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Review

The role of mitochondria in metastasis development

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Abstract

Metastasis is a hallmark of cancer and is responsible for the largest number of cancer-related deaths. However, it remains poorly understood. Recently, evidence has accumulated pointing to the role of mitochondria in the metastatic spread of cancer cells. Mitochondria are dynamic organelles that have significant metabolic activity and are considered signaling centers with biosynthetic, bioenergetic, and signaling functions that control key biological pathways. Also, data were presented that mitochondria can influence all processes associated with oncogenesis, from malignant transformation to metastatic dissemination. The role of mitochondria in cancer progression/metastasis includes alteration of glycolysis, regulation of ROS, and suppression of intrinsic apoptosis. This review will summarize the current knowledge on the contribution of mitochondria to tumor cell invasion and dissemination and the possible mechanisms behind this. Mitochondrial-targeted therapeutic strategies to combat metastatic cancer will also be proposed.

Keywords: Metastasis; Cancer; Mitochondria; Dissemination; Apoptosis

1. Introduction

Metastasis is a general term used to describe the spread of cancer cells from the primary tumor to surrounding tissues and distant organs. Metastasis is the leading cause of death from cancer and accounts for about 90%. This estimate has changed little over more than 50 years [1]. Cancer patients release large numbers of cancer cells into the bloodstream every day; however, studies of melanoma in animal models indicate that less than 0.1% of tumor cells metastasize. To develop metastases, cancer cells must leave their primary site, circulate in the bloodstream, withstand pressure in the blood vessels, acclimatize to a new cellular environment in the secondary site, and avoid an immune response [2].

Metastasis to a particular organ is determined by several factors, such as the nature of the circulation. Efficient and direct blood flow may explain the likelihood of metastasis to certain organs, such as liver metastases, in colon cancer patients who receive direct blood flow from the primary site [3]. Another factor is vascular permeability, which greatly contributes to extravasation at the site of metastasis. At present, understanding of the molecular mechanisms of metastasis remains incomplete. Although cancer can spread to many different organs, there are recognizable patterns for specific primary and metastatic sites. The most common sites of spread are the lymph nodes, bones, brain, lungs, and liver [4].

Metastases have a wide variety of clinical manifestations, mainly depending on the location of the primary tumor. For example, breast cancer metastases may remain latent for several years of follow-up after surgical removal of the primary lesion, whereas metastases in patients with established pancreatic cancer and small-cell lung cancer are often widespread at the time of cancer diagnosis. In addition, glioblastoma is locally progressive and invasive but rarely involves secondary lesions outside the CNS [5].

Existing therapeutic approaches are often ineffective or provide limited clinical benefit. Even in tumors sensitive to radiation or chemotherapy, metastasis is often the main cause of treatment failure. Metastatic tumors are not only difficult to respond to traditional surgery or radiation therapy due to their anatomically diffuse localization in different organs, but in most cases, they are resistant to cytostatics. Although some of the twentieth-century technological advances in cancer cell imaging and identification have greatly improved our understanding of cancer metastasis, the molecular mechanisms underlying cancer metastasis and chemoresistance are largely unknown. Consequently,

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of more than 200 anticancer drugs approved for clinical use, none has a specific and effective inhibitory effect on cancer metastasis [5].

Mitochondria, the most abundant organelles in eukaryotic cells, are known to be the centers of ATP synthesis and have mechanisms for signaling cell death. Therefore, mitochondria and their cellular functions are well associated with various diseases, including cancer/cancer metastases. The first report on the involvement of mitochondria in the development of cancer was made by Otto Warburg in the 1920s. Since then, researchers have found that cancer and metastatic cancer are strongly associated with mitochondrial characteristics such as glucose metabolism and loss of apoptosis. In cancerous and metastatic cancer cells, changes in glucose metabolism and resistance to mitochondrial apoptosis are common features. These physiological changes create the right conditions for cancer progression, thereby increasing resistance to chemotherapy drugs [6]. Thus, mitochondria play an important role in metastatic spread and represent an attractive target for the development of new strategies for the treatment of metastatic cancer.

