



Review

Possible Roles of Mitochondrial Dynamics and the Effects of Pharmacological Interventions in Chemoresistant Ovarian Cancer



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ABSTRACT

Ovarian cancer is the major cause of death out of all the gynecologic cancers. The prognosis of this cancer is quite poor since patients only seek treatment when it is at an advanced stage. Any early biomarkers for this cancer are still unknown. Dysregulation of mitochondrial dynamics with associated resistance to apoptosis plays a crucial role in several types of human carcinogenesis, including ovarian cancers. Previous studies showed that increased mitochondrial fission occurred in ovarian cancer cells. However, several pharmacological interventions and therapeutic strategies, which modify the mitochondrial dynamics through the promotion of mitochondrial fission and apoptosis of cancer cells, have been shown to potentially provide beneficial effects in ovarian cancer treatment. Therefore the aim of the present review is to summarize and discuss the current findings from *in vitro*, *in vivo* and *clinical studies* associated with the alteration of mitochondrial dynamics and ovarian cancers with and without interventions.

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1. Introduction

Ovarian cancer remains the leading cause of gynecologic cancer death in the United States [1]. The 5-year relative survival rate is low since most of patients only seek treatment in advanced stages of the disease [1]. The majority of histological subtypes of ovarian cancers are epithelial cancers [2]. Recently, ovarian cancers have been subdivided into low-grade and high-grade cancers based on underlying molecular biological differences [3]. The primary treatment for ovarian cancer is surgical removal followed by systemic platinum-based chemotherapy [4]. The prognosis of ovarian cancers can be classified as poor when no clinical benefit or refractory condition occurs after two consecutive chemotherapy regimens, or when cancer recurs within 6 months after completion of treatment with chemotherapy or called platinum resistant condition [4]. On the contrary, the condition in which the cancer relapses after 6 months of initial chemotherapy is classified as the platinum sensitive condition [4]. Although many patients respond well to the first-line chemotherapy, some patients with an advanced stage ovarian cancer ultimately develop recurrent diseases with the platinum resistant condition [2]. Therefore, research into the identification of an early biomarker of ovarian cancers and into alternative strategies to treat patients with ovarian cancer is still needed.

Mitochondria are mobile organelles, undergoing consistent transformation, a process known as “mitochondrial dynamics” [5]. Mitochondrial dynamics consists of two processes, mitochondrial fusion and fission. Mitochondria can continuously join together by the process of fusion and divide into two mitochondria by the process of fission. The process of fission creates small and fragmented mitochondria, which can generate reactive oxygen species (ROS), cause mitophagy, or accelerate cell proliferation in response to nutrient excess and cellular dysfunction. An increase in mitochondrial fission has been observed in several human diseases including several types of cancer cells [6–12]. In contrast to mitochondrial fission, mitochondrial fusion results in a tubular or hyperfused mitochondrial network that allows diffusion of matrix content among mitochondria, diluting the accumulated mitochondrial DNA mutations and oxidized proteins [5,13]. Previous studies have reported an association between an increased mitochondrial fusion and chemoresistance in several cancer types, including breast, cervical and ovarian cancer [14,15]. An essential step in mitochondrial membrane fission is the recruitment of dynamin-related protein-1 (Drp1) to mitochondria and interaction with its outer mitochondrial membrane receptors, where membrane constriction fueled by GTPase activity is initiated [5]. With regards to mitochondrial fusion, the mitofusins, Mfn-1 and Mfn-2, along with optic atrophy protein 1 (Opa1), have been shown to mediate mitochondrial fusion [5]. Several previous studies have shown an imbalance of mitochondrial fission and fusion in several types of cancer [6–12]. Those studies demonstrated that increased fission activity and/or decreased fusion leading to a fragmented mitochondrial network have been observed in cancer cells [6–12].

Recent studies have demonstrated that ovarian cancer cells had an increase in mitochondrial fragmentation, Drp1 protein and mRNA levels, indicating a potential role of Drp1, a mitochondrial fission mediator in tumorigenesis in ovarian cancer [10,16]. In addition, a previous study reported the relationship between mitochondrial fusion and chemoresistance in ovarian cancer [15]. Furthermore, the mitogen-activated protein kinase/ extracellular signal-regulated (MAPK/ERK) pathway and estrogen-related receptor (ERR)- α (a co-transcription factor for gene expressions associated with mitochondrial fusion) have been shown to be associated with invasion, migration and aggressiveness in human ovarian cancer cells [17,18]. Hou and colleagues demonstrated that the inhibition of the MAPK/ERK pathway with a MEK inhibitor (MEKi) caused an increase in ERR- α positive ovarian cancer cells, resulting in weak tumor suppression activity [19]. However, the tumor suppression effect was enhanced when the treatment was combined with fulvestrant (a synthetic estrogen receptor (ER)

antagonist) [19]. In addition, Wang and colleagues observed that an increase in ERR- α was associated with an elevation in Mfn-1 and Mfn-2 mRNA expression, leading to an epithelial-mesenchymal transition (EMT), and finally resulting in increased ovarian cancer cell migration [18]. All of these findings suggest that alterations in mitochondrial dynamics with increased mitochondrial fusion could be a possible underlying mechanism responsible for the aggressiveness of ovarian cancers.

Moreover, increased Drp1 expression is associated with a hypoxia-driven migratory phenotype in multiple cancer types, and several studies have emphasized the important role of mitochondrial dynamics in cancer metastasis [12,20,21]. Therefore, the aim of this review is to summarize the existing evidence regarding the connection between mitochondrial dynamics and ovarian cancers and the effects of various pharmacological interventions on mitochondrial dynamics of ovarian cancers.

1.1. Search Strategy and Selection Criteria

The PubMed database was searched using the keywords: “ovarian cancers”, and “mitochondrial dynamics” from August 2013 to September 2017. The search was limited to research articles published in the English language.

2. Mitochondrial Dynamics under Physiological and Pathological Conditions

Mitochondria are dynamic organelles that have their own genome and process of protein synthesis [22]. Mitochondrial morphology varies across cell types and tissues through the regulatory process of mitochondrial dynamics: fusion and fission. In addition, mitochondria play a central role in many biochemical, fundamental cellular and physiological processes such as the generation of ATP and reactive oxygen species (ROS), calcium homeostasis, cell-cycle progression, apoptosis, mitophagy and oxygen sensing [5]. During their life cycle, mitochondria start with growth and division of pre-existing mitochondria (known as biogenesis) and end with degradation of damaged mitochondria by mitophagy (a process called turnover) [23]. Both fusion and fission enable the cells to create multiple heterogeneous mitochondria or interconnected mitochondrial networks, depending on the physiological conditions. Fission plays roles in the maternal inheritance and separation of organelles during cell division, the release of pro-apoptotic factors, the intracellular distribution, and the elimination of impaired organelles by mitophagy [23,24]. Fused mitochondrial networks are essential for the dissipation of metabolic energy and for the complementation of mitochondrial DNA (mtDNA) gene products in heteroplasmic cells to defend against aging [23]. The balance of these processes is essential for cell life and death.

