-2 were involved in the transport process of polycystin-2 mediated by members of the TRP ion channel family (TRPP2). PACS-2 can precisely identify and bind cargo proteins with acidic ionization clusters, facilitating their transportation towards relevant organelles and thereby influencing cellular activities ranging from calcium exchange and apoptosis to membrane transport (56).

Numerous studies suggested that PACS-2 influences immune-induced apoptosis by regulating MAMs and thereby altering mitochondrial division. Additionally, PACS-2 binds to CNX in the cytoplasm and regulates the distribution of CNX to MAMs (57). Moreover, PACS-2 can interact with BIM, inviting the recruitment of BIM to lysosomes in a mitogen-activated protein kinase-JNK-dependent manner to form the apoptosis complex (58). Deeper research indicates that interaction of PACS-2 with ataxia telangiectasia mutated (ATMs) can activate NF-κB to promote cell survival (59). Furthermore, previous evidence demonstrated that PACS-2 participates in DNA damage-related apoptosis through two independent mechanisms. Firstly, following DNA damage, PACS-2 employs its NLS domain to shuttle itself into the nucleus and interact with SIRT1, thus hindering the deacetylation of p53, leading to cell cycle arrest (60). Secondly, upon DNA damage, PACS-2 engages ATM to activate NF-κB, promoting the expression of the anti-apoptotic protein Bcl-xL (61). Factors such as TRAIL can induce dephosphorylation of PACS-2 at Ser437 indirectly via Akt, thereby stimulating mitochondrial membrane permeability increase and lysosomal membrane permeability increase (62). By contrast, the stable phosphorylation of PACS-2 is synchronous with the p53/p21 and NF-κB/Bcl-xL pathways, serving as a cytoprotective mechanism.

Mfn2. Initially recognized as an obligatory dynein-like protein integral to outer membrane fusion, Mfn2 has recently been revealed to be localized on the ER membrane, engaging in reciprocal interactions with the OMM. Research indicated that the expression of Mfn2 alters the MAM hierarchy and is capable of enhancing the ER-mitochondria distance within the cell (63), hinting that it plays a pivotal role in sustaining mitochondrial morphology and ER-mitochondria contact sites interconnection. Nevertheless, existing findings pose contradictions to this hypothesis, revealing that cells with Mfn2 variations or deprivation may actually enhance ER-mitochondria coupling (64,65), suggesting an imperative for further investigation into the precise impact of Mfn2 on the MAM.

Significantly, Mfn2 serves as a receptor during the PINK1-Parkin-mediated autophagy process, playing a critical role in interface management (66). Moreover, Mfn2 directly interacts with the mitochondrial transport machinery, encompassing MIRO1/2 transmembrane transporters, specifically linked to the function of MARC proteins (67). Mfn2 has been proven to influence the fatty acid metabolism of mitochondria

by binding mitochondrial with lipid particles (68) and facilitating the transfer of phosphatidylserine from the ER to the mitochondria.

The downstream repercussions of Mfn2 on mitochondrial functionality are manifold, including alterations in the mitochondrial ultrastructure, cristae and supramolecular structures, affecting the oxidative phosphorylation process (69,70). Furthermore, the MAM can also regulate the oxidative phosphorylation process through calcium ion signal transmission (71). Mfn2 is also implicated in modulations of mtDNA stability, potentially due to its fusion effect leading to decreased mtDNA copies and increased mtDNA deletion frequency (72) which is pivotal for the distribution of mitochondrial DNA proteins. Additionally, studies have highlighted the crucial role of Mfn2 in preserving podocyte apoptosis through regulating the PERK pathway (73). Therefore, the multifaceted functions of Mfn2 contribute to explaining why cells lacking Mfn2 display diminished mitochondrial respiration.

Other proteins. Despite the diverse proteins existing on MAMs, the functional studies of Mfn2, FUNDC1 and PACS-2 are more comprehensive. Moreover, the influence of these proteins on related diseases is more profound. In addition to these pivotal proteins, MAMs also harbor critical participants including DJ-1, TDP-43 and CypD, although they do not directly affect MAM structure but play a crucial regulatory role in specific MAM functions. IP3R is an important Ca^{2+} efflux channel located at the ER surface, which mediates the release of Ca^{2+} from the ER lumen to the cytoplasm (74). VDAC is an ion channel located at the outer mitochondrial membrane; it mediates the movement of various ions and metabolites into and out of mitochondria and is involved in a series of cellular activities, including cell apoptosis, metabolism and regulation of Ca^{2+} (75). IP3R and VDAC are linked by Grp75 to maintain MAM structure (76). It is known that overexpression of VDAC can enhance the connection between ER and mitochondria, thereby improving the flux of Ca^{2+} from the ER to the mitochondria (77); when silencing VDAC1, the connection between Grp75 and IP3R1 decreases, suggesting decreased ER-mitochondrial interaction (78). Cells overexpressing Grp75 exhibit more IP3R1-VDAC1 interaction sites (79). Silence of IP3R1 or Grp75 can also reduce the connection between VDAC1 and Grp75 or IP3R1 (80).