2. Functions of mitochondria in the vital activity of cells

2.1. Energy exchange

Mitochondria supply the cell with energy primarily by coupling the tricarboxylic acid (TCA) cycle to oxidative phosphorylation (OXPHOS). CTC is a series of chemical reactions catalyzed by enzymes that form a key part of aerobic respiration in cells. The catabolism of nutrients such as lipids, carbohydrates, and proteins leads to the formation of smaller units and metabolites, which fuse at the TCA level as the final integrated metabolic pathway for energy production. Although metabolites can enter the CTC in different ways, most nutrients often converge on the production of acetyl-CoA, an important fuel for the CTC, through different pathways. During glycolysis, glucose is oxidized in the cytosol to pyruvate. Pyruvate is then transported to the mitochondrial matrix, where it is oxidized and reacts with coenzyme A to form acetyl-CoA [7].

TCA enzymes produce electron carriers including nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FADH2). They, in turn, donate electrons to the ETC (electron transport chain), which consists of protein complexes (I-IV) and two soluble factors, cytochrome C and coenzyme Q. Complex I is the first and largest of the complexes, consisting of 45 main subunits. Complexes I and II mediate the transfer of two electrons from electron carriers (NADH/FADH2) respectively to coenzyme Q, a mobile electron carrier. The latter can also gain electrons from the breakdown of a number of nutrients, such as the oxidation of fatty acids, amino acids, and choline. Complex III is an adapter that receives two electrons from the reduced coenzyme Q and transfers one electron to cytochrome C. Complex IV completes the respiratory chain by accepting electrons from cytochrome C to completely reduce oxygen to water [8]. The successive reduction/oxidation reactions (redox) in the ETC cause conformational changes in the respiratory complexes that allow them to pump protons from the matrix into the intermembrane space, creating an electrochemical gradient known as the mitochondrial transmembrane potential. The proton gradient created by complexes I, III and IV creates a proton driving force used by (adenosine triphosphate) ATP synthase (complex V), which phosphorylates (adenosine diphosphate) ADP to form ATP [9].

2.2. Apoptosis

In addition to their fundamental role in energy production, mitochondria play a central role in the regulation of cell death. Apoptosis is a type of programmed cell death that is fundamental to development and physiology. The central place in apoptosis is occupied by a group of cysteine proteases (caspases), which are activated by the proteolytic processing cascade in response to proapoptotic signals [6]. The two main types of apoptosis are the extrinsic and intrinsic pathways.

Mitochondria are direct participants in the internal apoptotic signaling pathway. Signals such as DNA damage, intracellular Ca2+ overload, and oxidative or endoplasmic reticulum (ER) stress act at the mitochondrial level to stimulate the opening of the outer mitochondrial membrane. This leads to the subsequent release of proapoptotic factors usually found in mitochondria [10]. The proapoptotic factor, cytochrome C, an important electron transport chain protein, after being released into the cytosol, can assemble with Apaf-1, pro-caspase-9, and dATP, triggering the caspase cascade by activating caspase-9 [11]. The discovery that cytochrome C can promote apoptosis provided the first evidence for the involvement of mitochondria in cell death. This showed that cells can have a coordinated program of mitochondrial disruption during apoptosis. Later, mutational studies showed that it was oligomerization to Apaf-1, and not the function of electron transport, that was important for its role in cell death, separating the apoptotic and metabolic functions of cytochrome C [6].

Apoptosis-inducing factor (AIF) is also released from mitochondria during apoptosis, but it usually anchors near ETC complex I. Moreover, the second mitochondrial caspase activators (Smac) are proteins released from mitochondria into the cytosol during apoptosis and bind inhibitors of apoptotic proteins (IAPs), resulting in caspase activation [10].