Unopposed fusion leads to a hyperfused network and serves to counteract metabolic insults, maintain cellular integrity, and guard against autophagy. However, unopposed fission causes mitochondrial fragmentation, which can create greater ROS production, enable mitophagy, and accelerate cell proliferation. Not surprisingly, therefore, mitochondrial dysfunction or deregulation of mitochondrial dynamics have been found in conditions associated with aging and several diseases including obesity, cardiovascular, endocrine, neurodegenerative and neoplastic diseases or cancers [5,25,26].

3. Role of Mitochondrial Dynamics in Ovarian Cancer

Among six hallmarks proposed by Hanahan and Weinberg to characterize a cancer cell, resistance of cell death is involved in mitochondrial dynamics [27]. Alterations in mitochondrial dynamics that promote mitochondrial fission or impaired fusion have been observed in several types of cancer [6–12]. Previous studies demonstrated the role of Drp1 on tumorigenic cell proliferation in ovarian cancer [10,16]. Those studies found that ovarian cancer cells had increased

Drp1 protein and mRNA levels, when compared to normal ovarian surface epithelial cells, and the amount of Drp1 expression varied among different histological subtypes [10,16]. The decreased mitochondrial fission and/or increased fusion have been shown to be associated with chemoresistance in gynecological cancers including ovarian cancers [15]. In chemosensitive cancer cells, cisplatin has been shown to induce p53 phosphorylation and Drp1 dephosphorylation, and caused an increase in Bax translocation and apoptosis [28]. In chemoresistant cancer cells, however they found that the efficacy of cisplatin to perform this task was reduced, and there was also a shift in Opa1 processing to produce the short form of Opa1, which ultimately resulted in an increased mitochondrial fusion and decreased apoptosis [28]. These findings suggested that the activity of mitochondrial fusion was enhanced, but apoptosis was suppressed in chemoresistant cancer cells [28]. Moreover, in chemoresistant ovarian cancer cells it has been shown to have more tubular mitochondria than chemosensitive cancer cells, suggesting that mitochondrial fusion may contribute to chemoresistance [15]. Taken together, these findings suggest that mitochondrial fusion may play a vital role in mechanisms associated with chemoresistance and aggressiveness in ovarian cancers. All of those findings suggest that the imbalance of mitochondrial dynamics may be a potential factor in tumorigenesis, including that in ovarian cancers.

Due to the lack of early biomarkers and absence of specific clinical symptoms, patients with ovarian cancer are usually diagnosed at an advanced stage and eventually develop chemoresistant recurrent disease. The data on potential clinical utility of mitochondrial dynamics as biomarkers for screening as well as predicting prognosis and therapeutic responses or detecting of recurrence in ovarian cancer are limited and the topic requires substantial future studies. However, previous studies reported that upregulating Drp1 protein expression was found in patients with several malignancies such as in melanoma, lung adenocarcinomas, pancreatic cancers, brain tumors and chemosensitive ovarian tumors as well as downregulating Opa1 expression in hepatocellular carcinoma [6,10,29–32]. All of those findings suggest that the upregulation of Drp1 may be a biomarker for the prediction of cancer progression and response to chemotherapy in cancers. Understanding the mechanisms involved in mitochondrial dynamics in tumorigenesis and the chemoresistant process may provide insight into new biomarkers that could be employed for early detection, and prediction of chemosensitivity, and may be crucial for a new era of cancer therapeutics for clinical management of ovarian cancers.

The following paragraphs will summarize the existing evidence of mitochondrial dynamics in ovarian cancers with their interventions from both in vitro and in vivo studies.

4. Evidence of Mitochondrial Fission in Ovarian Cancer With Pharmacological Interventions: Reports From In Vitro Studies

Mitochondrial fission is mediated by a cytosolic GTPase protein Drp1, which translocates to the outer mitochondrial membrane and binds to non-GTPase receptor proteins including mitochondrial fission protein 1 (Fis1), mitochondrial fission factor (MFF), and mitochondrial elongation factor 1 [5]. Post-translational modification such as serine phosphorylation controls the activity of Drp1. Phosphorylation of Ser 616 and dephosphorylation of Ser637 was found to enhance mitochondrial fission. An imbalance of fission and fusion which results in a fragmentation of mitochondria has been reported in several cancer studies [6–12] (Fig. 1).

There is a great deal of evidence to demonstrate that fission precedes apoptosis and facilitates a more rapid release of mitochondrial pro-apoptotic factors such as cytochrome-c (Cyt C) [23]. With regards to apoptotic process, caspases are essential for signaling for ongoing apoptosis. Apart from inducing apoptosis, mitochondrial fission also facilitates mitophagy, one type of autophagy that can remove damaged mitochondria via the pink1-Parkin signaling pathway or the mitophagic receptors Nix and Bnip3 [33].

4.1. Effects of Platinum-based Chemotherapy on Mitochondrial Fission

Platinum-based chemotherapy, such as cisplatin or carboplatin alone or as a combined therapy, is the primary systemic chemotherapy for advanced stage ovarian cancers [4]. Previous studies have shown that cisplatin or paclitaxel induced ovarian cancer cell death by enhancing mitochondrial fragmentation, the down-regulation of phospho-Drp1 at serine 637 (p-Drp1 Ser637), and also the apoptosis of tumor cells by reducing cell viability and X-linked inhibitor of apoptosis protein (XIAP) level and increasing cell apoptosis and pro-apoptotic regulators such as p53 and caspase activity [15,34–37]. In addition, an increase in mitochondrial fragmentation of ovarian cancer cells following platinum-based therapy was found in the chemosensitive cancer cells, rather than chemoresistant cancer cells [36].

Due to the limited efficacy of chemotherapy in patients with recurrent platinum-resistant disease, the identification of new molecular targets or mitochondria-based cancer therapeutic agents to overcome drug resistance is central to the development of novel cancer therapeutics. There are several studies that have shown the effects of various non-chemotherapeutic agents on mitochondrial fission in ovarian cancer. Previous reports showed that phytochemical agents including piperlongumine, piceatannol, *Sambucus nigra* agglutinin (SNA), and cordycepin could induce both mitochondrial fission by decreasing p-Drp1 Ser637 and increasing Drp1 and Fis1 mRNA levels, and apoptosis by decreasing anti-apoptotic Bcl-2 and increasing pro-apoptotic regulators such as Bax and Cyt C levels; and caspase activity in both chemosensitive and chemoresistant ovarian cancer cells [18,34,35,38]. Interestingly, these phytochemicals also enhanced the cytotoxic effects of cisplatin when combination therapy was used.

4.2. Effects of p53 on Mitochondrial Fission

p53 is often in a mutated form in cancer cells and is associated with chemoresponsiveness [39]. Reconstitution of p53 induced mitochondrial fragmentation, L-Opa1 processing, Oma1 cleavage, and sensitized p53 mutant or null chemoresistant ovarian cancer cells to cisplatin-induced mitochondrial fragmentation and apoptosis [15].

4.3. Effects of Tumor Necrosis Factor-related Apoptosis Inducing Ligand (TRAIL) on Mitochondrial Fission

Tumor necrosis factor-related apoptosis inducing ligand (TRAIL), a novel anticancer agents, can selectively provoke apoptosis in many tumor cells without destroying normal cells [40]. TRAIL alone has been found to reduce the viability of ovarian cancer cells as well as increase the activity of caspase-3/7 and the number of Annexin V-positive apoptotic cells [41].

