

Anticancer Strategy Targeting Mitochondrial Biogenesis in Ovarian Cancer

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Abstract

Mitochondrial biogenesis (MtBIO) is the utmost requisite for cell's replication and survival, and it has been found to be involved in chemoresistance. The chemoresistance is the foremost obstacle in the treatment of patients with ovarian cancer. Several studies showed that modulation of MtBIO can lead to cancer cell death. Therefore targeting MtBIO in ovarian cancer could be a promising therapeutic approach possibly through overcoming the chemoresistance. Potential targets of MtBIO will be discussed focusing on ovarian cancer in this review.

Keywords: Mitochondrial biogenesis; Ovarian cancer; Therapeutic target; Chemoresistance

Introduction

Ovarian cancer is the most lethal gynecologic malignancy worldwide typically in the post-menopausal women and 5th leading cause of death in the United States [1-3]. About 80% of women are diagnosed at the advanced-stage of disease and have poor prognosis. The 5-year overall survival rate is 45% or below [4-6]. Despite the first complete response after the front-line platinum-based chemotherapeutic drugs [7,8], approximately 25% patients suffer from relapse within 6 months who are thought, by definition, to have a chemoresistance [9-12]. Combination of platinum and other drugs might improve the survival rate [13], but is not out of the danger of additive toxicity [14].

Several genetic alterations have been observed in ovarian cancer, involving deactivation mutations in tumor suppressor genes, such as p53, BRCA1 and BRCA2, and activation mutation and/or amplification of proto-oncogenes, like c-MYC, KRAS and AKT [15]. Recent genomic analysis of The Cancer Genome Atlas reported mutations in p53 gene in 96% of 316 cases of high-grade ovarian serous carcinoma (HGOSC) [16]. Other important genetic changes affect phosphatidylinositol-3-kinase (PI3K)-AKT-mammalian target of rapamycin (mTOR) cascade. The mTOR plays a central role in energy metabolism, cell growth/division through macromolecular synthesis and is found to be activated in ovarian cancer [6], which indicates a close relationship between genetic alteration and energy metabolism. It was observed that hexokinase (HK) II, the rate limiting initial enzyme in glycolysis, is overexpressed in ovarian cancer [12]. The genetic alterations and subsequent metabolic remodeling have been found to be associated with the chemoresistance [17], such as association of rictor (mTORC2 component) with resistance to cisplatin [2]. Cisplatin-induced caspase activation causing PTEN cleavage has also been reported as a potential mechanism of chemoresistance in ovarian cancer [18].

Mitochondria is a well-adapted endosymbiotic intracellular organelles, became efficient for energy production throughout the course of evolution [19]. They are critical for survival and proliferation of living organisms under aerobic conditions and produce ATP through oxidative phosphorylation (OXPHOS) [20]. Beyond the conventional function they have crucial role in certain neurodegenerative diseases and cancer [21-23]. Cellular proliferation largely depends on mitochondrial amount, governed by the process

of MtBIO [20]. MtBIO is the production of daughter mitochondria usually from previously existed one through a division process of called fission, subsequent growth, and maintenance by fusion and autophagy of mitochondria (mitophagy) [24]. Currently it has been observed that MtBIO is associated with cancer chemoresistance [25,26] through the modulation of associated proteins such as methylation-controlled J-protein (MCJ), also known as DNAJC15 [25,27], prohibitin 1 (PHB-1) [28-30], myeloid cell leukemia sequence 1 (MCL-1) [31,32] etc. in ovarian cancer. Thus it can be speculated that MtBIO has fine-tuned association at least in part with the chemoresistance of ovarian cancer and can serve as suitable target for therapy.