Because the release of mitochondrial proteins that activate effector caspases is key, permeabilization of the outer mitochondrial membrane represents a critical control point during apoptosis and is under the control of members of the Bcl-2 protein family. The Bcl-2 protein family has both proapoptotic (effector (Bax, Bak) and BH3 proteins (Bad, Bim, Bid, Bik, Noxa, Puma, HRK, BMF) and antiapoptotic functions (Bcl-2, Bcl-XL, Mcl-1, A1, Bcl-B, Bcl-w). Pro-apoptotic Bax and Bak are pore-forming proteins that can induce the release of pro-apoptotic proteins from mitochondria into the cytosol to trigger the caspase cascade [12].

2.3. Antiviral regulation

Mitochondria are dynamic organelles whose function is regulated by changes in size, number, and interactions with other organelles such as ER and peroxisomes through mechanisms such as fusion, fission, and autophagy [13]. The stress caused by a viral infection causes damage to the mitochondria. Asymmetric division of mitochondria promotes the separation of damaged mitochondria from healthy ones, which are subsequently removed by mitophagy. The remaining healthy mitochondria fuse back into the tubular mitochondrial network. Thus, mitochondria main-

tain homeostasis and determine the fate of the cell [14].

Mitochondria are also closely related to innate immunity. Mitochondria can indeed activate cytosolic signaling pathways through a variety of mechanisms, including changes in the AMP/ATP ratio, ROS production, and release of CTK metabolites. In addition, the innate immune response may be caused by the loss of mitochondrial DNA from damaged mitochondria. Therefore, mitochondria coordinate their actions to modify immune responses, and any modification of mitochondrial function can alter immune responses. In addition, immune regulatory proteins are located on the outer mitochondrial membrane. Thus, mitochondria can activate an inflammatory response, including mitochondrial antiviral signaling and the inflammasome of NOD-like receptor protein 3 (NLR) (NLRP3) [15].

3. Involvement of mitochondria in metastasis

3.1. Metabolic repurposing

The metastatic cascade is a multi-step process that includes (I) shedding of local tumor cells (anoikis resistance), (II) intravasation (with the potential requirement of an epithelial-mesenchymal transition, EMT), (III) circulatory survival, (IV) extravasation from circulation and (v) colonization of secondary sites [16]. At all these stages, metastatic cells adjust their mitochondrial metabolism to better adapt to the ever-changing environment [17].

During metastasis, tumor cells break away from the niche of the natural matrix. The first problem for cells before metastasis is how to skip anoikis, which is programmed cell death. Unlike normal cells, tumor cells have acquired resistance to anoikis, since many tumor cells already limit OXPHOS to detachment as a result of the Warburg effect (metabolic shift towards glycolysis) [18]. Thus, tumor cells may inherently provide a survival advantage when separated from the primary tumor [19].

Mechanically, pyruvate dehydrogenase kinases (PDKs), critical mitochondrial enzymes in glucose metabolism, can block OXPHOS and promote the Warburg effect [20]. High expression of PDK (for example, PDK1) in tumor cells will help to avoid excess ROS formed as a result of glucose oxidation, which protects tumor cells from ROS-induced anoikis and thus promotes metastasis [21].

In addition, pyruvate kinase M2 (PKM2) is another important mitochondrial enzyme in the glucose metabolic pathway, inhibition of which can convert glucose into the pentose phosphate pathway, creating sufficient reducing potential for ROS detoxification. Meanwhile, the oxidative branch of the pentose phosphate pathway produces large amounts of NADPH, which is an important cofactor for the replenishment of reduced glutathione (GSH), the most important antioxidant [21].