4.4. Effects of Bcl-2/Bcl-XL Inhibitor on Mitochondrial Fission

ABT737, a potent and selective small-molecule inhibitor of Bcl-2/Bcl-XL, alone has been shown to increase the fission proteins Fis1 and Drp1; ROS production; apoptosis by decreasing cell viability and anti-apoptotic Mcl-1 as well as increasing cell apoptosis and pro-apoptotic regulators (Cyt c and caspase activity); and mitophagy by increasing pink1 level in ovarian cancer cells [42,43]. ABT737 combined with Earle's balanced salt solution (EBSS) has also been found to promote cancer cells to undergo apoptosis and convert tubular mitochondria into small, fragmented morphologies [42].

4.5. Effects of Gene Silencing on Mitochondrial Fission

Dysregulation of microRNA (miRNA) has been reported in several human cancers including ovarian cancers [44–47]. Previous studies have shown that miR-488 significantly reduced chemoresistance in ovarian cancer cells via downregulation of cell viability and

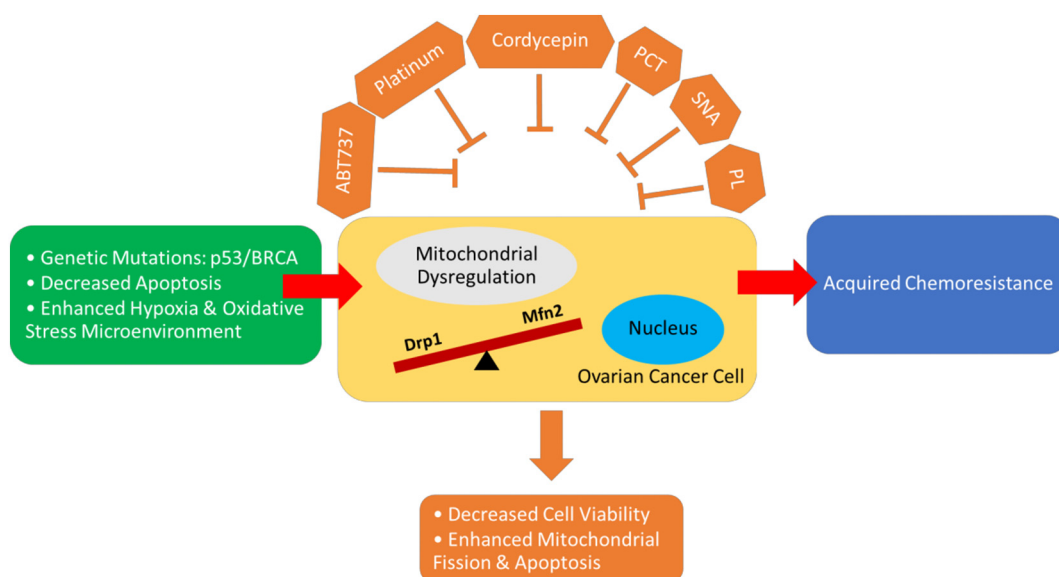


Fig. 1. The effects of pharmacological interventions on mitochondrial dynamics in ovarian cancer. Inherited genetic mutations (such as p53 or BRCA gene), altered oxidative stress, mitochondrial dysregulation (increase in mitochondrial fission) and decreased apoptosis play a role in maintaining the oncogenic phenotype and lead to the development of ovarian cancer. In addition, the enhancement of these factors leads to the acquired chemoresistant condition of disease. The pharmacological interventions have a cytotoxic effect on ovarian cancer cells by increasing mitochondrial fission, leading to cancer cell apoptosis. Abbreviations: ABT737: A potent and selective small-molecule inhibitor of Bcl-2/Bcl-XL; BRCA: Breast cancer susceptibility gene; Drp1: Dynamin-related protein-1; Mfn: Mitofusins; PCT: Piceatannol; PL: Piperlongumine; SNA: *Sambucus nigra* agglutinin.

upregulation of apoptosis. However, an miR-488 inhibitor showed the opposite effects [37]. They discovered that a miR-488 mimic downregulated the protein levels of p-Drp1, Drp1, Fis1 and Six1, while a miR-488 inhibitor upregulated these protein levels [37]. Moreover, they found that an oncoprotein Six1 is a positive regulator of mitochondrial fission and Drp1 phosphorylation, and may serve as a mediator of miR-488 induced chemosensitivity [37].

4.6. Effects of Mitochondrial Fission Inhibitor-1 on Mitochondrial Fission

Mdivi-1 (mitochondrial fission inhibitor-1) was the first selective inhibitor of the mitochondrial fission protein Drp1 and exerted different effects on cell survival depending on the cell type and setting. Mdivi-1 has been shown to confer cytoprotective effects on various cell types, particularly cardiomyocytes and neurons [48]. In addition, mdivi-1 exerted antiproliferative and cytotoxic effects in hyperproliferative cells such as cancer and immortalized cells [48]. Reports from previous studies have shown that a combination of Mdivi-1 with cisplatin or TRAIL induced synergistic apoptosis in both chemosensitive and chemoresistant ovarian cancer cells in a dose dependent manner [36,41]. Direct activation of caspase-3 by enhanced caspase-8 activity played a crucial role in the apoptosis via decreasing cell viability and increasing caspase activity initiated by a TRAIL and Mdivi-1 combination [41]. However, the results of another in vitro study demonstrated otherwise [43]. They demonstrated that pretreatment with mdivi-1, followed by treatment with Bcl-2/Bcl-XL inhibitor reduced mitochondrial fission by decreasing mitochondrial fragmentation, Drp1 and Fis1 protein levels, and reduced apoptosis by decreasing Cyt C and caspase activity [43]. Mitophagy was also reduced by Bcl-2/Bcl-XL inhibitor and Mdivi-1 via decreasing pink1 level in chemoresistant ovarian cancer cells. All of these findings suggested that apoptosis and mitophagy occurred at the downstream level of mitochondrial fission [43]. All these findings indicate that the enhancement of mitochondrial fission and apoptosis by potential cancer therapeutic agents could exert cytotoxic effects and result in the destruction of ovarian cancer cells during treatment. All of these findings are summarized in Table 1.

5. Evidence of Mitochondrial Fission in Ovarian Cancer Cells with Pharmacological Interventions: Reports from In Vivo Studies

There was only one in vivo study that reported the effects of pharmacological interventions on mitochondrial fission in ovarian cancer. The mice with implanted cisplatin-sensitive ovarian cancer cells were treated with combination of intraperitoneal piceatannol and cisplatin for 18 days. It was observed that both phytoalexin resveratrol (piceatannol) and cisplatin treatment could increase mitochondrial fragmentation and apoptosis via up-regulation of phospho-p53 at serine 15 and down-regulation of XIAP [35]. Moreover, these effects were enhanced when piceatannol was combined with cisplatin [35]. These findings suggest that piceatannol enhances cisplatin-dependent apoptosis in ovarian cancer cells, via regulating key factors related to the p53 tumor suppressor pathway [35]. The comprehensive summary of those findings is shown in Table 2.