Moreover, VAPB located within the ER membrane, participates in the activation of IRE1/XBP1 axis during the unfolded protein response in the ER (81,82). VAPB can form a complex with the outer mitochondrial membrane protein PTPIP51 and help maintain the structure of MAM. The mutant form of VAPBP56S, showing stronger affinity for PTPIP51, thereby promotes the transfer of Ca^{2+} from the ER to the mitochondria; knocking out any one of these two genes can reduce the transfer signal of Ca^{2+} (83) and decrease the level of contact between the ER and the mitochondria (84,85).

MOSPD2 is another member of the VAP family; it is a protein located on the surface of the ER membrane which can connect the ER and other membrane structures, and can also bind to small proteins that interact with VAP through the MSP (major sperm protein structural domain), a protein sequence motif called FFAT, such as PTPIP51 on the outer mitochondrial membrane (86). REEP1 is a protein located on the ER and the outer mitochondrial membrane. It has been demonstrated that REEP1 directly connects the ER and mitochondria through oligomerization and is involved in the formation of the MAM structure. Furthermore, REEP1 bends the ER membrane so that the ER can wrap around the mitochondria, which helps form MAMs (86). The complexity they participate in further highlights the complexity of MAMs, prompting to conduct more in-depth exploration (Table I) (Fig. 1).

4. MAMs in ovarian cancer

Cancer cells may modulate the expression of Ca^{2+} ion channels, influence signal transduction mechanisms (87,88), and modify the regulatory capacity of MAMs on ER-mitochondrial Ca^{2+} transport to generate a MDR phenotype (89). This allows them to evolve continuously and achieve resistance to apoptosis. Moreover, cancer cells necessitate additional mitochondrial ATP production to sustain their heightened proliferation activity. As Ca^{2+} sustains the activity of various enzymes in the mitochondrial energy cycle, an appropriate mitochondrial Ca^{2+} uptake is crucial for the survival of cancer cells. However, excessive mitochondrial Ca^{2+} uptake can lead to mitochondrial Ca^{2+} overload, subsequently triggering mitochondrial dysfunction and cancer cell death. Therefore, how to balance the control of multiple proteins through MAMs on the mitochondrial-ER complex mechanism is a pivotal strategy for cancer cells to acquire resistance to cell death. Currently, the study of Li *et al* (90) has identified GRP75 (a critical chaperone protein) as playing a pivotal role in the stability of MAMs by forming an IP3R/GRP75/VDAC1 complex. When GRP75 is absent, it results in a significant decrease in MAMs' stability, causing Ca^{2+} disorder between mitochondria and ER, leading to catastrophic reactive oxygen species (ROS) accumulation, and ultimately resulting in cell apoptosis. It is evident that targeting proteins on MAMs can be a key target for improving ovarian cancer research.

However, due to the particularity of MAMs' location and structure, there remains a lack of definitive direct correlation with ovarian cancer. Nevertheless, since MAMs are located between mitochondria and ER, most current studies primarily elucidate the impact on ovarian cancer from these two vital organelles, thereby indirectly indicating the potential application value of MAMs. Therefore, the following exploration of the relationship among mitochondria, ER, and ovarian cancer provides new perspectives and assistance for future direct study of MAMs in ovarian cancer (Table II).

Mitochondrial autophagy and ovarian cancer. Mitochondria are organelles involved in cellular energy production and biosynthetic processes (91). Both their content of mtDNA and expression levels of relevant mitochondrial mRNAs are altered during tumor progression, including the development of ovarian cancer. Investigations have suggested that suppressing mitochondrial autophagy may effectively mitigate the disease progression of cisplatin-resistant ovarian cancer (92,93). The studies by Yu *et al* (96) demonstrated that inducing mutations in the p62 UBA structural domain could regulate subcellular localization of HK2 in A2780 ovarian cancer cells' mitochondria, freeing PINK1/parkin-mediated mitochondrial autophagy to decrease cell sensitivity to

Table I. Functions of proteins on MAMs.

