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Review

Mitochondrial Dynamics in Ovarian Cancer: Pathophysiology and Therapeutic Implications

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Abstract: Background: Ovarian cancer is often characterized by aggressive growth and chemoresistance, leading to a poor prognosis. The energy and nutrient acquisition through metabolic reprogramming has been reported to facilitate cancer cell proliferation, invasion, and metastasis. Therefore, a therapeutic strategy to consider is to rewire energy metabolism. Mitochondrial dynamics have a profound impact on the metabolic profiles. In this review, we summarize the current understanding of the molecular mechanisms governing mitochondrial dynamics and their impact on cell proliferation and invasion and discuss future perspectives for therapeutic strategies and research directions. Methods: A search was conducted for literature published up to 30 June 2023 using the online databases PubMed and Google Scholar in this narrative literature review. Results: Mitochondria are essential for regulating metabolic reprogramming to meet the increasing energy demand for rapid cancer cell proliferation and invasion. A metabolic switch from OXPHOS to glycolysis may promote invasion, and OXPHOS-driven metabolism may be associated with proliferation, chemoresistance, and stemness. Many ovarian cancer cells are known to favor glycolysis over OXPHOS, but the opposite takes place in the subpopulation of cancer cells. The preference for glycolysis versus OXPHOS in ovarian cancer cells may be determined by histopathologic types, the unique genetic profile of energy metabolism, and intrinsic (e.g., oncogenic signaling) and extrinsic (e.g., nutritional status and hypoxia) factors. Conclusions: Preclinical studies suggest that mitochondrial dynamics regulators have therapeutic potential in ovarian cancer, but some factors limit their beneficial effects.

Keywords: metabolic dynamics; metabolic reprogramming; mitochondrial fission; mitochondrial fusion; ovarian cancer

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1. Introduction

Epithelial ovarian cancer is an aggressive gynecologic cancer with a poor prognosis due to resistance to chemotherapeutic agents [1]. Ovarian cancer has an ability to adapt to unfavorable environments, such as oxygen/nutrient deprivation and oxidative stress conditions, which contributes to its poor prognosis [2]. Cancer cells generally require high nutrients and energy to maintain their survival in such harsh environments. Tumor development is initially driven by a proliferative phenotype, and over time, the primary tumor escapes the tissue of origin and colonizes additional organs [1]. In recent years, mitochondria have been found to have a profound impact on metabolic profiles [3] and participate in the regulation of tumor initiation and progression [4]. Both glycolysis and mitochondrial oxidative phosphorylation (OXPHOS) are the dominant energy-generating pathways.

Therefore, mitochondria dynamics contribute to the maintenance of optimal glycolysis and OXPHOS activity through regulating mitochondrial transport, fusion, fission, and quality control [3,5–8]. Mitochondria regulate cellular energy through their dynamics or changes in mitochondrial architecture. Specifically, mitochondria play a role in regulating key tumorigenic processes, including metabolic rewiring, cell cycle, cell proliferation, cell migration, self-renewal capacity, and mitochondria-specific autophagy (mitophagy) [7,8]. Mitochondrial dynamics can dictate the cellular metabolic states, and vice versa [3]. Therefore, cancer cells can obtain optimal energy to survive by altering the metabolic profile between glycolysis and mitochondrial OXPHOS [9]. Indeed, many ovarian cancer cells primarily favor glycolysis over mitochondrial OXPHOS, but others are dependent on OXPHOS for energy production [2]. Adaptation to the dynamic tumor microenvironment has been reported to be controlled by alterations in the metabolic profiles (e.g., metabolic heterogeneity, plasticity, and reprogramming) [2]. Therefore, the deregulation of cellular energy or the reprogramming of energy metabolism has emerged as one of the hallmarks of ovarian cancer [2,4,9]. To understand the mechanisms involved in mitochondrial dynamics and therapeutic implications, some important issues need to be discussed. For example, what role do key regulators of mitochondrial dynamics actually play in ovarian cancer? How do mitochondria regulate cancer cell proliferation and invasion? What factors influence mitochondrial dynamics and energy metabolism? How do metabolic reprogramming and mitochondrial dynamics influence each other? What determines the metabolic preferences (i.e., glycolysis or OXPHOS) of ovarian cancer cells? Finally, how is the potential of therapeutic approaches based on mitochondrial dynamics modulation and the current status of treatment options? In this review, we focus on our current understanding of the molecular pathways involved in regulating mitochondrial dynamics and maintaining energy homeostasis and their roles in ovarian cancer proliferation and invasion and discuss treatment options and future research directions.

2. Materials and Methods

Search Strategy and Selection Criteria

We conducted a narrative review of the literature that focuses on mitochondrial dynamics in ovarian cancer. Electronic databases including PubMed and Google Scholar were searched for literature published up to 30 June 2023, combining the following keywords: "Mitochondrial fusion", "Mitochondrial fission", "Mitochondrial dynamics", "Metabolic reprogramming", and "Ovarian cancer".

3. Results

3.1. Mitochondrial Function

Mitochondria are believed to descend from ancient prokaryotes, i.e., endosymbiosed bacteria, which were engulfed by pre-eukaryotic cells several billion years ago [10]. These organelles consist of an outer mitochondrial membrane (OMM), inner mitochondrial membrane (IMM), and matrix [11]. Complex machinery composed of electron transport chain (ETC) assembly and OXPHOS is located in the folded IMM called cristae [11]. Mitochondria generate energy as adenosine 5′-triphosphate (ATP) through OXPHOS, mediate the metabolic pathways in bioenergetics, supply precursors for macromolecular synthesis, regulate the cytoplasmic oxidation-reduction (redox) state, heme synthesis, and calcium balance, and play a key role in the regulation of apoptosis and autophagy [12,13]. Since mitochondria also generate reactive oxygen species (ROS) as byproducts along with energy, cells must tightly adjust energy based on the metabolic demand and appropriately monitor its redox status [4,14]. Mitochondria exposed to oxygen-rich surroundings confer significant growth and survival advantages to the host cell to meet its energy needs and also have a spectrum of protective properties against toxic metabolites [15]. Mitochondria are not static bean-shaped organelles, and their morphology alters from the filamentous network structure to the fragmented form or vice versa [5,12] (Figure 1, Mitochondrial morphology). These organelles possess adaptive mechanisms to meet bioenergetic demands by changing

their shape, number, function, and distribution within the cytoplasm [3,16,17]. Mitochondria can move throughout the cytoplasm [18,19]. Upon nutrient starvation, mitochondria are often elongated and branched around the nucleus to enhance bioenergetics efficiencies, enabling cancer cells to survive under unfavorable conditions [3,16,20,21] (Figure 1, Environmental stressors). On the other hand, upon encountering hypoxia, cancer cells have fewer mitochondria, facilitating cell invasion [3,22]. This enables tumor cells to escape their hypoxic environment, leading to metastasis [22]. Mitochondrial functions can govern the adaptation to ever-changing extracellular environments (e.g., nutrient starvation and hypoxia) [23–25].