Once tumor cells overcome the risk of anoikis, they activate the EMT process, which helps to enter the blood or lymphatic vessels and causes metabolic rearrangement [16]. Metabolic reprogramming of tumor cells can be regulated by the EMT process with the help of many molecules, including HIF, Snail, p53, and KISS1 [22]. Among them, HIF promotes metastasis and inhibits oxidative metabolism. HIF-1 is an important regulator of glycolytic enzymes such as lactate dehydrogenase (LDH), hexokinase, and the monocarboxylate transporter (MCT), and therefore contributes to the glycolysis switch [23]. In addition, HIF-1 also inhibits oxidative metabolism by enhancing PDK, an inhibitor of pyruvate dehydrogenase (PDH), further preventing pyruvate from entering the CTC [22]. Another EMT inducer, Snail, regulates mitochondrial repression and ROS production by suppressing cytochrome C oxidase (COX) subunits or loss of fructose 1,6 bisphosphatase 1 (FBP1) [24]. Snail can also inhibit platelet phosphofructokinase (PFKP), which is involved in the process of glycolysis, which will lead to a greater shift in glucose flow towards the pentose phosphate pathway and an increase in NADPH production [25].

In order to survive in the blood or lymph vessels, the mitochondrial circuitry of cancer cells changes to adapt to the changing environment. Circulating breast cancer cells (CCCs) have been shown to primarily rely on OXPHOS and increase ATP production compared to primary tumor cells (PCCs). Further studies show that the transcription coactivator PGC-1α was a key factor in enhancing OXPHOS, oxygen consumption rate, and mitochondrial biogenesis [26].

Regulatory proteins p53 and KISS1, which suppress the Warburg effect and promote oxidative metabolism, can play a role in the reverse change in metabolism, which leads to the blocking of metastasis [27]. P53 promotes OXPHOS expression by enhancing the synthesis of cytochrome C oxidase, which is a member of the COX-2 assembly and is involved in oxidative metabolism as well as in the electron transport chain. KISS1 switches metabolism from aerobic glycolysis to OXPHOS by stabilizing PGC1α, a key positive regulator of metabolic gene transcription in the TCA and oxidative metabolism [28]. Thus, when metastatic cells spread through the bloodstream, p53 and KISS1, which traditionally act as antitumor regulators, can promote metastasis at this stage by shifting metabolism in a direction favorable for the survival of tumor cells in the bloodstream. However, so far this judgment remains only an assumption.

When CCCs reach and proliferate in secondary tissues, their mitochondrial metabolism is restored like primary tumors. There are similar levels of gene expression in OXPHOS and mitochondrial biogenesis between metastatic cancer cells (MCC) and CCC, suggesting that expression of these genes is restored when CCC colonizes their metastatic sites [26]. The general scheme of metabolic shift during metastasis is shown in Figure 1.

3.2. Dissemination of metastases

Mitochondria have been shown to promote metastatic dissemination through various mechanisms. Being extremely dynamic organelles, mitochondria continuously change their morphology, undergoing division (fragmentation) and fusion (elongation). These processes are regulated by highly conserved guanosine triphosphatases (GTPases) [29]. The division is controlled by cytosolic dynamin-related protein 1 (Drp1), which is recruited into the mitochondria by adapter proteins, including mitochondrial fission factor (Mff) and mitochondrial dynamics proteins Mid49/51, where it forms an oligomeric ring, structures and mediates mitochondrial division. Fusion is mediated by two outer mitochondrial membrane (OMM) GTPases, i.e., mitofusins 1 and 2 (Mfn1, 2), while inner mitochondrial membrane (IMM) fusion is mediated by the cristae-forming protein Opa1 [30]. In cancer cells, mitochondrial division/fusion is unbalanced due to mitochondrial dysfunction [31]. Several studies have shown that

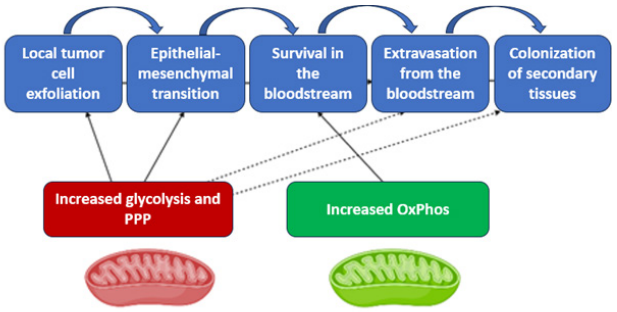

Fig. 1. Changes in the metabolism of tumor cells during metastasis.

