Molecular Medicine

REVIEW

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Mitochondria: a new intervention target for tumor invasion and metastasis

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Abstract

Mitochondria, responsible for cellular energy synthesis and signal transduction, intricately regulate diverse metabolic processes, mediating fundamental biological phenomena such as cell growth, aging, and apoptosis. Tumor invasion and metastasis, key characteristics of malignancies, significantly impact patient prognosis. Tumor cells frequently exhibit metabolic abnormalities in mitochondria, including alterations in metabolic dynamics and changes in the expression of relevant metabolic genes and associated signal transduction pathways. Recent investigations unveil further insights into mitochondrial metabolic abnormalities, revealing their active involvement in tumor cell proliferation, resistance to chemotherapy, and a crucial role in tumor cell invasion and metastasis. This paper comprehensively outlines the latest research advancements in mitochondrial structure and metabolic function. Emphasis is placed on summarizing the role of mitochondrial metabolic abnormalities in tumor invasion and metastasis, including alterations in the mitochondrial genome (mutations), activation of mitochondrial-to-nuclear signaling, and dynamics within the mitochondria, all intricately linked to the processes of tumor invasion and metastasis. In conclusion, the paper discusses unresolved scientific questions in this field, aiming to provide a theoretical foundation and novel perspectives for developing innovative strategies targeting tumor invasion and metastasis based on mitochondrial biology.

Keywords Mitochondria, Energy metabolism, Tumor, Invasion and metastasis, Signal transduction

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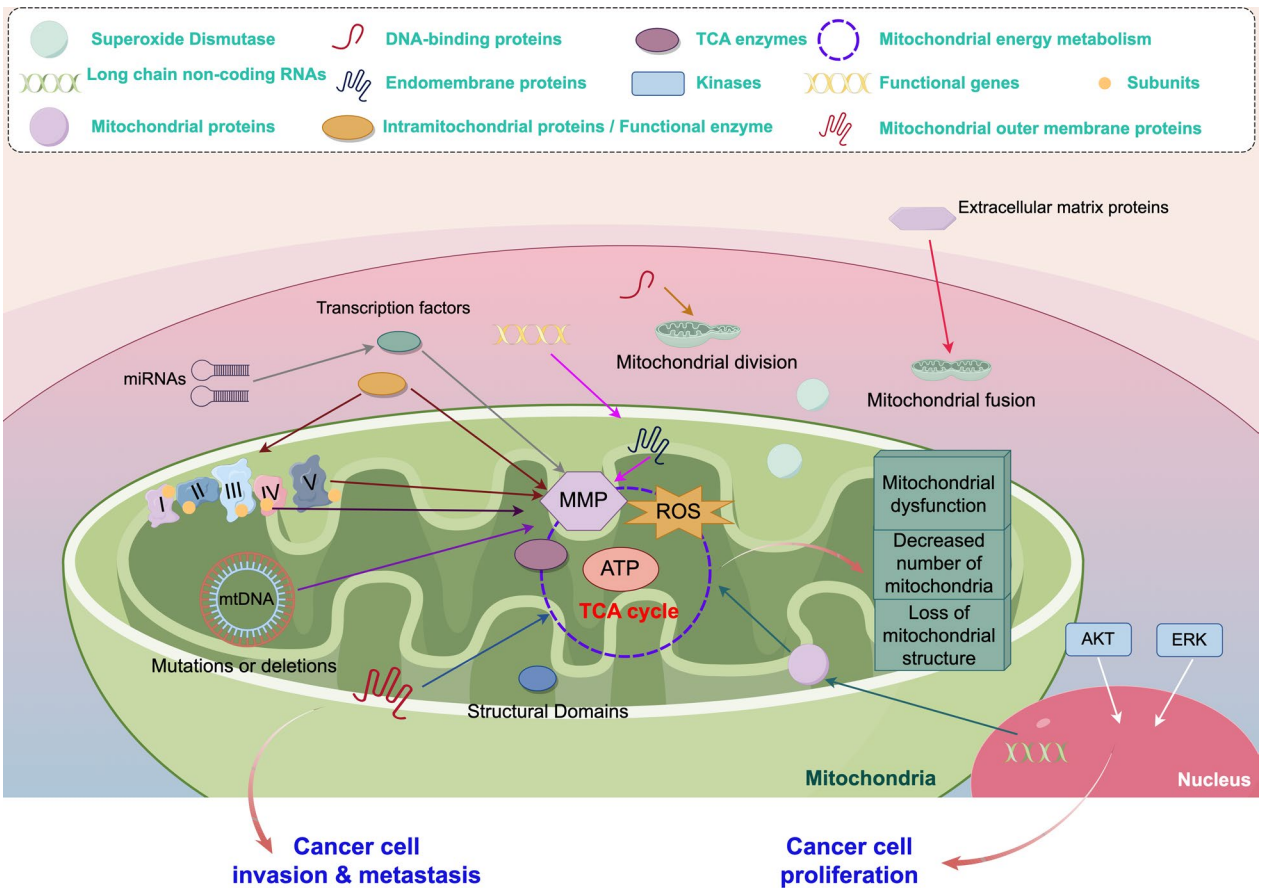
Graphical Abstract