6. Evidence of Mitochondrial Fission in Ovarian Cancer with Pharmacological Intervention: Reports from Clinical Studies

The cytotoxic effects of mitochondrial fission promotion following pharmacological intervention in *clinical studies* are summarized in Table 3. The exploratory analysis of the TCGA-EOC (The Cancer Genome Atlas-epithelial ovarian cancer) genome revealed that Drp1 and Mff mRNA levels were increased in patients with epithelial ovarian cancer [10]. There are limited clinical studies regarding the effects of pharmacological interventions on mitochondrial fission in ovarian cancers. Qian and colleagues showed that a combination of cisplatin and Mdivi-1 induced synergistic apoptosis in chemoresistant ovarian cancer cells (isolated from the ascites fluid of ovarian cancer patients) via decreased cell viability and increased caspase 3/7 activity in a dose dependent manner [36].

Another study by Wang and colleagues also demonstrated that mdivi-1 dose-dependently enhanced the sensitivity of ovarian cancer cells (isolated from the ascites fluids of three high-grade serous carcinoma (HGSC) ovarian cancer patients) to TRAIL via induced apoptosis in these cells [41]. These results were found to be consistent with in vitro studies [36,41].

Table 1
In vitro studies of mitochondrial fission in ovarian cancer with pharmacological interventions.

Models	Intervention Type/dose/route/duration	Major findings			Interpretations	References
		Mitochondrial fission	Apoptosis	Oxidative stress		
<ul style="list-style-type: none"> • OVCA420 cells (human, ovarian serous carcinoma) • OVCA433 cells (human, ovarian serous carcinoma) • ES-2 cells (human, ovarian clear cell carcinoma) • NOSE007 cells (human, normal ovarian surface epithelium) 	-	<ul style="list-style-type: none"> • ↑↑ Mitochondrial fragmentation • ↑↑↑ Drp1 protein • ↑ Mitochondrial fragmentation • ↑↑ Drp1 protein • ↑ Mitochondrial fragmentation • ↑↑ Drp1 protein • ↑ Mitochondrial fragmentation • ↑ Drp1 protein 	-	-	<ul style="list-style-type: none"> • Increased mitochondrial fission in ovarian serous carcinoma (OVCA420 cells) at a level greater than ovarian clear cell carcinoma (ES-2 cells) histological subtype 	[16] Dier U et al. (2014)
<ul style="list-style-type: none"> • OV2008 cells (human, cisplatin-sensitive ovarian cancer) 	<ul style="list-style-type: none"> • Treated with Cisplatin and Piperlongumine: 2.5, 5, 10 μM for 12 hrs 	<ul style="list-style-type: none"> • ↑ Mitochondrial fragmentation • ↓ p-Drp1 Ser637 	<ul style="list-style-type: none"> • ↑ Annexin-V-positive apoptotic cells 	-	<ul style="list-style-type: none"> • Cisplatin and piperlongumine induced both mitochondrial fission and apoptosis in chemosensitive ovarian cancer cells in a dose dependent manner 	[34] Farrand L et al. (2013)
<ul style="list-style-type: none"> • C13 cells (human, cisplatin-resistant ovarian cancer) 	<ul style="list-style-type: none"> • Treated with Cisplatin: 2.5, 5, 10 μM for 12 hrs • Treated with Piperlongumine: 2.5, 5, 10 μM for 12 hrs 	<ul style="list-style-type: none"> • ↔ Mitochondrial fragmentation • ↔ p-Drp1 Ser637 • ↑ Mitochondrial fragmentation • ↓ p-Drp1 Ser637 	<ul style="list-style-type: none"> • ↔ Annexin-V-positive apoptotic cells • ↑ Annexin-V-positive apoptotic cells 		<ul style="list-style-type: none"> • Only piperlongumine induced both mitochondrial fission and apoptosis in chemoresistant ovarian cancer cells in a dose dependent manner 	
<ul style="list-style-type: none"> • OV2008 and C13 cells 	<ul style="list-style-type: none"> • Treated with Cisplatin or Piperlongumine: 2.5, 5, 10 μM and Mdivi-1: 5, 10 μM for 12 hrs 	<ul style="list-style-type: none"> • ↓ Mitochondrial fragmentation 	<ul style="list-style-type: none"> • ↓ Annexin-V-positive apoptotic cells 		<ul style="list-style-type: none"> • Adding Mdivi-1 with both drugs attenuated both mitochondrial fission and apoptosis in ovarian cancer cells in a dose dependent manner 	
<ul style="list-style-type: none"> • OV2008 cells (WT-p53) (human, cisplatin-sensitive ovarian cancer) 	<ul style="list-style-type: none"> • Treated with Cisplatin: 10 μM for 24 hrs • Treated with Piceatannol: 10 μM for 24 hrs 	-	<ul style="list-style-type: none"> • ↓↓ Cell viability • ↓↓ Cell viability 	-	<ul style="list-style-type: none"> • Piceatannol alone reduced cell viability and markedly enhanced the cytotoxic effects of cisplatin in chemosensitive ovarian cancer cells 	[35] Farrand L et al. (2013)
<ul style="list-style-type: none"> • A2780s cells (WT-p53) (human, cisplatin-sensitive ovarian cancer) 	<ul style="list-style-type: none"> • Co-treated with Cisplatin: 10 μM and Piceatannol: 10 μM for 24 hrs 		<ul style="list-style-type: none"> • ↓↓↓ Cell viability 			
<ul style="list-style-type: none"> • OVCAR-432 cells (p53 mutant) (human, cisplatin-sensitive ovarian cancer) 						
<ul style="list-style-type: none"> • C13* cells (WT-p53) (human, cisplatin-resistant ovarian cancer) 	<ul style="list-style-type: none"> • Treated with Cisplatin: 10 μM for 24 hrs • Treated with Piceatannol: 10 μM for 24 hrs 	-	<ul style="list-style-type: none"> • ↓↓ Cell viability • ↓↓ Cell viability 	-	<ul style="list-style-type: none"> • Piceatannol induced sensitivity to cisplatin in chemoresistant ovarian cancer cells containing wild-type p53, but sensitivity less apparent in p53-deficient chemoresistant cells 	[35] Farrand L et al. (2013)
<ul style="list-style-type: none"> • A2780cp cells (p53 mutant) (human, cisplatin-resistant ovarian cancer) 	<ul style="list-style-type: none"> • Co-treated with Cisplatin: 10 μM and Piceatannol: 10 μM for 24 hrs 		<ul style="list-style-type: none"> • ↓↓↓ Cell viability • ↓ Cell viability 			
<ul style="list-style-type: none"> • SKOV3 cells (p53 null) (human, cisplatin-resistant ovarian cancer) 			<ul style="list-style-type: none"> • ↓↓ Cell viability • ↓↓ Cell viability 			
<ul style="list-style-type: none"> • OV2008 cells (WT-p53) (human, cisplatin-sensitive ovarian cancer) 	<ul style="list-style-type: none"> • Co-treated with Cisplatin and Piceatannol: 2.5, 5, 10 μM for 24 hrs 	-	<ul style="list-style-type: none"> • ↑↑↑ Cell apoptosis 	-	<ul style="list-style-type: none"> • Low dose piceatannol (2.5 μM) promoted cisplatin-induced apoptosis 2-fold in chemosensitive ovarian cancer cells 	[35] Farrand L et al. (2013)
<ul style="list-style-type: none"> • A2780s cells (WT-p53) (human, cisplatin-sensitive ovarian cancer) 			<ul style="list-style-type: none"> • ↑↑↑ Cell apoptosis 			
<ul style="list-style-type: none"> • C13* cells (WT-p53) (human, cisplatin-resistant ovarian cancer) 			<ul style="list-style-type: none"> • ↑↑↑ Cell apoptosis 		<ul style="list-style-type: none"> • High dose piceatannol (10 μM) promoted cisplatin-induced apoptosis 3-fold in chemoresistant ovarian cancer cells 	
<ul style="list-style-type: none"> • A2780cp cells (p53 mutant) (human, cisplatin-resistant ovarian cancer) 			<ul style="list-style-type: none"> • ↑↑ Cell apoptosis 			