increased division and/or decreased fusion are associated with malignant transformation in various types of cancer [29]. In addition, activation of mitochondrial division and increased expression of Drp1 have been shown to promote cancer metastasis [32]. For example, Drp1 overexpression was found in metastatic breast cancer cells compared to non-metastatic ones, while Drp1 silencing or Mfn1 overexpression resulted in mitochondrial elongation and significant suppression of the metastatic properties of breast cancer cells. Similarly, increased mitochondrial division has been observed in metastatic hepatocellular carcinoma (HCC) cells [33]. Recent evidence also suggests a link between mitochondrial fission and hypoxia-induced migration. Inhibition of Drp1 by Mdivi-1 leads to a decrease in hypoxia-induced migration [34]. Taken together, these studies provide evidence that mitochondrial division is necessary for cancer cell migration and to maintain the metastatic potential of cancer cells.

It has also been shown that a moderate increase in ROS levels supports the proliferation and migration of cancer cells and activates various signaling pathways associated with cell survival, promoting tumor growth and malignant transformation [35]. It has been demonstrated that the level of ROS activates the PI3K pathway. The primary known target of ROS in the PI3K pathway is the phosphatase and tensin homologue (PTEN). ROS promotes inactivation of the tumor suppressor PTEN by oxidizing cysteine residues in the active site, causing the formation of a disulfide bond that prevents PTEN inactivation of the PI3K pathway. Since ROS can inactivate protein tyrosine phosphatases by oxidizing cysteine residues, ROS can have many yet undiscovered effects on various mitogen-activated pathways that are usually inhibited by phosphatases [36]. ROS can stimulate mitogen-activated protein kinase (MAPK) and extracellular signal-regulated kinase (ERK) phosphorylation, cyclin D1 expression, and JUN N-terminal kinase (JNK) activation, all of which are associated with tumor cell survival and growth [37]. ROS can activate various processes associated with metastatic spread and invasion. They may be involved in cytoskeletal remodeling. The cytoskeleton of a cell is a dynamic structure consisting of microtubules and filaments. Cytoskeletal rearrangements are important for controlling cell migration and invasion through the formation of various types of cell protrusions, including filopodia, lamellipodia, and invadopodia [38]. Another mechanism by which ROS can promote tumor cell invasion is to stimulate the proteolytic degradation of extracellular matrix (ECM) components such as glycosaminoglycan (GAG), which promotes metastatic spread [38].

3.3. Apoptosis inhibition

In normal cells, apoptosis is the physiological process of removing damaged and unwanted cells. During internal mitochondrial apoptosis, numerous pro- and anti-apoptotic signals exist in the mitochondria. Under pathophysiological conditions such as DNA damage, oxidative stress, oncogene activation, or growth factor deprivation, OMM permeability increases. An increase in OMM permeability leads to the release of cytochrome C and other apoptogenic proteins that activate the caspase cascade, accompanied by apoptotic cell death [39].

Proteins of the Bcl-2 family play a crucial role in the regulation of the permeability of the outer mitochondrial membrane. Pro-apoptotic proteins such as Bax and Bid enhance the mitochondrial outer shell. membrane permeability. On the other hand, the anti-apoptotic proteins Bcl-2 and Bcl-xL inhibit the function of pro-apoptotic proteins by binding to pro-apoptotic proteins. A study was conducted that showed that the expression of Mcl-1, an anti-apoptotic protein of the Bcl-2 family, is increased during metastasis [40]. In addition, non-functional mutations or impaired expression of Bax and Bak have also been observed in cancer and metastatic cancer [41]. These observations suggest that overexpression of antiapoptotic proteins is associated with cancer metastasis and chemoresistance.