Protein name	Functional overview	Function	(Refs.)
IP3Rs-Grp75-VDACs	Calcium homeostasis	Regulation of apoptosis, metabolism and Ca^{2+}	(34)
α-Synuclein		Promotes Ca^{2+} by increasing endoplasmic reticulum and mitochondrial contact	(39)
CypD		Affects the transfer of Ca^{2+} between the two organelles	(44)
FATE1		Downregulation of the transfer of Ca^{2+}	(45)
Mfn1/MFN2	The architecture of MAMs	Maintain the structural aspects of MAMs and induce endoplasmic Reticulum stress.	(36)
MOSPD2-PTPIP51		Plays a role in connecting endoplasmic reticulum with other membrane structures	(37)
DJ-1		Enhances the connection between the ER and mitochondria	(40)
TG2		Increase the number of ER-mitochondrial contacts	(43)
NogoB		Increase the gap width of MAMs and affect their function	(45)

MAMs, mitochondria-associated endoplasmic reticulum membranes.

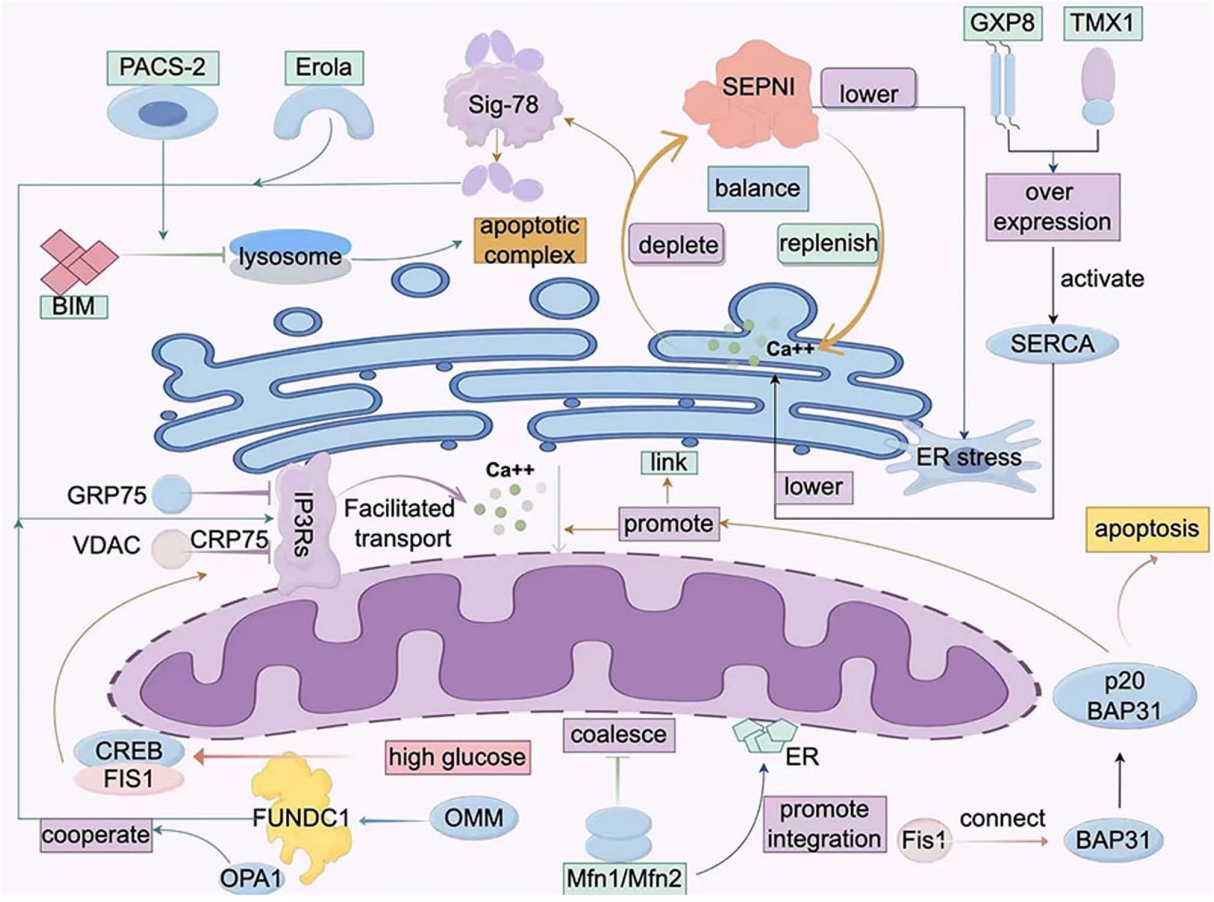


Figure 1. Structure of mitochondria-associated endoplasmic reticulum membranes.