Table 1 (continued)

Models	Intervention Type/dose/route/duration	Major findings			Interpretations	References
		Mitochondrial fission	Apoptosis	Oxidative stress		
<ul style="list-style-type: none"> OV2008 cells (WT-p53) (human, cisplatin-sensitive ovarian cancer) 	<ul style="list-style-type: none"> Treated with Cisplatin: 5 μM for 4–24 hrs Treated with Piceatannol: 10 μM for 4–24 hrs Co-treated with Cisplatin: 5 μM and Piceatannol: 10 μM for 4–24 hrs Treated with Cisplatin 5 μM or/and Piceatannol 10 μM and Mdivi-1: 5 μM for 24 hrs 	<ul style="list-style-type: none"> ↑ Mitochondrial fragmentation ↑ Mitochondrial fragmentation ↓ p-Drp1 Ser637 ↑↑ Mitochondrial fragmentation ↓ Mitochondrial fragmentation 	<ul style="list-style-type: none"> ↑ Activated caspase-3 ↑ Cell apoptosis ↑ p-p53 (Ser15) ↑ Activated caspase-3 ↑ Cell apoptosis ↔ p-p53 (Ser15) ↑↑ Activated caspase-3 ↑↑ Cell apoptosis ↑↑ p-p53 (Ser15) ↓ Activated caspase-3 ↓ Cell apoptosis 	-	<ul style="list-style-type: none"> Piceatannol enhanced cisplatin sensitivity in chemosensitive ovarian cancer cells through modulating p53, mitochondrial fission and apoptosis Adding Mdivi-1 with both drugs attenuated both mitochondrial fission and apoptosis in chemosensitive ovarian cancer cells 	[35] Farrand L et al. (2013)
<ul style="list-style-type: none"> A2780s cells (WT-p53) (human, cisplatin-sensitive ovarian cancer) 	<ul style="list-style-type: none"> Treated with Cisplatin: 10 μM for 6 hrs 	<ul style="list-style-type: none"> ↑ Mitochondrial fragmentation 	-	-	<ul style="list-style-type: none"> Cisplatin induced mitochondrial fission in chemosensitive ovarian cancer cells, but not in chemoresistant cells 	[15] Kong B et al. (2014)
<ul style="list-style-type: none"> A2780cp cells (p53 mutant) (human, cisplatin-resistant variant ovarian cancer) HEY cells (WT-p53) (human, cisplatin-resistant ovarian cancer) SKOV3 cells (p53 null) (human, cisplatin-resistant ovarian cancer) 		<ul style="list-style-type: none"> ↔ Mitochondrial fragmentation ↔ Mitochondrial fragmentation ↔ Mitochondrial fragmentation 				
<ul style="list-style-type: none"> A2780cp cells (p53 mutant) (human, cisplatin-resistant variant ovarian cancer) 	<ul style="list-style-type: none"> Treated with Cisplatin: 10 μM for 6–24 hrs 	<ul style="list-style-type: none"> ↔ Mitochondrial fragmentation ↔ L-Opa1 processing ↔ Oma1 protein 	-	-	<ul style="list-style-type: none"> Cisplatin alone had no effect on mitochondrial fission in p53-deficient chemoresistant ovarian cancer cells 	[15] Kong B et al. (2014)
<ul style="list-style-type: none"> SKOV3 cells (p53 null) (human, cisplatin-resistant ovarian cancer) 	<ul style="list-style-type: none"> Transfected with WT-p53 cDNA: 0–2 μg, 0.44 μg/well for 24 hrs Transfected with WT-p53 cDNA: 0–2 μg, 0.44 μg/well for 24 hrs and treated with Cisplatin: 10 μM for 6–24 hrs 	<ul style="list-style-type: none"> ↑ Mitochondrial fragmentation ↑ L-Opa1 processing ↑ Oma1 protein ↑↑ Mitochondrial fragmentation ↑↑ L-Opa1 processing ↑↑ Oma1 protein 	<ul style="list-style-type: none"> ↑ Cell apoptosis ↑↑ Cell apoptosis 		<ul style="list-style-type: none"> Reconstitution of WT-p53 increased mitochondrial fission in these cells and markedly increased their sensitivity to cisplatin-induced mitochondrial fission and apoptosis 	
<ul style="list-style-type: none"> A2780 cells (human, cisplatin-sensitive ovarian cancer) 	<ul style="list-style-type: none"> Treated with Cisplatin: 1–100 μM for 72 hrs 	-	<ul style="list-style-type: none"> ↓↓ Cell viability 	-	<ul style="list-style-type: none"> Cisplatin induced apoptosis in chemosensitive ovarian cancer cells to a greater extent than in chemoresistant cells in a dose dependent manner 	[36] Qian W et al. (2014)
<ul style="list-style-type: none"> A2780cis cells (human, cisplatin-resistant ovarian cancer) 			<ul style="list-style-type: none"> ↓ Cell viability 			
<ul style="list-style-type: none"> A2780cis cells 	<ul style="list-style-type: none"> Co-treated with Cisplatin: 1–100 μM and Mdivi-1: 20 μM for 72 hrs Co-treated with Cisplatin: 1–100 μM and Mdivi-1: 50 μM for 72 hrs 		<ul style="list-style-type: none"> ↓↓ Cell viability ↓↓↓ Cell viability 		<ul style="list-style-type: none"> Combination of cisplatin and mdivi-1 induced synergistic apoptosis in chemoresistant ovarian cancer cells in a dose dependent manner 	
<ul style="list-style-type: none"> A2780 cells (human, cisplatin-sensitive ovarian cancer) 	<ul style="list-style-type: none"> (1) Treated with TRAIL: 0.1, 1, 10 ng/ml for 16 hrs (2) Treated with Mdivi-1: 10, 20, 50 μM for 16 hrs (3) Co-treated with TRAIL: 0.1, 1, 10 ng/ml and Mdivi-1: 10, 20, 50 μM for 16 hrs 	-	<ul style="list-style-type: none"> (1) ↑ Caspase 3/7 activity ↓ Cell viability ↑ Annexin-V-positive apoptotic cells (2) ↑ Caspase 3/7 activity ↓ Cell viability ↑ Annexin-V-positive apoptotic cells 	-	<ul style="list-style-type: none"> Mdivi-1 enhanced death receptor-mediated apoptosis in both chemosensitive and chemoresistant ovarian cancer cells in a dose dependent manner, but not in non-transformed normal cells 	[41] Wang J et al. (2015)