Mitochondrial structure and function

The mitochondrion is a cellular organelle characterized with a structure comprising two membranes and two aqueous compartments: the outer membrane (OM), intermembrane space (IMS), inner membrane (IM), and matrix. The inner membrane contains the oxidative phosphorylation system, including respiratory complexes I to IV and the F1F0-ATP synthase responsible for ATP production. These hydrophobic membrane proteins form the core components of the mitochondrial inner membrane oxidative phosphorylation complexes,often assembling into complexes and supercomplexes, such as respiratory complexes and protein translocases (Pfanner et al. 2019; Morgenstern et al. 2021; Sung et al. 2020; Rath et al. 2021; Morgenstern et al. 2017; Wittig and Malacarne 2021). Mitochondria serve as the cellular powerhouse, performing various fundamental metabolic processes and regulating cell apoptosis. However, our understanding of the major components of mitochondrial genes and proteins, as well as the biological processes governing the stability and dynamic assembly of mitochondrial proteins, remains limited (Pfanner et al. 2019; Sung et al. 2020; Wittig and Malacarne 2021).

Human mitochondrial DNA (mtDNA) contains 37 genes, which encode 13 proteins for respiratory complexes I, III, IV, and V (Table 1). Additionally, mtDNA encodes 2 rRNAs and 22 tRNAs necessary for mitochondrial protein synthesis. MtDNA is a circular double-stranded DNA molecule approximately 16.5 kb in length in humans, which consists of a heavy chain (H-chain) rich in G and a light chain (L-chain) rich in C. Notably, the H-chain encodes the majority of mtDNA (Anderson et al. 1981). Furthermore, mtDNA possesses a unique regulatory region known as the displacement loop (D-loop), which includes a short single-stranded DNA molecule, the triple-stranded region 7S DNA (Nicholls and Minczuk 2014). Studies indicate that mutations or deletions in mtDNA can compromise energy metabolism, leading

Table 1 The major functions of mitochondrial proteins and their documented associations with specific cancer types

Respiratory complexes	Proteins	Function	Associated illnesses	References
NADH dehydrogenase (complex I)	MT-ND1	Contributes to NADH dehydrogenase activity. Enables protein binding, enables NADH dehydrogenase (ubiquinone) activity	Leber hereditary optic neuropathy (LHON), CRC	Lim et al. 2016; Majander et al. 1991; Xu et al. 2021)
	MT-ND2	Enables protein binding, enables NADH dehydrogenase (ubiquinone) activity, oxidoreductase activity, protein kinase binding, and ionotropic glutamate receptor binding	Leigh syndrome (LS), CRC, GC, BC	Ugalde et al. 2007; Cavalcante et al. 2019; Jayasekera et al. 2023; Li et al. 2015)
	MT-ND3	Enables protein binding and NADH dehydrogenase (ubiquinone) activity	LS, BC	Miller et al. 2014; Martínez-Ramírez et al. 2018)
	MT-ND4	Essential for the catalytic activity and assembly of complex I	LHON, BC,GC, Melanoma, LC	Cavalcante et al. 2019; Vries et al. 1996; Hofhaus and Attardi 1993; Bourges et al. 2004; Bushel et al. 2022; Mahmood et al. 2024; Dasgupta et al. 2012)
	MT-ND4l	Enables NADH dehydrogenase (ubiquinone) activity and oxidoreductase activity, acting on NAD(P)H	LHON	Guo et al. 2017; Brown et al. 1995)
	MT-ND5	Essential for the catalytic activity and assembly of complex I	LHON, LS, Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS)	Bourges et al. 2004; Liolitsa et al. 2003)
	MT-ND6	Enables NADH dehydrogenase (ubiquinone) activity	LHON, CRC, LC	Vries et al. 1996; Ugalde et al. 2003; Wallace et al. 2016; Yuan et al. 2015)
Coenzyme Q-cytochrome c reductase/cytochrome b (complex III)	MT-CYB	Enables ubiquinol-cytochrome-c reductase activity. Electron transfer activity. Oxidoreductase activity. Enables protein-containing complex binding and metal ion binding	LHON, mitochondrial myopathies,CRC, Prostate cancer,Liver cancer	Wallace et al. 2016; Andreu et al. 1999; Abril et al. 2008; Zhuang et al. 2020)
Cytochrome c oxidase (complex IV)	COX1	Contributes to cytochrome-c oxidase activity. Enables protein binding, heme binding and metal ion binding	LHON, Mitochondrial complex IV deficiency,	Varlamov et al. 2002; Lucioli et al. 2006)
	COX2	Enables cytochrome-c oxidase activity, copper ion binding, protein binding and ion binding	Mitochondrial complex IV deficiency	Power et al. 1989; Rahman et al. 1999)
	COX3	Contributes_to cytochrome-c oxidase activity. Enables protein binding and electron transfer activity	LHON, Mitochondrial complex IV deficiency, Pediatric Malignancies	Johns and Neufeld 1993; Keightley et al. 1996)