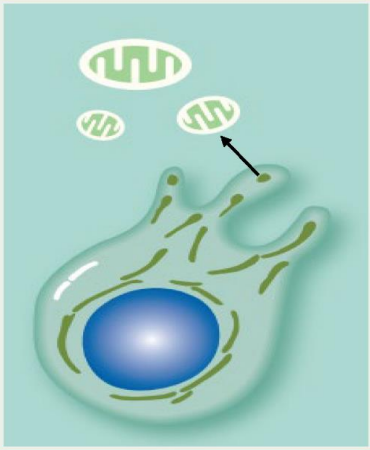
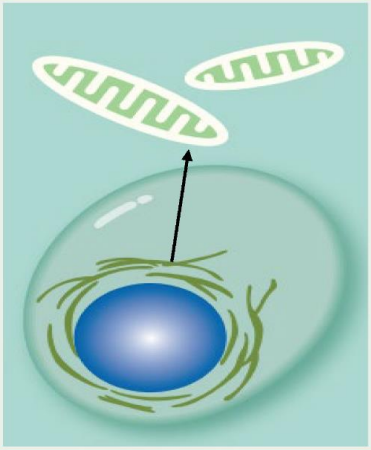
Mitochondrial dynamics	Fission	Fusion
Mitochondrial morphology		
Genes	DRP1	MFN1, MFN2, OPA1
Positioning	Repositioning of fragmented mitochondria to the lamellipodia of the peripheral cytoskeleton	Elongated and branched mitochondria around the nucleus
Intracellular transporter	↑ SNPH	↓ SNPH
Function	↑ Mitophagy ↑ Quality control	↓ Mitophagy
Oncogenic signaling	RAS-RAF-ERK MAPK-ERK PI3K-AKT	MYC
Metabolism	↑ Glycolysis ↑ GLUT ↓ ATP ↑ ROS ↓ OXPHOS	↑ OXPHOS ↓ ROS ↑ ATP
Phenotype	Invasive	Proliferative
Stemness	iPSC, CSC	Normal stem cells
Cell cycle	M phase	G1/S phase
Environmental stressors	Hypoxia	Nutrient starvation

Figure 1. Mitochondrial dynamics and their function.

AKT, AKT serine/threonine kinase 1; ATP, adenosine 5′-triphosphate; CSC, cancer stem cells; DRP1, dynamin-related protein 1; ERK, extracellular regulated MAP kinase; GLUT, glucose transporter; iPSC, induced pluripotent stem cells; MAPK, mitogen activated kinase-like protein; MFN1, mitofusin 1; MFN2, mitofusin 2; MYC, MYC proto-oncogene; OPA1, optic atrophy 1; OXPHOS, oxidative phosphorylation; PI3K, phosphatidylinositol

3-kinase; RAF, Raf oncogene; RAS, Ras oncogene; ROS, reactive oxygen species; and SNPH, syntaphilin.

3.2. Mitochondrial Dynamics

A recent study demonstrated that, in ovarian cancer, an imbalance between mitochondrial fission and fusion causes changes in mitochondrial morphology [26,27]. A detailed review of mitochondrial alterations, dynamics, and morphology and chemoresistance in ovarian cancer is reported in [28]. Here, we summarize our current understanding of key players controlling mitochondrial dynamics and their roles in cancer, particularly ovarian cancer, with a focus on the intricate interplay between mitochondrial dynamics and energy metabolism.

3.2.1. Mitochondrial Transports

Mitochondria do not stay in one place but can move along the microtubule network by using motor proteins [29]. Mitochondrial transport along microtubules is mediated by their motor-cargo, adaptor complex, and regulatory elements [30]. The plus end-directed motor protein, Kinesin-1 (KIF5), facilitates the anterograde transport and cell membrane targeting and is responsible for the transport of mitochondria from the perinuclear region to the plasma membrane [24,30] (Figure 2). On the other hand, the retrograde movement of mitochondria is quite dependent on the minus end-directed motor protein, Dynein complex [24,30]. A member of the kinesin family has been found to be a candidate gene associated with prognostic factors in ovarian cancer [31]. The loss of the dynein light chain, KM23 or DYNLL1 (dynein light chain LC8-type 1), has been reported to exhibit an important role in the tumor formation [32] and chemoresistance [33] of ovarian cancer. Furthermore, the syntaphilin (SNPH) protein anchors mitochondria to microtubules and turns the mitochondrial transfer switch on or off [24,25]. The upregulation of SNPH expression loses mitochondrial mobility, anchors mitochondria around the nucleus, and promotes their fusion. Conversely, the loss of SNPH expression enhances mitochondrial transport and facilitates their distribution to the cortical cytoskeleton [25]. However, studies on motor proteins and SNPH in ovarian cancer are still lacking.

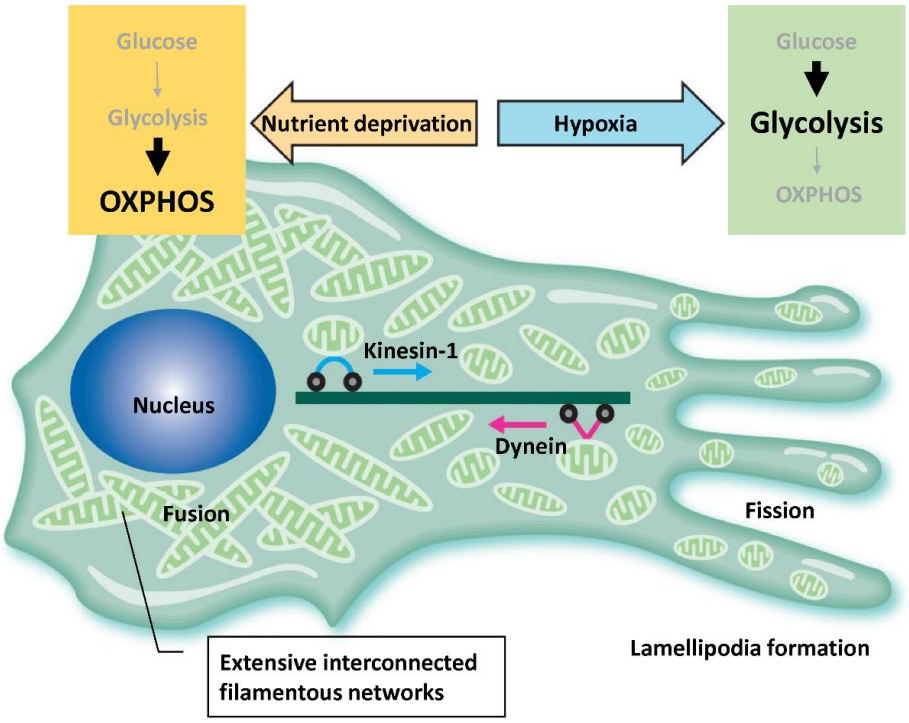


Figure 2. Regulation of mitochondrial dynamics, transport, and energy biogenesis. OXPHOS, oxidative phosphorylation.