cisplatin. Similarly, Vianello *et al* (94) observed an increase in the content of the mitochondrial autophagy receptor BNIP3 in cisplatin-resistant cells and in ovarian cancers resistant to platinum chemotherapy. Additionally, Zhou *et al* (95) revealed that the potent potential of a complex of glycosylated zinc (II)-cryptolepine could disrupt the mitochondrial autophagy

Table II. Application of MAMs in ovarian cancer.

Author, year	Overall	Pointcut	Outcomes	(Refs.)
Vianello *et al*, 2022	MAMs	Mitochondrial autophagy	Inhibition of mitochondrial autophagy can restore response sensitivity in cancerous cells to cisplatin.	(94)
Zhou *et al*, 2022			The aryl-glycosylated zinc (II)-cryptolepine complex disrupts aspects of the mitochondrial autophagy pathway to induce programmed cell death and autophagy in carcinoma cells.	(95)
Yu *et al*, 2017			ABT737 can induce mitochondrial autophagy, resulting in the release of cytochrome C.	(96)
Chen *et al*, 2021			Pardaxin, an antibacterial peptide, stimulates the process of apoptosis due to excess ROS production.	(97)
Wang *et al*, 2020			Elastin cell growth factor H propels the demise of cancer cells by catalyzing mitochondrial autophagy.	(98)
Katreddy *et al*, 2018			Both siRNA or Herdegradin activate mitochondrial autophagy to selectively eradicate cancer cells.	(99)
Meng *et al*, 2022			Cancer cell proliferation is suppressed by suppressing the gene chain CRL4cul4A/DDB1.	(100)
Yuan *et al*, 2023			The augmentation effect of cancer stem cells can be mitigated by judicious suppression of mitochondrial autophagy.	(101)
Martinez-Outschoorn *et al*, 2012			The absence of BRCA1 tumor suppressor gene triggers mitochondrial autophagy and catabolic processes.	(102)
Jin *et al*, 2020			The fucosylation of TGF-β1 has the potential to activate the regulatory function in ovarian cancer cells.	(103)
Yu *et al*, 2021			Enhancing PINK1/parkin mediated mitochondrial autophagy degrades the sensitivity of ovarian cancer cells to cisplatin.	(147)
Bae *et al*, 2021		Endoplasmic reticulum stress	Campesterol can inhibit ovarian cancer viainducing endoplasmic reticulum stress and amplify the efficacy of conventional anticancer drugs.	(104)
Cheng *et al*, 2022			The interaction between OMA1 and endoplasmic reticulum stress can deter drug resistance in cancer cells.	(114)
Jung *et al*, 2020			DPP23 can serve to diminish the resistance of ovarian cancer by invoking endoplasmic reticulum stress.	(115)
Xu *et al*, 2021			The PHLDA1 protein mediates ovarians cancer cell apoptosis versity through the endoplasmic reticulum stress response mechanism.	(116)
Kim and Lee, 2023			The validity of 6-gingerolovercoming resistance towards gefitinib in ovarian cancer cells is confirmed via stimulating endoplasmic reticulum stress.	(117)
Bahar *et al*, 2021			The combined administration of PARP inhibitor and cisplatin downregulated cisplatin-resistant OC cells, thereby mitigating endoplasmic reticulum stress and overcoming PARP inhibitor cross-resistance in OC.	(118)
Rezghi *et al*, 2021			Verified miR-3c-1-1p engages cell apoptosis through endoplasmic reticulum stress.	(120)
Kong *et al*, 2021			The nanoparticle's reduction-sensitive polymer form can escalate endoplasmic reticulum stress, thus enhancing therapeutic efficacy.	(121)
Wang *et al*, 2020			Epoxyeicosatrienoic acid H induces endoplasmic reticulum stress and stimulates apoptosis.	(122)
Wang *et al*, 2020			The chemical reagent DWP05195 triggers cellular apoptosis through the induction of endoplasmic reticulum stress.	(123)
Yart *et al*, 2022			Genomic reprogramming was accomplished via Activation of UPR subsequent to cell fusion, augmenting the traits of polytene cancers cells and *in vitro* development.	(124)

Table II. Continued.