Table 1 (continued)

Respiratory complexes	Proteins	Function	Associated illnesses	References
ATP synthase	MT-ATP6	Enables protein binding and transmembrane transporter activity. Contributes_to proton-transporting ATP synthase activity,	LHON, LS, Neuropathy, ataxia, and retinitis pigmentosa (NARP), Mitochondrial infantile bilateral striatal necrosis (MIBSN), Mitochondrial complex V deficiency, mitochondrial 1 (MC5DM1), Myopathy, lactic acidosis, and sideroblastic anemia 3 (MLASA3), Ataxia and polyneuropathy, adult-onset (APAO), Cardiomyopathy, infantile hypertrophic (CMHI), CRC, BC, Prostate cancer	Martínez-Ramírez et al. 2018; Wallace et al. 2016; Abril et al. 2008; Aggeler et al. 2002; Tebbenkamp et al. 2018; Holt et al. 1990; Castagna et al. 2007; Vries et al. 1993; Thyagarajan et al. 1995; Rantamäki et al. 2005; Burrage et al. 2014; Craig et al. 2007; Ware et al. 2009; Triska et al. 2019)
	ATP8	Enables protein binding and transmembrane transporter activity. Contributes_to proton-transporting ATP synthase activity	Mitochondrial complex V deficiency, mitochondrial 2 (MC5DM2), Cardiomyopathy, infantile hypertrophic (CMHI), GC, BC,	Aggeler et al. 2002; Ware et al. 2009; Mottaghi-Dastjerdi et al. 2023; Grzybowska-Szatkowska et al. 2014; Thapa et al. 2016)

to mitochondrial dysfunction, alterations in intracellular signal transduction, and impact on cellular biological functions. In extreme cases, such alterations can result in "mitochondrial diseases" (Guaragnella et al. 2014; Guerra et al. 2017; Alexeyev et al. 2004; Zeviani and Antozzi 1992). (Fig. 1.)

Mitochondria play a pivotal role in cellular energetics, metabolism, and signal transduction primarily through the generation of adenosine triphosphate (ATP) and intermediate metabolites (Pfanner et al. 2019; Morgenstern et al. 2021; Sung et al. 2020; Nunnari and Suomalainen 2012).Within mitochondria, metabolites produced by the tricarboxylic acid cycle (TCA cycle) and reducing equivalents enter the electron transport chain (ETC). The ETC utilizes oxygen as the terminal electron acceptor to catalyze the oxidation of reducing equivalents. Electron transfer couples with proton translocation across the inner mitochondrial membrane, generating an electrochemical gradient (mitochondrial membrane potential). This gradient, in turn, results in the production of ATP to supply energy to the cellular biological processes. Furthermore, mitochondria serve as a major source of reactive oxygen species (ROS) production within the cell. Consequently, mtDNA is more susceptible to fluctuations in ROS levels, leading to mitochondrial dysfunction and involvement in the processes of diseases such as cancer.

Of particular interest, recent studies demonstrate that mitochondria can undergo intra-cellular migration, maintaining their reticular structure stability through rapid fusion and fission processes. This phenomenon is referred to as mitochondrial dynamics. Mechanistic investigations reveal that a large family of GTPases primarily regulates mitochondrial dynamics. This regulation enables mitochondria to recruit to subcellular compartments requiring additional energy, thereby playing a crucial role in mitochondrial quality control and communication with the cytoplasm and the cell nucleus (Chen and Chan 2009).