3.2.2. Mitochondrial Fusion

Mechano-chemical dynamin-related GTPases (e.g., Mitofusin 1 (MFN1), Mitofusin 2 (MFN2), Optic atrophy 1 (OPA1), and Dynamin-related protein 1 (DRP1)) play critical roles in orchestrating mitochondrial dynamics, including constant fusion/fission [5–8]. The fusion of the OMM is mediated by MFN1 and MFN2, and OPA1 promotes IMM fusion (Figure 1, Fusion). The fusion events regulate mitochondrial bioenergetics [34], increase oxidative phosphorylation, enhance efficient ATP generation, decrease ROS production, protect cell viability, and avoid cell death [3,35] (Figure 1, Metabolism). For example, MFN2 has been reported to be associated with elevated pyruvate, fatty acid, and coenzyme Q levels, increased mitochondrial membrane potential, and enhanced bioenergy production via OXPHOS [34,36]. Mechanistically, mitochondrial fusion leads to the transfer, redistribution, dilution, and complementation of damaged mitochondrial content (e.g., mtDNA, oxidized lipids, or proteins) [3,5,12] and the protection of mitochondria from selective autophagic clearance, known as mitophagy [5,7,8,37]. MFN1, MFN2, and OPA1 protein and mRNA levels have been reported to be downregulated in different types of tumors such as the colon, lung, liver, stomach, bladder, and brain [6]. Indeed, a series of in vitro and in vivo xenograft experiments demonstrated that the loss of MFN2 promotes cancer cell migration [38,39]. In ovarian cancer cells, MFN2 suppresses cell proliferation and invasion by upregulating AMP-activated protein kinase (AMPK) and downregulating the mTOR (mammalian/mechanistic target of rapamycin)–ERK (extracellular regulated MAP kinase) axis [27]. In pancreatic cancer cells, the overexpression of MFN2 causes mitochondrial fusion, reduced mitochondrial mass and ATP production, and increased mitophagy [40]. The subsequent loss of mitochondrial mass suppressed tumor growth via reduced OXPHOS [40]. Furthermore, low MFN2 expression was reported to be related to poor prognosis in hepatocellular carcinoma cells [41]. Therefore, MFN2 may be recognized as a tumor suppressor gene. However, mitochondrial localization based on their dynamics can be reprogrammed by extracellular signals (e.g., nutrient and oxygen levels) and intracellular signals (e.g., oncogene activation) [3] (see Section 3.4). Upon nutrient starvation, mitochondria undergo a series of fusion events via the overexpression of MFN1/2 to evade mitophagy [20] (Figure 1, Environmental stressors). Additionally, OPA1 is required for angiogenesis in response to angiogenic stimuli and influences tumor growth and metastasis via the NF-κB (nuclear factor-kappaB)-dependent pathway [42]. Therefore, mitochondrial fusion is thought to contribute to tumor growth and progression through the metabolic shift from glycolysis toward OXPHOS and facilitating angiogenesis [43]. As described above, mitochondrial fusion is thought to have dichotomy effects on tumor suppression and promotion. This may depend on the degree of a metabolic shift from glycolysis to OXPHOS and mitochondrial stress.

3.2.3. Mitochondrial Fission

The master regulator in mitochondrial fission is DRP1 [39] (Figure 1, Fission). Mitochondrial fission causes their fragmentation, which is important in regulating cancer cell replication and death, possibly through the proper distribution of mitochondria, the stochastic replication of mitochondrial DNA, the partitioning of organelle genomes during cell division, cytochrome C release during caspase-dependent apoptosis, and removing damaged organelles by mitophagy [3,7,8]. mTOR regulates cancer cell proliferation by controlling MFN2-mediated mitochondrial fusion and PKM2-dependent glycolysis [44], suggesting that mitochondrial dynamics and metabolic changes may mutually adapt to maintain cancer cell survival. Furthermore, in addition to a decreased expression of MFN, an increased expression or enhanced activation of DRP1 have been found in many patient-derived cell lines and patient tumor samples [3,45], including the lung [46], breast [47], brain (glioblastoma) [48], colon [49], pancreas [50], skin (melanoma) [51], and thyroid [52], indicating a potential role of DRP1 as a cancer-promoting factor [5,23]. Tumor cells induce the subcellular repositioning of active mitochondria to the lamellipodia of the peripheral cytoskeleton to provide energy for rapid tumor motility and invasion [41]. To that end,

tumor cells upregulate DRP1 expression to trigger mitochondrial fission [53]. Indeed, a change in mitochondrial dynamics facilitates the increased production of ATP at the leading edge of lamellipodia in ovarian cancer cells [54]. A potential role of mitochondrial dynamics in tumor cell migration and invasion has also been identified in glioblastoma, breast, lung, thyroid, and prostate cancer [5,6]. DRP1-dependent mitochondrial fission or fragmented mitochondria may result in increased glycolysis in some cancers, including ovarian cancer [7,55] (Figure 1, Metabolism) (see Section 3.3). Cancer cells that rely on glycolysis over OXPHOS for energy production generate low levels of ROS. Therefore, mitochondria at the leading edge result in increased glucose uptake and glycolysis and decreased oxidative stress, counteracting the reduced efficiency of ATP synthesis, a loss of mitochondrial membrane potential, a decrease in oxygen consumption, and increased mitophagy [23]. However, long-term dependence on glycolysis eventually leads to decreased ATP generation and increased ROS production. Cellular stress such as acute and sustained hypoxia can induce extensive mitochondrial fission, leading to ovarian cancer cell proliferation and invasion, via the upregulation of HIF-1α (hypoxia inducible factor-1alpha) and DRP1 expression [56]. Salt-inducible kinase 2 (SIK2), an AMPK-like protein, has been identified as a key gene mediating this mechanism [57]. Additionally, hypoxia and nutrient starvation are known to induce SIK2 through LKB1, an important sensor of energy requirements [57] (Figure 1, Environmental stressors). Furthermore, nutrient deprivation such as glutamine promotes the malignant biological behavior (e.g., stemness and chemoresistance) of ovarian cancer cells via DRP1-induced mitochondrial fragmentation with enhanced glycolysis [58]. Ovarian cancer cells can reprogram mitochondrial function and localization in response to intracellular energetic demands, the nutrient supply, and a hypoxic environment [34,59,60]. In addition, mitochondrial dynamics contribute to maintaining the regenerative competence of not only cancer cells but also normal cells through the activation of genes that control mitochondrial fusion and fission [39,61] (Figure 1, Stemness). Mitochondrial fusion and fission are common in normal stem cells and cancer stem cells, including induced pluripotent stem (iPS) cells, respectively [6,39]. Considering the above, we believe that tumor cells may predominantly exhibit a proliferative phenotype when mitochondria are fused and localized perinuclearly, whereas mitochondria at the leading edge of tumor cells may be associated with an invasive phenotype (Figure 1, Phenotype).