(continued on next page)

Table 1 (continued)

Models	Intervention Type/dose/route/duration	Major findings			Interpretations	References
		Mitochondrial fission	Apoptosis	Oxidative stress		
• A2780cis cells (human, cisplatin-resistant ovarian cancer)			(3) ↑↑ Caspase 3/7 activity			
			• ↓↓ Cell viability • ↑↑ Annexin-V--positive apoptotic cells (1) ↑ Caspase 3/7 activity			
			• ↓ Cell viability (2) ↑ Caspase 3/7 activity			
			• ↓ Cell viability (3) ↑↑ Caspase 3/7 activity			
• SKOV3 cells (p53 null) (human, ovarian serous carcinoma)	• NHDF (normal human dermal fibroblast) (1), (2), (3)		• ↓↓ Cell viability			
	• ↔ Caspase 3/7 activity • ↔ Cell viability • Treated with SNA: 12 µg/ml for 4-24 hrs	• ↑ Drp1 mRNA • ↑ Fis1 mRNA	• ↑ Annexin-V/PI--positive apoptotic cells • ↑ TUNEL-positive cells • ↑ Cleaved caspase-3 • ↓ Bcl-2 • ↑ Cyt C • ↑ Cleaved caspase-3 • ↑ Cleaved caspase-9 • ↓ Bcl-2 • ↑ Bax • ↑ Cyt C • ↔ Annexin-V/PI--positive apoptotic cells • ↔ Cyt C	↑ ROS	• SNA induced oxidative stress, mitochondrial fission and apoptosis in ovarian cancer cells	[38] Chowdhury SR et al. (2017)
• OAW-42 cells (human, ovarian serous carcinoma)		• ↑ Drp1 mRNA	• ↑ Cleaved caspase-3 • ↑ Cleaved caspase-9 • ↓ Bcl-2 • ↑ Bax • ↑ Cyt C	• ↑ ROS		
• IOSE-364 cells (human, normal ovarian surface epithelium)		• ↔ Drp1 mRNA • ↔ Fis1 mRNA	• ↔ Annexin-V/PI--positive apoptotic cells • ↔ Cyt C	-		
• OVCA-3 cells (human, ovarian serous carcinoma)	• Treated with Cordycepin: 50, 100 µM for 24 hrs	• ↑ Mitochondrial fragmentation • ↑ Fis1 mRNA	-	-	• Cordycepin induced mitochondrial fission in ovarian cancer cells	[18] Wang CW et al. (2017)
• SKOV3 cells (human, ovarian serous carcinoma)	• Treated with ABT737: 1 µM for 24 hrs	↑ Drp1 protein ↑ Fis1 protein	Treated with ABT737: 1 µM for 24 hrs	↑ ROS	ABT737 alone induced mitochondrial fission and apoptosis in ovarian cancer cells	[42] Wang S et al. (2017)
	• Treated with EBSS for 24 hrs	• ↔ Drp1 protein • ↔ Fis1 protein	• Treated with EBSS for 24 hrs	• ↑ ROS	• EBSS alone induced apoptosis in ovarian cancer cells	
	• Treated with ABT737: 1 µM and EBSS for 24 hrs	• ↑↑ Drp1 protein • ↑↑ Fis1 protein	• Treated with ABT737: 1 µM and EBSS for 24 hrs	• ↑↑ ROS	• ABT737 combined with EBSS dramatically increased oxidative stress, mitochondrial fission and apoptosis in ovarian cancer cells	
• SKOV3 cells (human, cisplatin-sensitive ovarian cancer)	1) Treated with ABT737: 1.25-100 µM for 3-24 hrs (2) Treated with ABT737: 15 µM for 6-24 hrs	-	(1) ↓ Cell viability (2) ↑ Cell apoptosis (1) ↓↓ Cell viability (2) ↑↑ Cell apoptosis	-	• ABT737 inhibited viability in chemoresistant ovarian cancer cells more than it did in chemosensitive cells in a dose and time dependent manner • ABT737 induced apoptosis in chemoresistant ovarian cancer cells more effectively than in chemosensitive cells	[43] Yu Y et al. (2017)
• SKOV3/DDP cells (human, cisplatin-resistant ovarian cancer)						

Table 1 (continued)

Models	Intervention Type/dose/route/duration	Major findings			Interpretations	References
		Mitochondrial fission	Apoptosis	Oxidative stress		
• SKOV3/DDP cells (human, cisplatin-resistant ovarian cancer)	• Treated with ABT737 (potent and selective small-molecule inhibitor of Bcl-2/Bcl-xL): 15 μM for 12-24 hrs	• ↑↑ Mitochondrial fragmentation • ↑↑ Drp1 protein • ↑↑ Fis1 protein	• ↑↑ Cyt c • ↑↑ Cleaved caspase-3 • ↑↑ Cleaved caspase-9 • ↑↑ PINK1	–	• ABT737 induced mitochondrial fission, apoptosis and mitophagy in chemoresistant ovarian cancer cells	[43] Yu Y et al. (2017)
	• Treated with Mdivi-1: 50 μM for 1 hr	• ↔ Mitochondrial fragmentation • ↔ Drp1 protein • ↔ Fis1 protein	• ↔ Cyt c • ↔ Cleaved caspase-3 • ↔ Cleaved caspase-9 • ↔ PINK1			
	• Pretreated for 1 hr with Mdivi-1: 50 μM, followed by treatment with ABT737: 15 μM for 12-24 hrs	• ↑ Mitochondrial fragmentation • ↑ Drp1 protein • ↑ Fis1 protein	• ↑ Cyt c • ↑ Cleaved caspase-3 • ↑ Cleaved caspase-9 • ↑ PINK1		• Mdivi-1 weakened ABT737-induced mitochondrial fission, apoptosis and mitophagy in chemoresistant ovarian cancer cells	
• SKOV3 cells (human, ovarian serous carcinoma)	• Treated with Cisplatin: 10 μM or Paclitaxel: 5 μM for 24, 48 hrs	–	• ↓↓ Cell viability • ↑↑ Cell apoptosis	–	• miR-488 reduced chemoresistance in ovarian cancer cells via upregulation of apoptosis	[37] Yang Z et al. (2017)
	• Transfected with miR-488 mimic and treated with Cisplatin: 10 μM or Paclitaxel: 5 μM for 24, 48 hrs		• ↓↓↓ Cell viability • ↑↑↑ Cell apoptosis			
• OVCAR3 cells (human, ovarian serous carcinoma)	• Treated with Cisplatin: 10 μM or Paclitaxel: 5 μM for 24, 48 hrs		• ↓↓ Cell viability • ↑↑ Cell apoptosis			
	• Transfected with miR-488 inhibitor and treated with Cisplatin: 10 μM or Paclitaxel: 5 μM for 24, 48 hrs		• ↓ Cell viability • ↑ Cell apoptosis			
• SKOV3 cells (human, ovarian serous carcinoma)	• Transfected with Six1 plasmid	• ↑ p-Drp1 protein • ↑ Drp1 protein • ↑ Fis1 protein	• ↓ Cell viability • ↑ Cell apoptosis	–	Six1 induced mitochondrial fission in ovarian cancer cells	[37] Yang Z et al. (2017)
	Transfected with Six1 siRNA	↓ p-Drp1 protein ↓ Drp1 protein ↓ Fis1 protein ↓ Six1 protein				
	• Transfected with miR-488 mimic	• ↓ p-Drp1 protein • ↓ Drp1 protein • ↓ Fis1 protein • ↓ Six1 protein & mRNA	• ↓↓ Cell viability • ↑↑ Cell apoptosis		miR-488 suppressed mitochondrial fission in ovarian cancer cells	
• OVCAR3 cells (human, ovarian serous carcinoma)	• Transfected with Six1 plasmid and miR-488 mimic	• ↑ p-Drp1 protein • ↑ Drp1 protein • ↑ Fis1 protein	• ↓ Cell viability • ↑ Cell apoptosis		Six1 restored the reduction of mitochondrial fission and abrogated the apoptosis inducing effect of miR-488 in ovarian cancer cells	
	• Transfected with Six1 Plasmid	• ↑ p-Drp1 protein • ↑ Drp1 protein • ↑ Fis1 protein • ↑ Six1 protein	– –			
	• Transfected with miR-488 inhibitor	• ↑ p-Drp1 protein • ↑ Drp1 protein • ↑ Fis1 protein • ↑ Six1 protein & mRNA	–		• Six1 induced mitochondrial fission in ovarian cancer cells	