Over the past decade, the understanding of the relationship between mitochondria and tumor invasion and metastasis has deepened (Guaragnella et al. 2014; Guerra et al. 2017; Guantes et al. 2015; DeBalsi et al. 2017). Notably, changes in mitochondrial dynamics, such as increased fission and reduced fusion, are commonly observed in clinical tumors and are closely associated with tumor metastasis (Trotta and Chipuk 2017). Furthermore, the instability of mtDNA is closely linked to the occurrence and metastasis of various cancers (Wallace 2012; Choudhury and Singh 2017; Bussard and Siracusa 2017). Recent large-scale analyses of various types of cancer within The Cancer Genome Atlas (TCGA) dataset reveal significant depletion of mtDNA content in tissues of several tumors, including breast cancer (BRCA) and esophageal cancer (ESCA). This depletion leads to reduced expression of mitochondrial respiratory chain genes, showing a negative correlation with the expression of immune response and cell cycle genes (Reznik et al. 2016). These findings indicate that mitochondrial gene expression, protein structures, and their interactions, as well as mitochondrial metabolic abnormalities and dynamic changes, play crucial roles in tumor development, particularly in the invasion and metastasis of tumor cells. This suggests that mitochondria might represent potential novel targets for clinical intervention in cancer. (Table 2).

Mitochondria and cancer invasion and metastasis

Mitochondria and lung cancer

Lung cancer (LC), one of the most common malignancies, continues to exhibit a rising global incidence and mortality (Sung et al. 2021). Studies reveal that mitochondria play a crucial in the onset and progression of lung cancer. Specifically, abnormalities in the expression of mitochondrial functional genes can trigger a series of complex effects, actively participating in the invasion and metastasis of lung cancer.

Abnormal expression of functional genes can impact mitochondrial function through various mechanisms, including alterations in respiratory chain electron transfer, metabolic remodeling, and mitochondrial dynamics. For instance, overexpression of the NDUFA4 subunit of mitochondrial respiratory chain complex IV alters electron transfer in the mitochondrial respiratory chain, and promotes the growth and migration of human lung cancer cells. This effect is closely linked to the abnormal activation of the AKT and ERK pathways, key drivers of cell proliferation and survival. Real-time PCR assays confirm a significant increase in NDUFA4 expression in lung cancer tissues compared to normal controls, along with corresponding increases in the protein levels of NDUFA4, Akt, p-Akt, Erk, and p-Erk (Lei et al. 2017). The S100A4 protein, also known as metastasin-1 or fibroblast-specific protein-1 (FSP1), is another critical player. It is a well-established marker for epithelial-mesenchymal transition (EMT) and is implicated in tumor metastasis (Grigorian et al. 1996). Liu et al. discover that the mitochondrial complex I subunit NADH dehydrogenase (ubiquinone) Fe-S protein 2 (NDUFS2) is regulated in a S100A4-dependent manner. Cells lacking S100A4 or NDUFS2 undergo a metabolic shift toward glycolysis through upregulation of hexokinase. The S100A4/NDUFS2 axis reshapes mitochondrial metabolism and promotes the invasion and metastasis of lung cancer. Quantitative analysis of oxygen consumption rate (OCR) data reveals that S100A4 knockdown significantly decreases