Metabolic Remodeling of Ovarian Cancer and its Relationship to the Chemoresistance

Important clinicopathologic and genetic alterations

According to the Gynecologic Oncology Group and European-Canadian investigators, platinum- and taxane-based chemotherapy after surgery has been considered as the effective treatment regimen against ovarian cancer [33] with 60% to 80% in overall response rate. However, among the relapsed patients response rate decreased to 15% to 35% to the same treatment regimen [34]. Different genetic alterations have been identified in ovarian cancer. HGOSC almost universally showed p53 gene mutation, followed by genomic instability, DNA copy number abnormalities etc. [16,35]. The PI3K/AKT/mTOR pathway is one of the most important genetic alteration in ovarian cancer, mostly activated due to the mutations in *PI3KCA* gene. Alteration of *PI3KCA* also leads to mTOR phosphorylation and enhance tumor survival. Activation of PI3K pathway causes overexpression of *BAD*,

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PAK1, *GSK3B* etc. [36]. Other alterations are observed in RB, RAS and NOTCH pathways. *RB1* itself is found to be deleted or mutated. CDK inhibitor (*p16*) inactivation allows the amplification of Cyclin E1 which further inhibits *RB1* via Cyclin D1 and Cyclin D2 genes. Deletion or mutation of *NF1* activate *KRAS-BRAF* linked survival pathway [35]. *NOTCH* gene gets activated either via JAG1-2 or MAML1-3. Moreover, deregulated JAG1-NOTCH1 signaling can activate group of oncogenes, including *MYC* families possibly associated with ovarian cancer progression [37]. It was observed that FOXM1 transcription factor network is activated in 84% of cases [35]. Deletion mutations in *BRCA1* and *BRCA2* are also common in HGOSC. In low grade ovarian serous carcinoma, most prevalent mutations are detected in *PI3KCA*, *BRAF* and *KRAS* genes. *ARID1A* is frequently mutated in clear-cell and low-grade endometrioid ovarian cancer [38]. One-third of clear cell cancers contain *PIK3CA* gene mutations. Mucinous type is reported to contain nearly 100% *KRAS* mutation and a high frequency of *HER2* amplification [38]. Thus genetic changes are closely associated with clinicopathologic features of ovarian cancer patients.

Metabolic remodeling in relation to genetic alterations

Genetic alterations many of the time causes metabolic changes within a cell. Genetic alteration is presumed to be linked to the metabolic reprogramming in ovarian cancer because of the involvement of *p53* gene in metabolic pathways [6]. The *p53* is found to be involved in the regulation of cellular metabolic pathways besides its classical tumor suppressive functions, such as glycolysis, OXPHOS, and amino acid metabolism [39-43]. It also plays an important role in lipid and lipoprotein metabolism [44]. Thus it can be assumed that mutant *p53* could play a greater role in metabolic reprogramming. In HGOSC mutant *p53* can enhance lipid anabolism through the interaction with sterol regulatory element-binding proteins and guanidinoacetate N-methyltransferase, leading to fatty acids and cholesterol biosynthesis and the inhibition of fatty acid oxidation (FAO) [45]. PI3K signaling is one of the major regulators of glucose metabolism through the expression of glucose transporter GLUT1 by AKT [46,47]. AKT enhances glycolytic flux partially by the maintenance of HK [48], supports cancer cells for enhanced proliferation [12]. Glucose metabolism also can be promoted by RAS through enhancing glucose uptake [49]. AKT plays an important role in glucose transport and regulates glucose storage by GSK3 inhibition. AKT also involved in gluconeogenesis and FAO through FOXOs [50,51]. Recently its role in regulating lipid metabolism has been shown via modulation of cAMP [51].

Chemoresistance associated with metabolic remodeling

Metabolic remodeling of cancer cells makes the cells resistant to certain chemotherapeutics. One of the major chemoresistant mechanisms adopted by the cancer cells is the avoidance of apoptosis. A key event of early apoptosis is the permeabilization of outer mitochondrial membrane (OMM) which causes the release of cytochrome-c. Permeabilization can be achieved by voltage-dependent anion channel (VDAC) and mitochondrial apoptosis-induced channel (MAC) resides in the OMM, and mitochondrial permeability transition pore (MPTP) which consists of VDAC at OMM and adenine nucleotide transporter (ANT) at inner mitochondrial membrane (IMM). These pore systems rely on pro-apoptotic protein Bax, Bad for opening thus under the regulation of anti-apoptotic BCL-2 family proteins, such as BCL-X_L. OMM permeabilization is further achieved by the interaction of VDAC and ANT proteins. Malignant ovarian cancer cells frequently overexpress HK II, which is found to prevent tumor apoptosis through binding with VDAC or through inhibition of