3.3. Factors That Influence Energy Metabolism

The altered metabolic profile is now recognized as a defining hallmark of cancer [9]. Mitochondrial dynamics and metabolic reprogramming are known to influence each other [62]. Cancer cells switch their metabolic profile in response to intracellular and extracellular stimuli to produce ATP and essential building blocks to maintain energy demand and support proliferation, respectively [6,7,63]. Normal cells produce ATP through mitochondrial OXPHOS in the presence of oxygen, whereas cancer cells rely on glycolysis instead of OXPHOS to produce ATP and lactate, a phenomenon called the Warburg effect [9]. Cancer cells rely on the Warburg effect to meet the energy required for rapid DNA replication and proliferation. First, we briefly overview the mechanisms underlying the metabolic switch between glycolysis and OXPHOS (Figure 3). Pyruvate dehydrogenase kinase (PDK) [64] and the M2 isoform of pyruvate kinase (PKM2) [65], as glycolytic enzymes, are known to be two major effectors influencing metabolic rewiring. Pyruvate dehydrogenase (PDH) converts pyruvate to acetyl-CoA, switches metabolism from glycolysis toward OXPHOS, and induces mitochondrial oxidation [66]. Hypoxia-activated HIF-1α and TGF-β (transforming growth factor-beta) upregulate PDK expression, which suppresses PDH activity [67–69]. Therefore, the HIF-1α/TGF-β-PDK-PDH signaling pathway induces a metabolic shift from OXPHOS toward glycolysis. On the other hand, PKM2 promotes mitochondrial fusion through MFN2, resulting in a metabolic shift from glycolysis to OXPHOS [44]. PKM2 regulates the final step of glycolysis and converts phosphoenolpyruvate (PEP) to pyruvate [65]. PDK and PKM2 are believed to serve as biological switches that toggle between glycolysis

and OXPHOS. Therefore, these glycolytic enzymes are key players that link mitochondrial dynamics and energy metabolism.

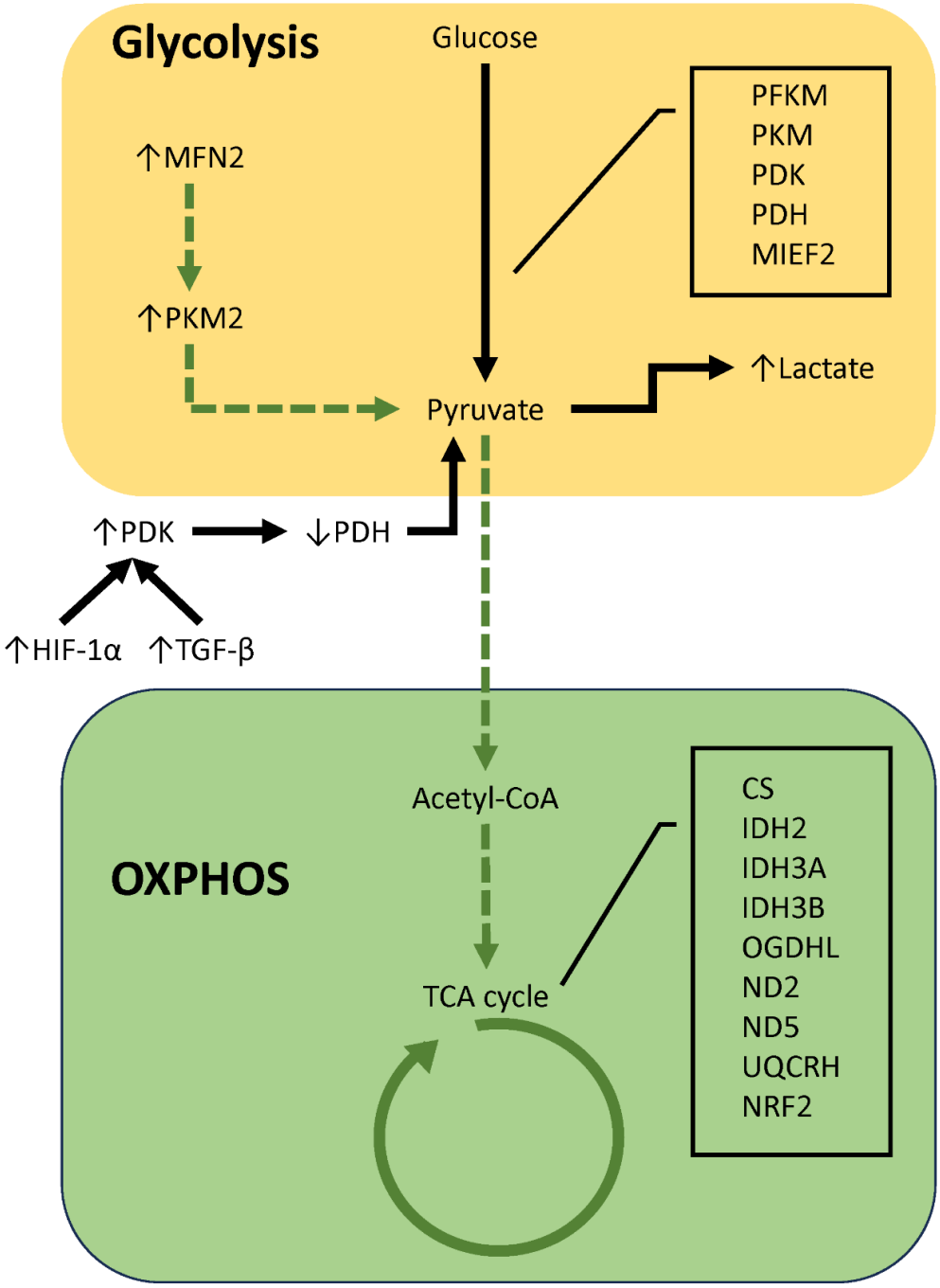


Figure 3. Factors that influence energy metabolism in ovarian cancer.