Author, year	Overall	Pointcut	Outcomes	(Refs.)
Chen *et al*, 2022			Suppressing ENTPD5 can inhibit the proliferation and migration of PSMA-positive cells, and impede the activation of the GRP78/p-eIF-2α/CHOP pathway.	(125)
Barez *et al*, 2020			It stimulates intra-endoplasmic reticulum stress of cystathionine-12/3 and Bax/Bcl-2 proteins, restraining the proliferation of cancerous cells.	(126)
Zundell *et al*, 2021			Simultaneously, the IRE1a/XBP1 pathway demonstrates therapeutic efficacy in ovarian carcinoma harboring ARID1A mutations.	(127)
Ma *et al*, 2019			Hypoglycemia and metformin induce apoptosis of malignant cells via endoplasmic reticulum stress.	(128)
Lin *et al*, 2021			Suppressing over-expression of CARM1 exhibits efficacy in ovarian cancer treatment.	(129)
Xiao *et al*, 2022			The WEE1 inhibitor AZD1775 triggers cell apoptosis, and the combination of AZD1775 with the IRE1α inhibitor MKC8866 synergistically exhibits anticancer efficacy.	(130)
Zhang *et al*, 2019			ANGII exhibits inhibitory effects on endoplasmic reticulum stress and induces the morphogenesis and migration of ovarian cancer spheroids.	(131)
Singla *et al*, 2022			Natural compounds exhibit potent inhibitory properties against endoplasmic reticulum stress.	(132)
Hong *et al*, 2022			The mountain yam flavonoids can catalyze endoplasmic reticulum stress.	(133)
Li *et al*, 2019			Chiwanol I molecules can induce the death of cancer cells by stimulating the endoplasmic reticulum stress pathway.	(134)
Bae *et al*, 2020			Fucosterol elicits endoplasmic reticulum stress, which subsequently suppresses the proliferation of cancer cells.	(135)
Zhu *et al*, 2023			Two mechanisms have been identified to synergistically counteract the resistance of SKOV3/DDP cells against cisplatin.	(136)
Bae *et al*, 2020			The phlorotannins in *Fucus evanescens* can inhibit ovarian cancer cell proliferation by regulating endoplasmic reticulum stress.	(138)
Kim and Ko, 2021			In traditional Chinese medicine, JIO17 induces apoptosis of cancer cells.	(139)
Abdullah *et al*, 2022			The mechanism by which endoplasmic reticulum stress triggers the release and embrace of calreticulin in ovarian cancer cells has been scrutinized.	(140)
Bi *et al*, 2021			Methanesulfonylamine can initiate extranuclear stress to consequently trigger immunogenic cell death in ovarian cancer.	(142)
Lau *et al*, 2020			Taxol elicits mechanical stress within the endoplasmic reticulum, leading to immunogenic cell death in malignant cells.	(143)
Song *et al*, 2018			Endoplasmic reticulum stress IRE1a/XBP1 could potentially influence the antitumor immunity of ovarian cancer patients by manipulating T cells.	(145)
Cao *et al*, 2019			The evidence underscores the capacity to release T cell-mediated antitumor immunity by blocking Chop or endoplasmic reticulum stress.	(146)

MAMs, mitochondria-associated endoplasmic reticulum membranes.

pathway and induce autophagy and apoptosis in SKOV-3/DDP cells, highlighting its capability in developing chemotherapeutic drugs against cisplatin-resistant SKOV-3/DDP cells. Simultaneously, Yu *et al* (96) confirmed that ABT737, a potent inhibitor of BCL2/BCLXL, could considerably elevate the concentration of DRP1 in mitochondria, thus triggering the release of Cytochrome C in mitochondria and their autophagy in SKOV3/DDP cells. This finding underscores the suitability of targeting antiapoptotic proteins of the BCL2 family as a novel therapeutic strategy for treating patients with ovarian cancer with cisplatin resistance.