VDAC-ANT interaction [6]. AKT, a metabolic regulator of glycolysis, is overexpressed in ovarian cancer and evidence suggests that it enhance OMM stability, thus inhibiting apoptotic cell death. AKT is found to inactivate caspase-9 and induce *XIAP* expression. Activated AKT blocks ubiquitination of FLIP in p53 dependent manner [52], inhibits Bax oligomerization and inactivates Bad through phosphorylation. Further, AKT activation facilitates BCL-X_L and HK II translocation to mitochondrial pore complex especially to VDAC [6]. In addition to BCL-X_L, MCL-1 is upregulated frequently in ovarian cancer and correlated with chemoresistance. CD95 expression in ovarian cancer is reported to be linked to the chemoresistance. *HIF-1 α* , another important gene associated with ovarian cancer, upregulate IPA-2, MDM2 and VEGF and inhibits TRAIL induced Bax translocation on mitochondria [52].

MtBIO and its Association with Chemoresistance in Ovarian Cancer

The level of cellular energy depends on the amount of mitochondria or mitochondrial biomass, strictly controlled by MtBIO and essential for cellular proliferation [20]. MtBIO is a complicated process involving transcription of nuclear and mitochondrial DNA (mtDNA), nuclear and mitochondrial communications including protein import, mitochondrial dynamics (fission and fusion) and mitophagy [24]. Fission of depolarized mitochondria along with mitophagy balances the total mitochondrial mass in a cell. The first step of MtBIO deregulation is the mutation, either in nuclear DNA or mtDNA. Frequent mutations in mtDNA have been recently detected in ovarian cancer [53]. It is reported that ubiquinol-cytochrome c reductase core protein I (UQCRC1), a nuclear encoded component of mitochondrial complex III can affect mitochondrial morphology and/or physiology, and found to be overexpressed in ovarian cancer cells in experimental animals [54]. A number of studies demonstrated that MtBIO are enhanced in oncogene-transformed (*HRAS*) epithelial cancer cells evident by increased mitochondrial mass [55]. A mitochondrial import protein, MCJ found to overexpress in ovarian cancer cell line which is an indicative of upregulated MtBIO [25]. Few clinical studies have shown MtBIO in ovarian cancer [56]. A multicenter based case-control (1815 and 1900) study was conducted on Caucasian women with epithelial ovarian cancer (EOC) and revealed 128 single nucleotide polymorphisms (SNPs) from 22 genes/regions of mtDNA and 2,839 nuclear-encoded SNPs localized to 138 genes involved in MtBIO. Among the genes, nuclear respiratory factor 1 (*NRF1*), mitochondrial transcription terminator factor (*MTERF*), peroxisome proliferator-activated receptor gamma coactivator 1-alpha (*PPARGC1 α* or *PGC-1 α*), estrogen-related receptor alpha (*ERR α*) and calcium/calmodulin-dependent protein kinase type II delta (*CAMK2D*) found to be strongly associated with EOC risk [57]. Liu et al. found 60% somatic mutations from 10 ovarian carcinoma patients, mostly T→C or G→A transitions, restricted in the D-loop, 12S rRNA, 16S rRNA, and cytochrome-b region of mitochondrial genome [58]. The expression of mitochondrial transcription factor A (TFAM) was evaluated clinically on 60 patient's tissue samples with serous ovarian cancer. Immunohistochemical analysis revealed 56.7% positivity, and univariate survival analysis showed significantly worse overall 5-year survival rate for TFAM-positive cancer patients [59].