Next, we summarize the biological properties of specific genes and proteins related to energy metabolism and mitochondrial dynamics in ovarian cancer. The gene expression profile downloaded from The Gene Expression Omnibus database identified hexokinase 2 (HK2), lactate dehydrogenase A (LDHA), and enolase 1 (ENO1) as glycolytic biomarkers in ovarian cancer [70] (Figure 3). Furthermore, quantitative proteomics studies were conducted to compare human ovarian cancer tissues and the controls to identify ovarian cancer-specific mitochondrial differentially expressed proteins [71]. The proteins significantly enriched in ovarian cancer are PKM (pyruvate kinase M1/2), PFKM (phosphofructokinase, muscle), PDHB (pyruvate dehydrogenase E1 subunit beta), CS (citrate synthase), IDH

(isocitrate dehydrogenase (NADP+)), OGDHL (oxoglutarate dehydrogenase-like), ND5 (mitochondrially encoded NADH dehydrogenase subunit 5), ND2, UQCRH (ubiquinol-cytochrome c reductase hinge protein), MIEF2 (mitochondrial elongation factor 2), and Nrf2 (nuclear factor erythroid 2-related factor 2) [71]. These genes encode proteins involved in glycolysis and mitochondrial respiration [71]. They are mainly associated with energy metabolism pathways and provide the energy required for the biosynthesis of cellular building blocks and the respiratory pathways of glycolysis, the tricarboxylic acid (TCA) cycle, and the mitochondrial ETC [4,72]. Moreover, several genes affecting energy metabolic pathways have also been reported in ovarian cancer cells. Small nucleolar RNA host gene 3 (SNHG3) fine-tunes energy metabolism by regulating the expression of PKM, PDHB, IDH2, and UQCRH in ovarian cancer and is also associated with chemoresistance [73]. The SNHG3 gene has been reported to promote the progression of breast cancer [74]. Additionally, human pituitary tumor-transforming gene (PTTG) plays an important role in upregulating the expression of enzymes involved in aerobic glycolysis (e.g., PKM2, LDHA, and GLUT1) [75]. PTTG, a multifunctional proto-oncogene, is overexpressed in various tumors including ovarian cancer [75]. This subsection describes the representative molecular players involved in energy metabolism pathways. PKM generates ATP and pyruvate. PKM has been found to bind the OPA protein involved in cancer cell proliferation. PFKM catalyzes the phosphorylation of fructose-6-phosphate (F6P) to fructose-1,6-bisphosphate and is downregulated in ovarian cancer. The PDH complex catalyzes the conversion of pyruvate to acetyl-CoA, attenuates the production of lactate, contributes to enhanced OXPHOS activity, and provides a metabolic shift from glycolysis toward OXPHOS. PDH expression is downregulated in ovarian cancer and is associated with poor prognosis [76]. CS is a TCA cycle enzyme that catalyzes the synthesis of citrate from oxaloacetate and acetyl-CoA. CS being overexpressed in ovarian cancers reportedly promotes cell proliferation, invasion, and migration [77]. IDH catalyzes the oxidative decarboxylation of isocitrate to 2-oxoglutarate and plays a role in intermediary metabolism and energy production [78]. The upregulation of IDH expression has been reported to promote ovarian cancer growth through metabolic and epigenetic alterations [78]. OGDHL degrades glucose and glutamate and can suppress cancer cell growth via downregulating the AKT (AKT serine/threonine kinase 1) signaling cascade. ND5 promotes cancer metastasis through enhancing OXPHOS activity [79]. UQCRH may suppress carcinogenesis through promoting mitochondria function [80]. Since ovarian cancer is characterized by a high oxidative stress status and decreased antioxidant activity, Nrf2 functions as a key regulator of many genes related to the antioxidant processes [81]. It is well known that mitochondria are the powerhouse of eukaryotic cells and ROS are metabolic byproducts. Energy production through glycolysis allows ovarian cancer cells to minimize ROS generation. Fine-tuning metabolic reprogramming enables ovarian cancer cells to survive in an oxidative stress-rich tumor microenvironment. In addition, a metabolomics analysis revealed that MIEF2 is overexpressed in ovarian cancer cells [82,83]. MIEF2 increases the expression of enzymes (e.g., GA3P (glyceraldehyde 3-phosphate), G6P (glucose 6-phosphate), 3PG (3-phosphoglycerate), F6P, and lactate) associated with the glycolytic pathway and decreases the production of TCA cycle intermediates (e.g., α-ketoglutarate, aconitate, citrate, malate, and fumarate) [82]. MIEF2 may promote the progression of ovarian cancer through inducing a metabolism switch from OXPHOS to glycolysis [82]. Overall, these data suggest that ovarian cancer cells control cell proliferation and survival by regulating energy metabolism.

Finally, ovarian cancer is a heterogeneous disease. High-grade serous carcinoma (HGSC) and clear cell carcinoma (CCC) are representative subtypes of epithelial ovarian cancer with unique genetic and clinicopathological features. CCC is characterized by an increased expression of oxidative stress and glycolysis-related genes [55]. Hepatocyte nuclear factor 1beta (HNF1B), a CCC-specific transcription factor [84–87], and PDK [88] favor aerobic glycolysis. Conversely, ARID1A (AT-rich interaction domain 1A), an SWI/SNF subunit gene that is mutated in approximately 50% of CCC [89], has been reported to regulate mitochondrial dynamics, resulting in a metabolic shift from glycolysis to OX-

PHOS [90]. Transcriptional programs of HNF1B, PDK, and ARID1A may orchestrate energy metabolism to match the needs of the cell, i.e., carcinogenesis, proliferation, invasion, and survival. Furthermore, the expression of glycolysis-related proteins, glucose transporter-1 (GLUT1), hexokinase 2 (HKII), PKM2, and LDHA, is also upregulated in HGSC [91]. However, there are also reports that HGSC, ovarian cancer stem cells, and metastatic ovarian tumors mainly rely on OXPHOS for their energy needs [92,93]. For a detailed and up-to-date review of ovarian cancer and metabolism, see ref. [94]. Many ovarian cancer cells favor energy production, primarily by glycolysis over mitochondrial OXPHOS, but some cancer cells behave distinctly in the opposite way. The preference for glycolysis versus OXPHOS in ovarian cancer cells may be determined by histopathologic types or the unique genetic profile of energy metabolism.

The solid black arrows indicate glycolysis and the dotted green arrows indicate OXPHOS. CS, citrate synthase; HIF-1α, hypoxia inducible factor-1alpha; IDH2, isocitrate dehydrogenase2; IDH3A, isocitrate dehydrogenase3A; IDH3B, isocitrate dehydrogenase3B; MFN2, mitofusin 2; MIEF2, mitochondrial elongation factor 2; ND2, mitochondrially encoded NADH dehydrogenase subunit 2; ND5, mitochondrially encoded NADH dehydrogenase subunit 5; NRF2, nuclear factor erythroid 2-related factor 2; OGDHL, oxoglutarate dehydrogenase-like; PDH, pyruvate dehydrogenase; PDK, pyruvate dehydrogenase kinase; PFKM, phosphofructokinase, muscle; PKM, M isoform of pyruvate kinase; PKM2, M2 isoform of pyruvate kinase; TCA, tricarboxylic acid cycle; TGF-β, transforming growth factor-beta; and UQCRH, ubiquinol-cytochrome c reductase hinge protein.