In addition to the dysregulation of intrinsic mitochondrial apoptosis in metastatic cancer cells, other indirect mechanisms may be related to disruption of the p53 signaling pathway. Mutations in the p53 gene have been found in more than half of human tumors at the metastatic stage. In addition to the p53-associated effects of downstream gene transcription, the p53 mutation also affects Bak activation on the outer mitochondrial membrane, leading to disruption of the apoptosis mechanism [41].

4. Targeting Mitochondria to Treat Metastases

4.1. Mitochondrial Metabolism Modulators

Metastatic tumors have been shown to reprogram their metabolism to successfully metastasize [42]. Accordingly, significant efforts have been made to target the metabolism of cancer cells in various tumors to prevent the progression of metastasis. For example, the antidiabetic drug metformin has been shown to have antitumor properties in various types of cancer [43]. Metformin is a complex I inhibitor that reduces cancer metabolism by suppressing mitochondrial glycerophosphate dehydrogenase (mGPDH) and inhibiting OXPHOS, resulting in reduced metastasis in a mouse model of thyroid cancer [44]. At low concentrations, metformin inhibits the invasion and metastasis of breast cancer by suppressing the production of ROS, which suggests the use of metformin as a chemopreventive agent to block the invasiveness of cancer cells [43]. Although the exact mechanisms of action of metformin are still under discussion, a number of clinical studies have confirmed its antitumor properties [45].

4.2. Bcl-2 family member regulators

Since the expression of Bcl-2 family proteins has been found in metastases of various tumors, another possible approach to cancer therapy may focus on targeting members of the Bcl-2 family. BH3 mimetics are promising therapeutic agents that mimic endogenous antagonists of members of the Bcl-2 family, thereby acting on some of them to reverse their anti-apoptotic functions. Initially,

BH3 mimetics showed encouraging results in hematological malignancies, including lymphoma, lymphocytic leukemia, acute myeloid leukemia, small lymphocytic lymphoma, and mantle cell lymphoma [46]. Thus, first-generation BH3 mimetics such as ABT-737 and its orally available derivative navitoclax (ABT-263), which are Bcl-2 and Bcl-W inhibitors, have shown clinical efficacy [47]. Clinical studies of ABT-199 in chronic lymphocytic leukemia and non-Hodgkin's lymphoma showed impressive antitumor efficacy with a higher response rate than navitoclax and without thrombocytopenia [48]. The BH3 mimetic ch282-5 (2-aminoethanesulfonic acid, sodium gossypolone) induced the death of colon cancer cells in vitro and in vivo. Treatment with Ch282-5 activated a mitochondria-dependent apoptotic pathway accompanied by impaired mitophagy and activation of the mTOR pathway. In addition, Ch282-5 provided suppression of migration, invasion, and metastasis of colon cancer cells into the liver [49].

4.3. Regulators of mitochondrial K + / H +balance

Another interesting approach to metastatic cancer is the regulation of mitochondrial K + /H + balance. Salinomycin is an antibiotic from the group of polyester ionophores widely used in agriculture [50]. It has recently been shown to have antitumor properties in various types of cancer [51]. Salinomycin can target chemoresistant tumor cells by inhibiting Wnt/β-catenin and Sonic Hedgehog signaling pathways [50]. In addition, it inhibits the migration of colorectal, breast, lung, and colon cancer cell lines, as well as the invasion of nasopharyngeal and bladder cancer cells in vitro [50]. Accordingly, in vivo studies have shown that salinomycin can reduce the formation of metastases in a mouse breast tumor model, a rat bladder tumor model, and a mouse tumor model when administered intravenously [52]. It is important to note that salinomycin is able to suppress the late stages of autophagy, promoting the formation of ROS and mitochondrial dysfunction [53]. This may explain the mechanism by which salinomycin targets mitochondrial K + /H + balance and prevents migration, invasion, and metastasis. The action mechanisms of the considered therapeutic agents are summarized in Table 1.