MtBIO and metabolism

MtBIO can influence metabolic remodeling of cancer cells through a number of ways, such as, production of different metabolites, generation of reactive oxygen species (ROS), stabilization of hypoxia

inducible factors (HIFs), calcium ion flux etc. Mitochondria produce ROS from superoxide ($O_2 \rightarrow \bullet O_2$) at about eight different sites on its membrane in response to different cellular stress, and upon oncogenic-transformation through a variety of means, such as deregulated electron transport, less scavenging of ROS or altered mitochondrial dynamics [60,61]. Oxygen is critical for the survival of aerobic organisms. Enhanced ROS help cancer cells to adapt in low oxygen level or hypoxia (0.3-3% O_2). The HIF family (HIF-1 and HIF-2) can initiate the production of glycolytic enzymes to maintain ATP levels [61], thus regulate energy metabolism of cancer cells [60]. MtBIO and metabolism in malignant cells intimately related to “Warburg/reverse Warburg effect” [62,63]. Dysfunctional mitochondria which was the major explanation by Otto Warburg in cancer cells for enhanced aerobic glycolysis lacks sufficient evidence [64] and recently investigation by independent researchers leading to two possible explanations, glycolytic dysregulation and cancer-stromal cells metabolic coupling [65,66]. Glycolytic dysregulation not necessarily involve mitochondria, on the other hand, cancer-stromal cells metabolic coupling has shown that “Warburg effect” takes place in the stromal cells not in cancer cells. Cancer cells utilize the nutrient from adjacent stromal cells and maintain MtBIO for its energy needs, known as reverse Warburg effect [67].

Chemoresistance associated with MtBIO

The connection between chemoresistance and MtBIO recently has been established in ovarian cancer [25,26] and it has been shown that mitochondrial networks of chemoresistant cells are well distributed throughout the cells as compared to chemosensitive ones [68]. An important step in MtBIO is the mitochondrial import of cytosol-synthesized proteins. A mitochondrial import regulatory protein MCJ, is recently found to be involved in the development of chemoresistance in ovarian cancer [25] through its reduced expression [27]. Nuclear-mitochondrial communication is necessary for the regulation of MtBIO [24]. Prohibitin (PHB), a conserved protein containing PHB domain, has been shown to regulate MtBIO [29], by regulating nuclear-mitochondrial communications [30]. It has been observed that prohibitin 1 (PHB-1) overexpression is related to chemoresistance in ovarian cancer [28]. MCL-1 is a member of the BCL-2 family proteins, involved in mitochondrial protein synthesis, apoptosis and autophagy. Of the different members of BCL-2, MCL-1 is commonly amplified in human tumors, including ovarian cancer, and is associated with

the relapse and chemoresistance [31,32]. Taken together, it can be considered that there is a strong relationship between chemoresistance and MtBIO in ovarian cancer. Therefore, the several pathways related to MtBIO could be the plausible targets for overcoming chemoresistance in ovarian cancer.