3.4. Relationship between Metabolic Reprogramming and Mitochondrial Dynamics

In this section, we summarize the metabolic reprogramming that affects mitochondrial dynamics in ovarian cancer. The specific metabolic preferences of tumor cells may be determined by extrinsic (e.g., nutritional status and hypoxia) and intrinsic (e.g., oncogenic signaling) factors.

3.4.1. Extrinsic Factors

Cancer cells exhibit intertumoral and intratumoral heterogeneity, and their phenotype may be regulated by signals originating from the surrounding tumor microenvironment [6,23]. For example, under hypoxic conditions, tumor cells favor glycolysis over mitochondrial OXPHOS via upregulating the HIF-1α-PDK axis [95] (Figure 1, Environmental stressors). Tumor cells with a hypermetabolic and glycolytic phenotype can shift glucose metabolism into the pentose phosphate pathway (PPP), which produces NADPH to maintain the level of glutathione that helps protect cancer cells against oxidative damage and ribose-5-phosphate to synthesize nucleic acids [95]. Indeed, hypoxia promotes tumor cell migration through increased DRP1 expression, mitochondrial fragmentation, and mitosis in breast cancer [96] and glioblastoma cells [48]. Tumor cells must escape the lethal effects of the hostile environment and find safe places where they can form metastases and grow again [7,55]. In HGSC, exposure to hypoxia induces mitochondrial fragmentation, leading to enhanced metastasis [26]. Therefore, glycolytic tumors may be involved in the acquisition of an invasive phenotype through DRP1-dependent mitochondrial fission (Figure 1, Phenotype). On the other hand, mitochondrial elongation upon nutrient starvation is required to optimize mitochondrial substrate utilization and enhance ATP generation with the limited available resources, indicating that mitochondrial fusion is associated with a proliferative phenotype [34] (Figure 1, Environmental stressors and Phenotype). Unfavorable environmental conditions, such as hypoxia and nutrient starvation, may drive invasive and proliferative behavior, respectively [97].

3.4.2. Intrinsic Factors

Next, oncogenic RAS (Ras oncogene)–RAF (Raf oncogene)–ERK [98] signaling, MAPK (mitogen activated kinase-like protein)–ERK [99] signaling, PI3K (phosphatidylinositol 3-kinase)–AKT [100] signaling, and MYC (MYC proto-oncogene) [101] signaling are known

to govern the mitochondrial dynamics machinery (Figure 1, Oncogenic signaling). These oncogenic signaling pathways are also activated in ovarian cancer cells. RAS mutations, especially KRAS (KRAS proto-oncogene, GTPase) mutations, were detected in approximately 6 to 65% of ovarian cancer [102]. The somatic copy number alterations of PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) were also frequently increased (by approximately 20%) [103]. In particular, ARID1A (62%), PIK3CA (51%), KRAS (10%), PPP2R1A (protein phosphatase 2 scaffold subunit A alpha) (10%), and PTEN (phosphatase and tensin homolog) (5%) genes are frequently mutated in ovarian clear cell carcinoma (CCC) [104]. Oncogenic RAS–RAF–ERK [98] signaling, MAPK–ERK [99] signaling, and PI3K–AKT [100] signaling can mediate a metabolic switch from OXPHOS to glycolysis, promote DRP1-dependent mitochondrial fission, and eliminate damaged mitochondria through mitophagy [6]. Functionally, mitochondrial fragmentation promotes mitochondrial trafficking to the cortical cytoskeleton, induces lamellipodia formation, and enhances the bioenergetics of cell motility and invasion [99,100]. Conversely, oncogenic MYC overexpression may promote mitochondrial fusion [105]. Oncogenic MYC signaling induces mitochondrial fusion by upregulating PGC-1β (peroxisome proliferative activated receptor, gamma, coactivator 1 beta) and PLD6 (phospholipase D Family member 6, which is also known as mitoPLD) expression [101,105]. PGC-1β regulates mitochondrial biogenesis [106] and PLD6 facilitates mitochondrial fusion through the generation of phosphatidic acid [101]. Furthermore, the survival signaling pathways regulating mitochondrial biogenesis include AMPK-PGC-1α and SIRT1 (sirtuin1)-PGC-1α, metabolic sensors that control energy expenditure [107]. Several oncogenes, such as RAS, MAPK, and PI3K, induce mitochondrial fission, and MYC overexpression may drive mitochondrial fusion. The activation of oncogenes has been found to play important roles in the proliferation and invasion of various types of cancers by regulating mitochondrial dynamics [6]. In addition, mutations in tumor suppressor p53 are prevalent in high-grade serous ovarian carcinoma. p53 is involved in various cellular processes, such as mitochondrial elongation [108]. Therefore, the dysregulation of oncogenes or tumor suppressor genes has been implicated in mitochondrial dynamics and tumor progression by fine-tuning a relative balance between mitochondrial biogenesis and mitophagy, known as mitochondrial quality control mechanisms.

Overall, tumor cells may primarily utilize OXPHOS via mitochondrial fusion for proliferation and activate glycolysis via mitochondrial fission for invasion, although the results remain inconsistent [109]. Although the metabolic switch from OXPHOS to glycolysis regulates the invasion cascade, OXPHOS is indeed essential for the growth, survival, and stemness of tumor cells [110]. Indeed, the upregulation of mitochondrial OXPHOS activity has been reported to be involved not only in proliferating tumor cells but also in metastatic tumor cells, chemoresistant tumor cells, and cancer stem cells [109]. Therefore, mitochondrial dynamics are essential for tumor formation and progression, including tumor invasion and proliferation, cancer stemness, and chemoresistance. Differences in such intrinsic or extrinsic factors among cancer cells may be the reason for the inconsistent results.

3.5. Therapeutic Strategies Targeting Mitochondrial Dynamics

Finally, this section summarizes therapeutic strategies targeting mitochondrial dynamics that affect energy metabolism in ovarian cancer. The energy metabolism relies on the activation of distinct mitochondrial dynamics that are often deregulated in cancer [5,47,111]. Thus, targeting mitochondrial dynamics represents an attractive approach for therapeutic intervention.