5. Discussion

Mitochondria are intracellular organelles that produce most of the energy in cells, providing ATP synthesis by oxidative phosphorylation (OXPHOS). In addition to energy production, mitochondria perform many functions, including the generation of reactive oxygen species (ROS), production of metabolites, and modulation of cell death pathways. In addition, mitochondria are involved in the regulation of signaling pathways associated with cell proliferation, differentiation, and many others [54]. Mitochondria's multiple functions allow cells to adapt to environmental changes, including the availability of nutrients and oxygen, making them ideal stress sensors. These functions also determine the crucial role of mitochondria in the development and progression of cancer. Indeed, mitochondria can drive tumor progression by adapting to changing metabolic needs, contributing to chemoresistance and regulating cell death pathways [55]. In addition, mitochondria have been shown to be associated with the metastatic spread of cancer cells. It is important to note that mitochondrial turnover, i.e. fission/fusion, is deeply involved in the regulation of various mitochondrial functions and the metastatic cascade. However, the mechanisms linking mitochondrial dynamics with the development of metastases remain poorly understood. In addition, mitochondrial flexibility, which depends on various factors, i.e. tumor type, microenvironment, site of metastasis formation, etc., must be taken into account to successfully fight cancer. A better understanding of this metabolic plasticity will allow the designing of specific therapeutic approaches to better target metastatic cancer cells.

In this review, several mitochondrial-targeting strategies have been proposed to combat metastatic cancer, namely modulators of mitochondrial metabolism, regulators of Bcl-2 family members, and regulators of mitochondrial K+/H+ metabolism. Also, in addition, an impact on the regulation of mitochondrial ROS, which, as mentioned earlier, is involved in the regulation of tumor growth and metastization, can be considered as a promising approach for cancer treatment [56]. However, in some studies, the treatment with antioxidants was shown to be ineffective, which could be due to their non-specificity. They can also regulate many different processes associated with tumor growth and metastasis [57]. On the other hand, it has been shown that inhibition of ROS by antioxidants specifically targeting mitochondrial oxidative stress can stop metastatic spread [56]. Thus, ROS targeting is more complex than previously thought and requires further detailed study.

6. Conclusion

In summary, mitochondria are very important and complex organelles that influence oncogenesis and metastatic spread through various mechanisms, including redox

Table 1. Therapeutic agents targeting mitochondrial function for the treatment of metastases.

Therapeutic strategy	Drug compound example	Action mechanisms
Mitochondrial metabolism modulators	Metformin	Inhibition of complex I and GPDH leading to OXPHOS inhibition in tumor cells.
Bcl-2 family member regulators	Ch282-5	Activation of the mitochondria-dependent apoptotic pathway and mTOR pathway in tumor cells.
Regulators of mitochondrial K + / H +balance	Salinomycin	Inhibition of Wnt/β-catenin and Sonic Hedgehog signaling pathways in tumor cells. Inhibition of autophagy and induction of mitochondrial dysfunction in tumor cells.

signaling, mitochondrial biogenesis, regulation of Bcl-2 family members, and metabolic reprogramming. Ultimately, we now have an understanding that mitochondria play a more important role in metastasis than previously thought. In fact, the scale of the mitochondrial contribution to metastasis is increasing almost daily. Direct causal relationships are still being developed, but accumulating evidence continues to support a multiple role for mitochondria in cancer development, especially in metastasis. As with any newly discovered relationship, the data raises new and interesting questions. A better understanding of the mechanisms and interactions with mitochondria may provide new therapeutic approaches to target metastatic diseases. Currently, several promising drugs targeting the mitochondria are under development.

Conflict of Interests
The author has no conflicts with any step of the article preparation.

Consent for publications
The author read and approved the final manuscript for publication.

Ethics approval and consent to participate
No human or animals were used in the present research.

Informed Consent
The authors declare not used any patients in this research.

Availability of data and material
The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions
All authors had equal role in study design, work, statistical analysis and manuscript writing.

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