Inducing mitochondrial autophagy may trigger the process of programmed cell death in ovarian cancer cells at the terminal stage. Chen *et al* (97) discovered that the antimicrobial peptide pardaxin can stimulate PA-1 and SKOV3 cells to generate excessive ROS. This surplus ROS accomplishes this by decreasing the destruction of fusion proteins, declining the expression of mitochondrial transporters 1/2 and L-/S-OPA1, inducing the expression of fusion proteins DRP1 and FIS1 to enhance mitochondrial fission rates, and at the same time initiating the expression of autophagy-related proteins Beclin, p62 and LC3 to stimulate the apoptotic pathway. Furthermore, Wang *et al* (98) revealed that the epoxidecolchicine H derived from the metabolism of *Phomopsis* was capable of effectively increasing the ROS levels in cells, weakening the mitochondrial membrane potential, thereby causing damage to mitochondria, activating the mitochondrial autophagy process. Concurrently, this compound is also able to mediate apoptosis pathways associated with ER stress, further propelling the apoptotic process of ovarian cancer A2780 cells (98). Katreddy *et al* (99) study identified that high malignant epidermal growth factor receptors (EGFR) are frequently overexpressed in solid tumors. The use of siRNA or synthetic EGFR downregulating peptides (Herdegradin) can effectively downregulate the expression of EGFR protein. Notably, this downregulation is achieved by activating the mTORC2/Akt pathway, stimulating selective mitochondrial autophagy, and achieving the selective elimination of ovarian cancer cells (100).

Moderate suppression of mitochondrial autophagy may restrain the tumor's metastatic capacity. Yuan *et al* (101) indicated that mice exposed to BPA/BPS are more susceptible to tumor metastasis, as BPA/BPS can enhance the stem cell characteristics of ovarian cancer cells via a non-normal PINK1/p53 mitochondrial autophagy process, and the moderate suppression of mitochondrial autophagy can restrain this augmentation effect.

Focusing on the mitochondrial autophagy, researchers aim to elucidate novel targeted targets in ovarian cancer therapy. Martinez-Outschoorn *et al* (102) have elucidated that BRCA1 tumor suppressor gene deletion can instigate hydrogen peroxide production, wherein the hydrogen peroxide produced by BRCA1-null ovarian cancer cells stimulates NFB activation in stromal fibroblasts, inducing oxidative stress and consequently triggering mitochondrial autophagy and catabolic processes. Concurrently, MCT4 marker upregulation and Cav-1 expression loss also occur. Jin *et al* (103) further discovered that fucosylation of TGF-β1 augments Trk-like autophosphorylation via the PI3K/Akt and Ras-Raf-MEK-ERK pathways, thereby enabling ovarian cancer cell regulatory functions. This provides an alternate research avenue for TGF-β1 targeting in ovarian cancer therapy. Bae *et al* (104) identified that campesterol influences mitochondrial function, triggering excessive calcium accumulation and the creation of ROS, thereby inflicting ER stress and thereby inhibiting ovarian cancer. They observed in experimental settings that campesterol amplified the efficacy of conventional anticancer drugs, presenting potential as a novel drug for future treatment of ovarian cancer; however, this enhanced anticancer effect requires further study.

In summary, mitochondrial autophagy plays a substantial role in ovarian cancer therapy. It not only enhances the sensitivity of ovarian cancer cells to chemotherapy drugs and reduces drug resistance by inhibiting mitochondrial autophagy; but also triggers mitochondrial autophagy to drive ovarian cancer cell apoptosis. Moreover, manipulating mitochondrial dynamics, enhancing mitochondrial autophagy, or prodigiously initiating ROS generation and suppressing mitochondrial autophagy can ultimately lead to ovarian cancer cell demise. Hence, regulating the mechanisms of mitochondrial autophagy may be conjectured as a potential strategy for ovarian cancer therapy.

ER stress and ovarian cancer. Based on the presence or absence of ribosomes at the cisternal face of cell membranes, ER can be classified as RER and SER. These constitute distinct spatial domains that are nevertheless integrally related constructs (105). Moreover, the ER can also be classified based on its membrane structure features. These structures encompass the outer nuclear membrane, flared ER pools, and a polygonal pipeline system composed of triangular junction rings (106).

The ER lies in proximity to numerous other organelles and boasts extensive volumes within cells, the magnitude of which is contingent upon the type of cell. Notably, the interaction with mitochondria merits special mention. Given the pivotal role of mitochondria in organs (specifically their function during apoptosis), this association assumes paramount importance (107,108). In fact, this connection between the ER and mitochondria is predominantly mediated by the MAM (109). Additionally, MAM synergizes with the cell membrane to maintain its stability and growth. This interplay is controlled by Ca^{2+} levels and several proteins, including stromal interaction molecule 1 located in the ER and calcium release-activated calcium channel protein1 residing in the cell membrane (110). Notably, the ER appears to also partake in autophagy processes, as observed by linking endocytic vesicle systems (111). When contacted with specific ER assemblies known as sub-Golgi bodies, one of the core structures of autophagosomes-the phagophore will proliferate and mature into a mature autophagosome (112,113).