Abbreviations: ABT737: A potent and selective small-molecule inhibitor of Bcl-2/Bcl-xL; Bcl-2: B-cell lymphoma 2; Bax: Bcl2-associated X protein; Bak: Bcl2-antagonist/killer; Cyt c: Cytochrome complex; Drp1: Dynamin-related protein-1; EBSS: Earle's balanced salt solution; Fis1: Mitochondrial fission 1 protein; L-Opa1: Long form of optic atrophy protein 1; Mdivi-1: Mitochondrial Division Inhibitor 1; Mcl-1: Myeloid cell leukemia 1; miR-488: microRNA-488; Oma1: A novel mitochondrial metalloproteinase responsible for L-Opa1 processing; PINK1: PTEN-induced putative kinase 1; p: Phosphorylation; ROS: Reactive oxygen species; Ser: Serine; SNA: *Sambucus nigra* agglutinin; Six1: Six1; TRAIL: Tumor necrosis factor-related apoptosis-inducing ligand; TUNEL: Terminal deoxynucleotidyl transferase dUTP nick end labelling.

Due to the different effects on cell survival varying between cell types and also the limited understanding of the pharmacokinetics and cytotoxic profile of Mdivi-1, the details of the clinical application of Mdivi-1 is still limited and requires further study.

7. Evidence of Mitochondrial Fusion in Ovarian Cancer with Pharmacological Interventions: Reports From In Vitro Studies

Cancer cells often exhibited high levels or enhanced activation of Drp1 and/or downregulation of fusion mediators such as Mfn-2 [49]. In addition by comparing the percentage of cells with tubular

mitochondria in chemosensitive and chemoresistant ovarian cancer cells, a higher proportion of cells with tubular mitochondria have been observed in chemoresistant cells [15]. This finding suggested that chemoresistant ovarian cancer cells are prone to form more interconnected mitochondrial networks and that mitochondrial fusion may be responsible for chemoresistance.

There are a limited number of studies regarding the effects of pharmacological intervention on mitochondrial fusion in ovarian cancer cell lines. *Sambucus nigra* agglutinin (SNA) and Cordycepin treatment led to mitochondrial dysfunction through suppressed mitochondrial fusion indicated by a decrease in expression of the fusion gene Mfn-1 and

Table 2
In vivo studies of mitochondrial fission in ovarian cancer with pharmacological interventions.

Models	Intervention Type/Dose/Route/Duration	Major Findings			Interpretations	References
		Mitochondrial fission	Apoptosis	Oxidative stress		
<ul style="list-style-type: none"> • OV2008 cells (human, cisplatin-sensitive ovarian cancer) implanted in male athymic nude mice 	<ul style="list-style-type: none"> • Treated with Cisplatin: 1.8 mg/kg, 1 time/week for 18 days • Treated with Piceatannol: 20 mg/kg, 5 times/week for 18 days • Co-treated with Cisplatin: 1.8 mg/kg, 1 time/week and Piceatannol: 20 mg/kg, 5 times/week for 18 days 	<ul style="list-style-type: none"> • ↑ Mitochondrial fragmentation • ↑ Mitochondrial fragmentation • ↑↑ Mitochondrial fragmentation 	<ul style="list-style-type: none"> • ↑ TUNEL-positive cells • ↑ p-p53 (Ser15) • ↓ XIAP • ↑ TUNEL-positive cells • ↑ p-p53 (Ser15) • ↓ XIAP • ↑↑ TUNEL-positive cells • ↑↑ p-p53 (Ser15) • ↓↓ XIAP 	–	<ul style="list-style-type: none"> • Combination of Piceatannol and Cisplatin increased mitochondrial fission and apoptosis via modulation of p53 in a mouse model of chemosensitive ovarian cancer cells to a greater extent than cisplatin or piceatannol alone 	[35] Farrand L et al. (2013)

Abbreviations: p: Phosphorylation; Ser: Serine; TUNEL: Terminal deoxynucleotidyl transferase dUTP nick end labelling; XIAP: X-linked inhibitor of apoptosis protein.

Mfn-2 in ovarian cancer cells [18,38]. Additionally, previous studies had indicated a correlation between nutrient stress and Bcl-2 anti-apoptotic proteins [42]. They found that Earle's balanced salt solution (EBSS) alone increased the level of the mitochondrial fusion proteins Mfn-2 and Opa1, and also that most mitochondria formed a tubular hyperfused network [42]. By contrast, ABT737 combined with EBSS could suppress mitochondrial fusion in ovarian cancer cells [42]. These accumulated data indicated that inhibition of mitochondrial fusion events with pharmacological agents could exert cytodestructive effects via promoted mitochondrial fragmentation in ovarian cancer cells. These findings are summarized in Table 4.

8. Conclusion

Mitochondrial dynamics play important roles in normal cell function and tissue development. An imbalance of the fission and fusion activities is associated with several age-related and certain oxidative stress-associated human diseases, including cancers. Growing evidence suggests that increased Drp1 might be used as a predictive biomarker for cancer progression and response to chemotherapy in ovarian cancers. In addition, growing evidence indicates that an increase in mitochondrial fusion is correlated with the increased degree of chemoresistance in gynecologic cancers including ovarian cancers. Primary-systemic platinum-based chemotherapy used in a clinical setting promotes mitochondrial fission and apoptosis of tumor cells.