Anti-Cancer Strategy Targeting MtBIO

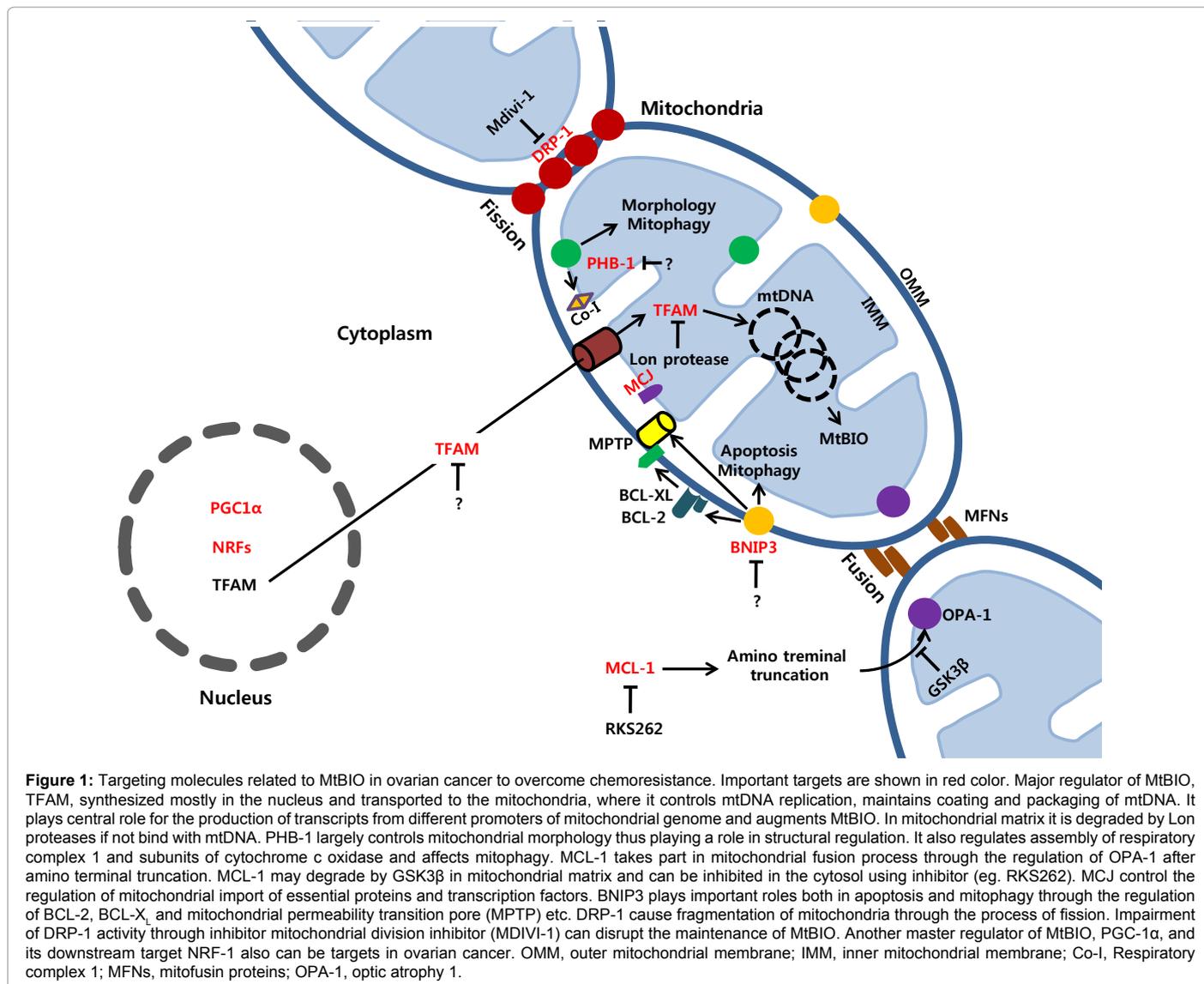
There are evidences that ovarian cancer cells maintain intact OXPPOS competent on mitochondria with functional TCA cycle for their survival in terms of membrane potential, ATP biosynthesis and oxygen consumption [30] even though their mitochondria might contain mutated DNA and accumulate different harmful products, such as ROS. Cancer cells in ovarian cancer can protect themselves through the maintenance of well distributed mitochondrial biomass and, MtBIO makes cancer cells resistant to chemotherapeutics and is considered as an emerging mechanism of chemoresistance. Mitochondria are required for the survival of organisms living under the aerobic environment. Thus MtBIO is supposed to be the ideal target for fast growing cancer cells. Here we show a number of molecules regulating MtBIO summarized in Table 1, which can be considered as useful anticancer targets in ovarian cancer (Figure 1).

Mitochondrial transcription factor A (TFAM)

TFAM (also known as mtTFA) is a nuclear encoded 25 kDa protein member of the high mobility group (HMG) box protein family and a key regulator of MtBIO. Upon import to mitochondria it performs multiple regulatory functions including mtDNA transcription, maintenance of mtDNA looping, coating and packaging (mitochondrial nucleoids) [59,69,70]. It contains facets for binding nuclear respiratory factor (NRF) 1 and NRF2 which act on the promoter of D-loop region leading to increased mtDNA copy number [71]. Significant overexpression of TFAM was observed in human serous ovarian cancer in association with poor 5-years survival. TFAM also works through binding with its downstream target BCL-X_L. The study has proposed TFAM as a noble therapeutic target for ovarian cancer [59]. Beside ovarian cancer, TFAM upregulation is also observed in breast, colorectal, bladder, endometrial and arsenic induced skin cancer with subsequent increase in MtBIO and cellular proliferation. Many study show similar results both in experimental and clinical settings [71-77]. Such findings suggest TFAM as one of the most important therapeutic targets in chemoresistant ovarian cancer.