First, DRP1 is overexpressed in a variety of human cancers [5,6,23,45]. DRP1 overexpression has been reported to be closely associated with the invasive phenotype of cancer cells in in vivo and in vitro studies [52,56]. An increasing number of studies have demonstrated that high DRP1 expression is associated with invasion, lymph node metastasis, and poor prognosis, whereas low MFN2 expression is correlated with decreased overall survival in patients with breast, gastric, and glioma cancer [47,112]. Therefore, DRP1 and MFN2 may

show a considerably promising strategy for cancer treatment. The development of DRP1 inhibitors, MDIVI-1 and peptide P110, represents an attractive therapeutic opportunity for inhibiting mitochondrial fission [111]. MDIVI-1 inhibits mitochondrial complex I (NADH dehydrogenase) activity. P110 is an inhibitor of DRP1-FIS1 (mitochondrial adaptor fission 1) interaction. MDIVI-1 triggers mitochondrial uncoupling in combination with cisplatin, decreases ATP levels, and disrupts essential metabolic signaling pathways [113]. Moreover, the silencing of DRP1 or the overexpression of MFN1 inhibits cell scattering and lamellipodia formation, reduces cell migration and invasion, enhances apoptosis, and suppresses cell proliferation in various types of cancers such as colon, breast, brain, and lung cancer [111]. Indeed, leflunomide, a potent activator of mitochondrial fusion proteins, inhibited the growth of ovarian, glioma, and prostate cancer cell lines [8,114]. However, whether DRP1 modulates therapeutic efficacy in cisplatin-resistant ovarian cancer cells remains inconclusive. Since the upregulation of DRP1 expression is a common phenomenon in human cancers, researchers believe that DRP1 inhibitors are good candidates for overcoming cisplatin resistance [111,113,115]. However, it has been reported that DRP1 expression is downregulated and MFN2 expression is upregulated in the highly proliferative and cisplatin-resistant ovarian cancer SKOV3 cell line [116]. Therefore, there have been contradictory reports that the downregulation of DRP1 expression or the upregulation of MFN2 expression induces [116–118] or prevents [111,113,115,119] cisplatin resistance in ovarian cancer cells. The selection of DRP1 inhibitors as a treatment strategy may conceivably depend on the cancer phenotype (e.g., DRP1 overexpressing ovarian cancer that have acquired a more invasive and aggressive phenotype). To date, no clinical trials have been conducted with specific inhibitors targeting DRP1 and MFN2. Proteins involved in mitochondrial dynamics such as DRP1, MFN1, MFN2, OPA1, and SNPH would be of great interest in future drug development. Additionally, targeting mitophagy to promote apoptosis appears to be a promising therapeutic strategy for overcoming chemoresistance, improving drug sensitivity, and enhancing ovarian cancer treatment efficacy [120]. Although there is so far a lack of clinical studies on the efficacy of mitochondrial inhibitors, one clinical trial has been reported. A multicenter, open-label, phase Ib study was conducted to assess the safety, pharmacokinetics, and preliminary efficacy of ME-344, a mitochondrial inhibitor, administered in combination with conventional chemotherapy, in patients with previously treated ovarian cancers (NCT02100007) [121]. ME-344, (3R,4S)-3,4-bis(4-hydroxyphenyl)-8-methyl-3,4-dihydro-2H-chromen-7-ol is a novel cytotoxic isoflavone. Among the 32 patients with recurrent ovarian cancer enrolled, 1 patient (3%) achieved a partial response, and 21 patients (66%) had stable disease. ME-344 was a safe and tolerable drug, but the initial expectations were unmet.

Second, cancer cells commonly favor enhanced glycolysis, but OXPHOS can also be upregulated in certain cancers [122,123]. OXPHOS upregulation seems to be limited to some cancer subtypes, including leukemias, lymphomas, pancreatic ductal adenocarcinoma, high OXPHOS subtype melanoma, endometrial cancer, ovarian cancer [123], the chemotherapy-resistant cancer stem cell subpopulation [124], and slow-cycling tumor cells [125]. Therefore, OXPHOS inhibition is considered to be an effective therapeutic approach for cancer cells that favor energy production by mitochondrial OXPHOS over glycolysis [122,123]. OXPHOS inhibitors include metformin (1,1-dimethylbiguanide; antidiabetics), fenofibrate and simvastatin (antilipidemic), atovaquone (antimalaria), macrolides, clindamycin, tetracycline, and chloramphenicol (antibiotic or anti-parasitic agents) [123,124]. These drugs have an inhibitory effect on the expression and activity of ETC complexes [124]. For example, metformin inhibits the mitochondrial respiratory chain complex 1 [123]. Ashton et al. summarized the current understanding of OXPHOS inhibitors and discussed the feasibility of these compounds as clinically relevant anticancer therapeutics [123]. Researchers are beginning to provide evidence that the impairment of OXPHOS can help control ovarian cancer progression [126]. Indeed, ovarian cancers defective in homologous recombination (HRD) typically rely on OXPHOS over glycolysis for energy, suggesting that HRD cells may be more sensitive to OXPHOS inhibitors, such as metformin [127]. Moreover, OXPHOS

inhibitors block the platinum-induced ovarian cancer stem cell enrichment [128]. Additionally, the observation that certain cancer cells may be more sensitive to OXPHOS inhibitors has led to clinical trials of the inhibitors aiming at cancer treatment. The first-in-human study assessed the feasibility of IM156, a novel potent biguanide, in 22 patients with refractory advanced solid tumors, including 3 patients with ovarian cancer [129]. Seven (32%) patients had stable diseases [129]. Furthermore, phase 1 trials evaluating several inhibitors (e.g., metformin, BAY 87-2243, or niclosamide) have been completed or are in progress [124]. Therefore, some OXPHOS inhibitors may have antitumor activity, but the evidence is insufficient (or not yet published) to evaluate effectiveness. Nayak et al. summarized potential agents and critical control points in the OXPHOS pathway and discussed potential barriers that can reduce the efficacy of the OXPHOS inhibitors [92]. Current OXPHOS inhibitors that directly suppress ETC activity damage not only cancer tissues but also normal tissues by causing an increase in harmful ROS [92]. Therefore, these inhibitors can cause severe adverse effects that threaten to limit their efficacy [130]. Additionally, the upregulation of endogenous Nrf-2 may promote the OXPHOS inhibitor resistance of cancer cells via the enhanced expression of ROS-scavenging proteins [92]. Furthermore, cancer cells with dysfunctional mitochondria can promote metabolic reprogramming, inducing shifts toward glycolysis [131]. As mentioned above, OXPHOS inhibitors have been reported to have antitumor activity [124], but various important issues remain unresolved.

Finally, cancer cell lines with oncogenic RAS-RAF-ERK signaling [98] or the activation of MAPK-ERK [99] and PI3K-AKT [105] signaling are characterized by mitochondrial fragmentation [8]. Therefore, anticancer therapies such as MAPK inhibitors and PI3K inhibitors may promote mitochondrial fusion, leading to the inhibition of tumor invasion [98,99,105]. We also searched the US National Institutes of Health Ongoing Trials Register (ClinicalTrials.gov; https://clinicaltrials.gov/, accessed on 20 October 2023) to identify ongoing trials. This search found eight, five, and eight clinical trials for aberrant RAS, MAPK, and PI3K signaling, respectively. Combination trials of serine threonine kinase (STK) inhibitors including MAPK inhibitors and PI3K inhibitors currently in development with chemotherapy and/or targeted therapies may have acceptable toxicity and efficacy in ovarian cancer [132]. The efficacy of emerging STK inhibitors for ovarian cancer has been published, with a response rate of approximately 25% and a clinical benefit rate of approximately 70% [132]. STK inhibitors may be associated with the inhibitory properties of mitochondrial fission and thus contribute significantly to the suppression of tumor invasion. Overall, the signaling pathways that regulate mitochondrial dynamics may lead to promising new therapeutic options in the treatment of ovarian cancer.