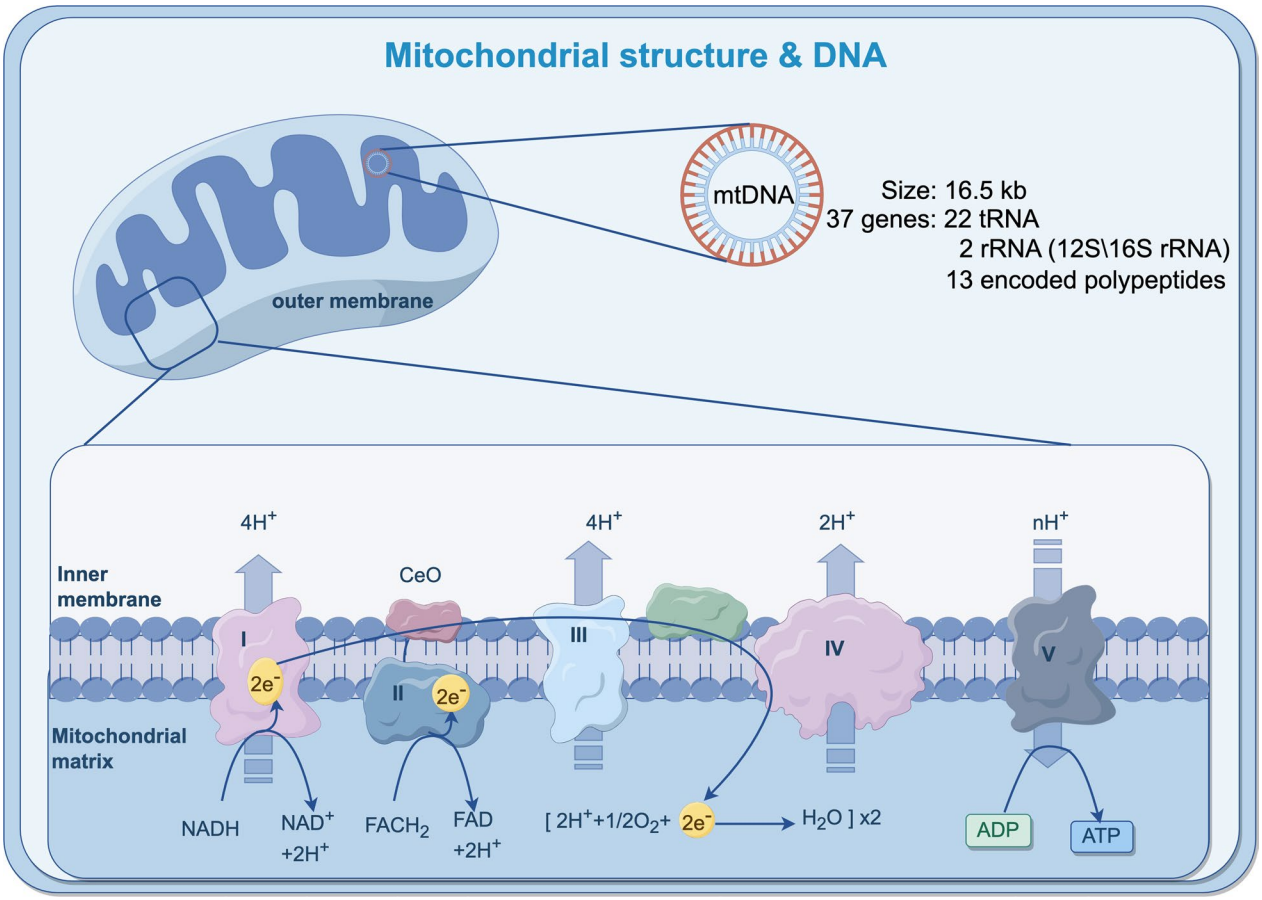


Fig. 1 Mitochondrial structure and DNA. Size and content of mitochondrial DNA; ATP production by the mitochondrial respiratory chain. (By Figdraw.)

Table 2 Mitochondria-related alterations and related cancers

Mitochondria-related alterations	Tumors	References
Signal transduction	Gastric cancer, liver cancer, lung cancer, cervical cancer, breast cancer, thyroid cancer, colorectal cancer, pancreatic cancer	Frezza and Gottlieb 2009; Liu 2020; Zhao et al. 2013; Chen et al. 2022; Yu et al. 2019; Wan et al. 2021; Lei et al. 2017; Zou et al. 2019)
Gene mutation	Prostate cancer, lung cancer, liver cancer, gastric cancer, colorectal cancer, breast cancer	Ippolito et al. 2019; Grigorian et al. 1996; Chen et al. 2022; Papadaki et al. 2023; Gibellini et al. 2018; Li et al. 2021)
Mitochondrial dynamics	Liver cancer, gastric cancer, breast cancer, lung cancer, colorectal cancer	Lei et al. 2017; Gibellini et al. 2018; Li et al. 2021; Ga et al. 2023; Wu et al. 2023)
Protein & nucleotide expression	Lung cancer, liver cancer, breast cancer, gastric cancer, colorectal cancer, esophagus cancer	Li et al. 2021; Bai and Jiao 2020; Sasaki et al. 2021; Wang et al. 2021; Tang et al. 2018; Lai et al. 2016)

basal respiration, maximal respiration, and spare capacity in lung cancer cells, indicating a predominant effect on mitochondrial respiration (Liu et al. 2019). Zinc finger E-box-binding homeobox 1 (ZEB1), a transcription factor, induce EMT and facilitate metastasis. Bai et al. have revealed that the upregulation of miR-199a-3p leads to the downregulation of ZEB1, subsequently causing mitochondrial dysfunction. This dysfunction includes biological changes such as a decrease in mitochondrial membrane potential, reduced SOD activity, and elevated levels of MDA and LDH, all contributing to the growth and migration of tumor cells (Bai and Jiao 2020).