Protein family/type	Targeting molecules	Function	Study samples	References
High mobility group (HMG) box protein	TFAM	mtDNA transcription, maintenance, coating and packaging	Human Cell lines and tissue samples	[59,69,70]
Stomatin/prohibitin/flotillin/HflK/C (SPFH) domain containing protein	PHB-1	Express in mitochondria, nucleus, cytosol and maintain communication among them	Human Cell lines and tissue samples	[28,78-80,95]
Anti-apoptotic B-cell lymphoma 2 (BCL-2) family protein	MCL-1	Optic atrophy 1 (OPA-1) mediated mitochondrial fusion	Human Cell lines	[81-84,86]
A member of the Bcl-2 family	BNIP3	Induction of cell death through mitochondrial dysfunction in response to hypoxia inducible factor-1 (HIF-1)	Human Cell lines	[89-91]
Mitochondrial methylation-controlled protein	MCJ	Involved in mitochondrial import and regulation of mitochondrial permeability transition pore (MPTP) complex	Human Cell lines	[25,27,87,88]
Dynammin-related protein	DRP-1	Important key fission protein involved in mitochondrial dynamics	Human Cell lines and in vivo in mice	[26]
Nuclear respiratory factor	NRF-1	Transcription of TFAM	Multicenter case-control study with Caucasian EOC patients	[57]
Peroxisome proliferator-activated receptor gamma coactivator	PGC-1 α	Transcription of essential factors for mitochondrial biogenesis including NRF1 and NRF2	Multicenter case-control study with Caucasian EOC patients	[57]

Table 1: Possible anticancer targets involved in MtBIO in ovarian cancer.



Prohibitin 1(PHB-1)

Prohibitin belongs to a conserved protein family, which contain a prohibitin (PHB) domain more specifically, stomatin/prohibitin/flotillin/HflK/C (SPFH) domain, observed in a diverse group of organisms from prokaryote to human [28]. It is expressed ubiquitously in different compartments of the cell such as mitochondria, nucleus and cytosol, and shuttled among them. PHB-1 has been found to be involved in chemoresistance in ovarian cancer cells and primarily associated with mitochondria. It is overexpressed in papillary serous ovarian carcinoma as well as endometrioid ovarian adenocarcinoma. This highly conserved protein can regulate cell cycle at G0/G1 phase and also confer cell survival [78]. In mitochondria, PHB-1 regulates assembly of respiratory complex 1 and subunits of cytochrome c oxidase; in addition, it affects mitophagy. Inactivation of PHB-1 function can cause defects in mitochondria respiratory chain and morphological deformation of mitochondria [79,80]. Targeting PHB-1 in ovarian cancer might lead to a promising outcome in ovarian cancer therapy.

Myeloid cell leukemia sequence 1 (MCL-1)

MCL-1 is an anti-apoptotic BCL-2 family protein [81] and its continuous transcription is required for the inhibition of apoptosis [82]. Chemoresistant A2780 cells were found to express about 8 fold higher level of MCL-1 than parental [83] and its downregulation by another member of BCL-2 family protein called PUMA (p53 upregulated modulator of apoptosis) was found to chemosensitize ovarian cancer cells (A2780 and SKOV-3) [81]. Suppression of MCL-1 by a potent anti-cancer agent RKS262 was found to enhance cell death in ovarian cancer cell line, OVCAR-3 [84]. It is evident from recent researches that BCL-2 family plays an important role in the regulation of fission-fusion dynamics of mitochondria through ionic homeostasis and autophagy. As a member of BCL-2 family, MCL-1 plays a noble role in mitochondrial dynamics. To perform such task it needs to be truncated at amino terminal and to be transported in to the mitochondrial matrix. Once in matrix it regulates mitochondrial fusion perhaps in conjunction with optic atrophy 1 (OPA-1) [85]. It was observed that inhibition of MCL-1 causes reduction of OPA-1 activity, which leads to the impairment of mitochondrial fusion, in