4. Discussion

In this review, we summarize our current understanding of the molecular mechanisms controlling mitochondrial fusion/fission dynamics in ovarian cancer and the effects of changes in mitochondrial shape and function on energy metabolism, cell proliferation, invasion, and cell death and discuss future research directions and perspectives for therapeutic strategies. First, mitochondria have the unique ability to regulate their morphology in response to various intracellular and extracellular stimuli [6]. Based on the type, severity, and duration of stress insult, mitochondria undergo fusion or fission to determine both cell homeostasis and death decisions [5]. Cancer cells often encounter nutrient starvation and hypoxia (Figure 2). During nutrient deprivation, mitochondria fuse with adjacent mitochondria through upregulating MFN1, MFN2, and OPA1 expression and create extensive interconnected filamentous networks in order to facilitate the equilibration of mitochondrial components such as mtDNA, proteins, metabolites, and ETC components and maintain the functionality of the OXPHOS system [6,27] (Figure 1). The minimal energy generated by mitochondrial fusion allows cancer cells to survive but is still insufficient for cancer cell invasion. Cancer cell invasion requires the assembly of actin fibers and lamellipodia formation in the peripheral cytoskeleton, an area of high energy demand [27,35]. Increased energy generation over time allows small, fragmented mitochondria to travel from the

perinuclear area to the distant lamellipodia at the front edge of migrating cells [133]. Increased fission has been reported to promote tumorigenesis and invasion [40,47,48,99]. Also, fission allows for an equal distribution of mitochondria during mitosis [133]. Furthermore, a hypoxic environment can shift energy metabolism toward glycolysis over OXPHOS and promote mitochondrial fragmentation via the upregulation of DRP1 expression [47] (Figure 1). Fusion is essential for ensuring an optimal mitochondrial network by allowing for the exchange of contents between fusing mitochondria, while fission maintains the mitochondrial number, movement, cellular location, and proper distribution in the daughter cells [8]. Mitochondria are thought to contribute to maintaining energy homeostasis under nutrient deprivation and hypoxia by regulating their dynamics [5]. Furthermore, ovarian cancer cells regulate mitochondrial dynamics through the activation of oncogenic RAS, MAPK, PI3K, or MYC signaling [98,99,105]. RAS, MAPK, and PI3K may promote mitochondrial fission, and MYC may enhance mitochondrial fusion (Figure 1). From the above, ovarian cancer cells fine-tune mitochondrial dynamics to determine the cell fate in response to extrinsic factors such as environmental changes (nutrient starvation and hypoxia) and intrinsic factors specific to cancer cells (oncogenic signaling). However, the preference for glycolysis versus OXPHOS in ovarian cancer cells may be determined by histopathologic types or the unique genetic profile of energy metabolism.

Second, the therapeutic targeting of mitochondrial dynamics regulators is attracting increasing attention for the treatment of ovarian cancer. DRP1 inhibitors and MFN activators have emerged as therapeutic strategies as mitochondrial fission has been identified in many human cancers [5,6,23,45,52,56], including ovarian cancer [4,26–28,55,92,116,134]. However, in some ovarian cancers, DRP1 inhibitors can unexpectedly exert the opposite effect on the therapeutic activity. DRP1 inhibition promotes [116–118] or suppresses [111,113,115,119] chemoresistance in ovarian cancer cells. It is becoming apparent that DRP1 inhibition or increased OXPHOS dependence via mitochondrial fusion is often associated with resistance to chemotherapy in several cancer cells [5,109]. Therefore, we cannot definitively conclude that the chemosensitivity of ovarian cancer cells is improved by the inhibition of mitochondrial fission [37]. Mitochondrial dynamics determine the decision between cell death and survival in response to various intrinsic (e.g., histotype, phenotype, and molecular features) and extrinsic (e.g., microenvironmental stimuli) factors [118]. Therefore, tumor phenotypic heterogeneity and plasticity, the aberrant expression of mitophagy-related genes, acquired drug resistance, and alterations in the surrounding tumor microenvironment may limit the therapeutic efficacy of DRP1 inhibitors. In addition, OXPHOS inhibitors have the same problems.

In conclusion, our knowledge about pathophysiologic processes, including many molecular events involved in mitochondrial fusion and fission, is still in its infancy. Although mitochondrial dynamics regulators have exhibited therapeutic potential in preclinical studies, the results remain inconsistent. To optimize the efficacy of these regulators, it is necessary to accurately understand the current bioenergetic pathways and mitochondrial function and their quality control for each patient with ovarian cancer.

5. Future Perspectives

Here, we highlight future directions for ovarian cancer research focusing on mitochondrial dynamics. High-throughput technologies such as transcriptomic and proteomic interrogation can provide effective and efficient patient-tailored treatment [135]. Liquid biopsy is a noninvasive technique that identifies the diagnostic information of cancer and reduces the need for tissue biopsy [136]. Analysis for rapidly and precisely characterizing the expression patterns and profile of fission- and fusion-related genes based on mitochondrial dynamics is essential to predict tumor aggressiveness. The identification of alterations in mitochondrial dynamics relies on relevant biomarker genes, including DRP1, MFN1, MFN2, and OPA1. To understand current bioenergetic pathways, it is essential to identify the expression of specific genes (PFKM, PKM, PDK, PDH, and MIEF2 for glycolysis-related genes and CS, IDH2, IDH3A, IDH3B, OGDHL, ND2, ND5, UQCRH, and NRF2 for

OXPHOS-related genes). Bespoke minimal biomarker panels should include these candidate genes. For example, ovarian cancer cells overexpressing mitochondrial fusion genes often rely on OXPHOS for energy supply, and thus MFN or OPA1 inhibitors may be effective. These inhibitors may suppress mitochondrial fusion and induce mitophagy, leading to cell death. On the other hand, the subpopulation of ovarian cancer cells overexpressing mitochondrial fission genes may exhibit an invasive phenotype. Therefore, inhibitors of DRP1 may block mitochondrial transfer, downregulate energy-supplying processes, and reduce invasiveness. The biomarker panel can be used in the discovery of unique and targetable biomarkers, in appropriate drug selection, in monitoring or predicting cancer progression, and in response to therapy. Mitochondrial dynamics regulators may provide a promising therapeutic strategy for ovarian cancer patients. A deeper understanding of what regulates mitochondrial dynamics in each patient and when and how may lead to more rational treatment strategies.

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