Other pharmacological interventions such as phytochemical agents, TRAIL, anti-apoptotic inhibitors, and the administration of Mdivi-1 in combination with aforementioned drugs could increase ovarian cancer cell apoptosis. Such interventions have been shown to provide cytodestructive effects in vitro, in vivo, and in *clinical studies* of ovarian cancer treatment. However, patients with advanced-stage disease often develop recurrence along with platinum resistance and often leads to poor outcomes. At this time, the molecular mechanisms involved in ovarian carcinogenesis and chemoresistance indicate the potential roles of mitochondrial dynamics. Identifying molecular or mitochondria-based target therapies might be a novel therapeutic strategies to mitigate both ovarian cancer progression and chemoresistance in ovarian cancers.

9. Outstanding Questions

This review focuses on mitochondrial dynamics in ovarian cancer. Mitochondria play a crucial role in carcinogenesis for associated resistance to apoptosis or cell death. These information releases new questions regarding the pathogenesis of ovarian cancer. How can the alterations of mitochondrial function drive cancer? Does an increase in mitochondrial dysregulation correlate with the increasing degree of chemoresistance in gynecologic cancers? Can the mitochondrial dysregulation become a potential biomarker or a prognostic feature for ovarian cancer? Essentially, can the mitochondria-based target therapies be a

Table 3
Clinical studies of mitochondrial fission in ovarian cancer with pharmacological interventions.

Models	Intervention Type/dose/route/duration	Major findings			Interpretations	References
		Mitochondrial fission	Apoptosis	Oxidative stress		
<ul style="list-style-type: none"> • Relative cisplatin-resistant ovarian cancer cells • Cisplatin-resistant ovarian cancer cells 	<ul style="list-style-type: none"> • Treated with Cisplatin: 1–100 μM for 72 h • Co-treated with Cisplatin: 1–100 μM and Mdivi-1: 20 μM for 72 h • Co-treated with Cisplatin: 1–100 μM and Mdivi-1: 50 μM for 72 h 	–	<ul style="list-style-type: none"> • ↑ Caspase 3/7 activity • ↓ Cell viability • ↑↑ Caspase 3/7 activity • ↓↓ Cell viability • ↑↑↑ Caspase 3/7 activity • ↓↓↓ Cell viability 	–	<ul style="list-style-type: none"> • Combination of cisplatin and mdivi-1 induced synergistic apoptosis in chemoresistant ovarian cancer cells in a dose dependent manner 	[36] Qian W et al. (2014)
<ul style="list-style-type: none"> • TCGA-EOC genomic data 	–	<ul style="list-style-type: none"> • ↑ Drp1 mRNA • ↑ Mff mRNA 	–	–	<ul style="list-style-type: none"> • Increased mitochondrial fission in TCGA-EOC patients 	[10] Tanwar DK et al. (2016)
<ul style="list-style-type: none"> • Isolated primary EOC cells from HGSC ovarian cancer (Ex vivo: 3 patients) 	<ul style="list-style-type: none"> • Treated with TRAIL: 100 ng/ml for 16 h • Treated with Mdivi-1: 10, 20, 50 μM for 16 h • Co-treated with TRAIL 100 ng/ml and Mdivi-1: 10, 20, 50 μM for 16 h 	–	<ul style="list-style-type: none"> • ↓ Cell viability • ↓ Cell viability • ↓↓ Cell viability 	–	<ul style="list-style-type: none"> • Mdivi-1 enhanced the sensitivity of human ovarian cancer cells to TRAIL via induced apoptosis in these cells in a dose dependent manner 	[41] Wang J et al. (2015)

Abbreviations: Drp1: Dynamin-related protein-1; EOC: Epithelial ovarian cancer; HGSC: High-grade serous carcinoma; Mdivi-1: Mitochondrial Division Inhibitor 1; Mff: Mitochondrial fission factor; TCGA: The Cancer Genome Atlas; TRAIL: Tumor necrosis factor-related apoptosis-inducing ligand.

Table 4
In vitro studies of mitochondrial fusion in ovarian cancer with pharmacological interventions.

Models	Intervention Type/dose/route/duration	Major findings			Interpretations	References
		Mitochondrial fusion	Apoptosis	Oxidative stress		
<ul style="list-style-type: none"> A2780s cells (WT-p53) (human, cisplatin-sensitive ovarian cancer) A2780cp cells (p53 mutant) (human, cisplatin-resistant variant ovarian cancer) HEY cells (WT-p53) (human, cisplatin-resistant ovarian cancer) SKOV3 cells (p53 null) (human, cisplatin-resistant ovarian cancer) SKOV3 cells (p53 null) (human, ovarian serous carcinoma) IOSE-364 cells (human, normal ovarian surface epithelium) OVCAR-3 cells (human, ovarian serous carcinoma) SKOV3 cells (human, ovarian serous carcinoma) 	<ul style="list-style-type: none"> – • Treated with SNA: 12 µg/ml for 4 h • Treated with Cordycepin: 100 µM for 24 h • Treated with ABT737: 1 µM for 24 h • Treated with EBSS for 24 h • Treated with ABT737: 1 µM and EBSS for 24 h 	<ul style="list-style-type: none"> • ↑ Tubular mitochondria • ↑↑ Tubular mitochondria • ↑↑ Tubular mitochondria • ↑↑ Tubular mitochondria • ↓ Mfn-1 mRNA • ↓ Mfn-1 mRNA • ↓ Mfn-1 mRNA • ↓ Mfn-2 mRNA • ↓ Tubular mitochondria • ↓ Mfn-2 protein • ↓ Opa1 protein • ↑ Tubular mitochondria • ↑ Mfn-2 protein • ↑ Opa1 protein • ↓↓ Tubular mitochondria • ↓↓ Mfn-2 protein • ↓↓ Opa1 protein 	<ul style="list-style-type: none"> – – – – – – – – 	<ul style="list-style-type: none"> – – – – – – – – • SNA suppressed mitochondrial fusion in ovarian cancer and normal epithelial ovarian cells • Cordycepin suppressed mitochondrial fusion in ovarian cancer cells • ABT737 suppressed mitochondrial fusion in ovarian cancer cells • EBSS induced mitochondrial fusion in ovarian cancer cells • ABT737 combined with EBSS suppressed mitochondrial fusion in ovarian cancer cells 	<ul style="list-style-type: none"> [15] Kong B et al. (2014) [38] Chowdhury SR et al. (2017) [18] Wang CW et al. (2017) [42] Wang S et al. (2017) 	

Abbreviations: ABT737: A potent and selective small-molecule inhibitor of Bcl-2/Bcl-xL; EBSS: Earle's balanced salt solution; Mfn: Mitofusin; Opa1: Optic atrophy protein 1; SNA: *Sambucus nigra* agglutinin.

novel therapeutic strategies to mitigate both ovarian cancer progression and chemoresistance in ovarian cancers?

Conflict of Interest

The authors declare that they have no conflict of interest.

Contributors

CK, KC, SK, NC, and SCC designed and edited this manuscript. CK, KC, SK, NC and SCC contributed to the literature search, data collection, and manuscript writing. CK, NC, and SCC designed the figure.

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