turn mitochondrial fragmentation increases. Such fragmentation was rapid and independent of dynamin-related protein-1 (DRP-1) without significant ATP depletion and alteration of mitochondrial complexes (I-V) [31]. In mitochondrial matrix, MCL-1 can be degraded by GSK3 β [86]. MCL-1 can serve as another target to restrict MtBIO for overcoming the chemoresistance in ovarian cancer.

Mitochondrial methylation-controlled J protein (MCJ)

Mitochondrial MCJ protein is associated with the import of cytosolic proteins to mitochondria and its transcriptional silencing due to hypermethylation has been associated with increased chemoresistance in ovarian cancer. Normal ovarian epithelial cells express MCJ, while it showed no or low level of expression both in primary ovarian tumors and ovarian carcinoma cell lines [87,88]. The MCJ reside in IMM and involved in the regulation of MPTP complex both in normal and cancer cells [27]. It has been found that MCJ interacts with translocase of the inner membrane 23 (TIM23) core proteins for the import of different proteins and transcription factors in to the mitochondria [25]. When MCJ is overexpressed, it can import more mitochondrial proteins or may lead to the opening of MPTP thus initiating the release of apoptotic factors [27]. As MCJ perform two different tasks, it can be conceptualized that cancer cells tightly regulate such balance for its survival and its activation might be an effective anticancer approach.

Bcl-2/adenovirus E1B Nineteen Kilodalton Interacting Protein (BNIP3)

BNIP3 is another member of the Bcl-2 family and found to be overexpressed in the hypoxic zone of many tumors, including breast cancer, glioma and ovarian cancer [89,90]. It is expressed on OMM and involved in mitochondrial fission and mitophagy, thus reducing total mitochondrial biomass [91]. The other function of BNIP3 is to induce cell death through mitochondrial dysfunction in response to HIF-1. However, when its transmembrane domain is lost or truncated, it failed to perform the above task. It has been observed that in ovarian cancer cells such kind of truncated BNIP3 with the loss of transmembrane domain is overexpressed [89]. Involvement of intact BNIP3 in the regulation of mitochondrial biomass is critical for cancer cells death, thus BNIP3 can be a suitable molecular target for ovarian cancer.

Other Targets

In ovarian cancer, besides the above mentioned molecules targeting MtBIO, there are other possible ones, such as DRP1 [26], NRF1, MTERF, PPARGC1A, ESRRA, CAMK2D and UQCRC1 [57]. DRP1 is the important key fission protein involved in mitochondrial dynamics. It has been observed that increase of mitochondrial fission was induced by increasing activity of DRP-1 in *in vitro* and *in vivo* in ovarian cancer. Inhibition of DRP-1 using mitochondrial division inhibitor (MDIVI-1) can reduce fragmentation of mitochondria, resulting reduced cellular proliferation [26]. ERRA was frequently over-expressed in advanced-stage ovarian cancer and has been implicated as a prognostic marker recently [92-95]. Further research is necessary to determine the most appropriate target of MtBIO to combat against the chemoresistant ovarian cancer.

Summary and Future Prospects

Mitochondria play dual role in cell survival and cell death and thus serve as critical organelles of eukaryotes. Extensive studies revealed highly dynamic behavior of mitochondria and opened up many facets of research recently, as well as, the possibility of finding noble targets in cancer resistance. Resistance to anti-cancer drugs achieved through

the adaptive evolution of malignant cells towards major signaling pathways usually at the upstream of MtBIO. Complete inhibition or overexpression of upstream signaling molecules largely affect cells and induce cytotoxicity even in normal cells. Directly targeting MtBIO may hit the “Achilles’ heel” of cancer cells and may serve as a keen approach to exploit the loopholes of chemoresistance. In depth understanding of the key differences between normal and malignant cell’s MtBIO in the future will help to design anti-cancer agents for highly specific targets.

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