Recent scientific literature from recent years suggests that ER stress can significantly diminish the resistance of ovarian cancer cells. Cheng *et al* (114) discovered in their research that mitochondrial protease OMA1 not only triggers the morphogenesis of mitochondrial structures by cleaving OPA1 but also significantly reduces the drug resistance of ovarian cancer cells by integrating ER stress through its interaction with the PHB2/OMA1/DELE1 pathway. Additionally, Jung *et al* (115) identified that DPP23, functioning as an initiator of ER stress, effectively combats ovarian cancer resistance. Xu *et al* (116) revealed that PHLDA1 fine-tunes the apoptotic sensitivity

of ovarian cancer cells via the ER stress response process. Kim and Lee (117) corroborated that 6-gingerol induces ER stress in ovarian cancer cells and successfully overcomes resistance to gefitinib, thus providing a novel strategy for treating ovarian cancer using the combination of gefitinib and 6-gingerol. Lastly, Bahar *et al* (118) suggested that the combination of PARPis and cis-diminution of cis-OC cells may present an efficacious method to broaden therapeutic potential in response to ER stress, thereby overcoming platinum chemotherapy resistance in OC and PARPi cross-resistance.

ER stress is progressively emerging as a novel treatment approach for ovarian cancer (119). Rezghi *et al* (120) demonstrated using experimental evidence that miR-3c-1-1p regulates XBP30/CHOP/BIM-mediated ER stress, suppresses transcription of XBP2 in ovarian cancer cells and consequently triggers the activation of the apoptosis pathway. Kong *et al* (121) utilized platinum (IV) prodrug and near infrared II (NIR II) photothermal agent IR1048 as the foundation, generating enhanced ER stress through formation of reduced-sensitive polymer nanoparticles to amplify therapeutic effects against ovarian cancer. Wang *et al* (122) found that during their research, Erythropoietinaxin 2A9 (EpoxiDRESSIN H), was capable of triggering apoptosis pathways related to mitochondria and ER stress, thereby stimulating apoptosis of human ovarian cancer A2780 cells further. Similarly, Wang *et al* (123) reported that DWP05195 could induce ER stress via the ROS-p38-CHOP pathway in human ovarian cancer cells, triggering cell apoptosis. Yart *et al* (124) discovered that activation of UPR by cellular fusions increases the generation of polyploid multi-cancer cells *in vitro* and bestows them with new attributes, and also established that regulation of UPR in patients with ovarian cancer could represent an intriguing and potent therapeutic strategy. Chen *et al* (125) efficiently suppressed proliferation and migration of prostate specific membrane antigen (PSMA)-positive cells by inhibiting ENTPD5 and at the same time, blocked the activation of GRP78/p-eIF-2α/CHOP pathway, providing potential effective therapeutic targets for investigating prostate cancer treatment. Barez *et al* (126) confirmed in the context of studying IRE1a inhibitor STF-083010 that suppressing caspases-12/3 and Bax/Bcl-2 proteins could effectively inhibit ovarian cancer proliferation, revealing STF-083010 as a novel potential therapeutic target for treating ovarian cancer cells associated with ER stress. Moreover, in addition to IRE1a inhibitors, Zundell *et al* (127) posited that IRE1a/XBP1 pathway carries innovative therapeutic potential against ARID1A-mutated ovarian cancers, providing scientific basis for drugs concurrently utilizing the IRE1a/XBP1 pathway. Ma *et al* (128) identified that under low glucose and metformin's effect, ANGII triggers inhibited ER stress, inducing the formation and migration of ovarian cancer spheroids. By contrast, Lin *et al* (129) found that this pathway had comparable effects on ovarian cancer cells expressing CARM1 and could achieve the therapeutic objective by decreasing overexpressed CARM1. Additionally, Xiao *et al* (130) used WEE1 inhibitor AZD1775 to stimulate PERK, thereby triggering apoptosis of ovarian cancer cells, and in clinical practice, combined AZD1775 with IRE1α inhibitor MKC8866 to achieve synergistic anti-ovarian cancer effects. Zhang *et al* (131) observed that ANGII regulates lipid desaturation, triggering suppression of ER stress, resulting in the formation and migration of ovarian cancer spheroids.

Singla *et al* (132) asserted that naturally occurring compounds play a pivotal role in regulating ER stress, further demonstrating that various such natural substances, such as quercetin, curcumin and resveratrol, exhibit effective ER stress inhibitor effects in the context of ovarian cancer. Hong *et al* (133) employed the action of mountain heteroflavone complex extracted from tricuspid fruit on ovarian cancer cells, observing apoptosis of cancer cells; subsequent studies revealed that mountain heteroflavone can interfere with mitochondrial co-localization through inhibiting the PI3K/AKT and MAPK pathways and initiate ER stress. Li *et al* (134) identified cucurbitacin I as inducing death of ovarian cancer cells via the ER stress pathway. Bae *et al* (135) discovered that fucosterol (present in algae) could induce mitochondrial dysfunction and ER stress, thereby suppressing the proliferation of ovarian cancer cells. Zhu *et al* (136) elucidated that naringin could regulate the PI3K/AKT/mTOR signaling pathway to suppress SKOV3/DDP cell autophagy, and also facilitate SKOV3/DDP cell apoptosis by targeting ER stress; these two mechanisms synergistically counteract tolerance to cisplatin exhibited by SKOV3/DDP cells. This experimental outcome strongly supports the extensive application prospects of natural compounds in treating ovarian cancer therapies (137). Bae *et al* (138) discerned the regulatory effect of fucosanglioside in maqueigao (Centricellularis longicaudata), a natural compound, on ER stress to restrain the proliferation of ovarian cancer cells. Kim and Ko (139) also posited that JIO17 from traditional Chinese medicine can induce ovarian cancer cell apoptosis through the NOX4/PERK/CHOP pathway.

Abdullah *et al* (140) investigated the mechanism by which ER stress induces release and binding of calreticulin in ovarian cancer cells, hypothesizing that calreticulin has a profound connection with immunogenic cell death in ovarian cancer cells; meanwhile, existing experiments have confirmed the value of calreticulin in prognostic evaluation and prediction (141), and future research remains necessary. Bi *et al* (142) triggered immunogenic cell death in ovarian cancer through initiating ER stress using a mitochondrial uncoupling agent benzylamine, and remarkably inhibited tumor progression. Separately, Lau *et al* (143) discovered that paclitaxel triggers generation of ER stress through the TLR4/IKK2/SNARE pathway, leading to immunogenic cell death in ovarian cancer cells, suggesting a higher occurrence rate of immunogenic cell death in ovarian cancer and therefore possessing significant research significance; the importance of CALR as a crucial indicator for paclitaxel chemotherapy in ovarian cancer was also underscored.

Beyond addressing mortality, the immune system also plays a significant role in tumor cells (144,145). For instance, Song *et al* (145) discovered that ER stress IRE1a/XBP1 potentially influences T cell metabolic adaptability and antitumor potency, thereby influencing the antitumor immunity of patients with ovarian cancer, providing a novel therapeutic approach in immunotherapy. Furthermore, Cao *et al* (146) elucidated the central function of Chop in tumor-induced dysfunction of CD8 T cells, and the potential for therapeutic efficacy to release T cell-mediated antitumor immunity through blocking Chop or ER stress.

5. Conclusions

In light of the comprehensive factors, MAM carves a unique functional role as a link between the mitochondria and ER. It exhibits

superior performance during mitochondrial autophagy and ER stress response. It is capable of sequentially regulating these two crucial processes to suppress the malignant proliferation, migration and drug resistance ability of ovarian cancer. Notably, its intrinsic regulatory mechanism implicates numerous proteins, some of which may precisely be key players in a certain disease's progression. Consequently, meticulously exploring its potential application value and vast research prospects warrants more time and effort. Nonetheless, the present review elucidated the correlation between mitochondrial autophagy, ER stress and MAMs, with an expectation of conducting more thorough research on this topic in subsequent efforts. Furthermore, given that MAMs have not been extensively validated in ovarian cancer-related studies, the integrated analysis related to ovarian cancer outcomes remains relatively thin. It is expected that in future research endeavors, such research can be more profoundly conducted.

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Authors' contributions

JHZ and YLX were involved in the writing of the original manuscript. YFD and JZ completed the original manuscript. HPL completed manuscript revisions. WJP was involved in drawing the diagram. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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