In addition, mitochondrial abnormalities in ketone metabolism are significant features of cancer cells (Corbet et al. 2018; Li et al. 2017; Lu et al. 2018). Mitochondrial pyruvate carrier 1 (MPC1), located on the inner

mitochondrial membrane, is a crucial protein responsible for transporting and oxidizing pyruvate (Herzig et al. 2012; Bricker et al. 2012; McCommis et al. 2016). Zou et al. have revealed that low MPC1 expression in lung adenocarcinoma (LAC) is associated with abnormal mitochondrial function and altered signal transduction. MPC1's role in enhancing pyruvate entry into mitochondrial oxidation and reducing lactate production in tumor cells suggests its impact on tumor cell invasion and metastasis. Further studies examining MPC1 expression in LAC tissues compared to versus adjacent non-tumor tissues corroborate these findings. Additionally, the human PINK1 gene (PTEN-induced kinase 1, Park6), a significant gene in Parkinson's disease, accumulates in the outer mitochondrial membrane and serves as a crucial marker of mitochondrial damage. It triggers autophagy to eliminate depolarized mitochondria. Studies shown that PINK1 knockdown leads to mitochondrial dysfunction, increased ROS generation, and decreased mitochondrial membrane potential, which culminates in suppressed autophagy and affects tumor cell proliferation and migration. Immunohistochemical staining reveals higher PINK1 expression in tumor tissues, which is strongly linked to the tumor-node-metastasis classification and is associated with longer overall survival in non-small cell lung cancer (NSCLC) patients (Zou et al. 2019; Poewe et al. 2017; Schulz et al. 2015; Lu et al. 2020).

It is noteworthy that certain functional genes can also interact with mitochondrial transcriptional regulatory factors. Signal transducer and activator of transcription 3 (STAT3), as a transcription factor, regulates a series of genes related to cancer cell survival, proliferation, angiogenesis, invasion, and metastasis (Song et al. 2011). Studies indicate that the interaction between MPC1 and mitochondrial STAT3 (mito-STAT3) disrupts the distribution of STAT3, reduces the activity of cytoplasmic STAT3 (cyto-STAT3), and promotes the malignant progression of lung cancer, including invasion and metastasis. This suggests the importance of the MPC1/STAT3 axis in the progression of lung cancer and provides a new perspective for molecular targeting of the STAT3 pathway (Zou et al. 2019).

Furthermore, abnormalities in the expression of functional genes can also affect mitochondrial dynamics, contributing to the invasion and metastasis of tumor cells. For example, High Mobility Group Box 1 (HMGB1), belonging to the HMGB superfamily, is a DNA-binding protein that regulates various cellular processes such as inflammation, cell differentiation, and tumor cell migration (Tripathi et al. 2019). Recent studies highlight the crucial role of HMGB1 in tumorigenesis, epithelial-mesenchymal transition, and the prognosis of lung cancer (He et al. 2017). Mechanistically, HMGB1 can induce mitochondrial dynamics dependent on highly phosphorylated dynamin-related protein 1 (DRP1) through the RAGE-extracellular signal-regulated kinase (ERK) signaling pathway (Huang et al. 2018). Liu et al. further found that HMGB1 overexpression increases mitochondrial fission, promoting mitochondrial transport to the leading edge of filopodia through actin filaments and microtubules. This, in turn, enhances cell migration and motility, along with increased expression and phosphorylation of DRP1 in the nucleus and cytoplasm, thereby facilitating lung cancer migration (Liu et al. 2021). Additionally, certain critical structural domains of mitochondrial functional proteins also play important roles. For instance, in invasive lung adenocarcinoma, the expression of Ovarian Cancer Immunoreactive Antigen Domain 2 (OCIAD2) is significantly higher than in situ lung adenocarcinoma, and its abnormal expression correlates with poorer patient prognosis. OCIAD2 is mainly located on the mitochondrial membrane of lung adenocarcinoma cells. Inhibition of OCIAD2 induces a decrease in mitochondrial membrane potential, release of cytochrome c, loss of mitochondrial structure, and a reduction in mitochondrial quantity. Moreover, OCIAD2 inhibition leads to downregulation of cell growth, proliferation, migration, and invasion. Therefore, OCIAD2 may be an effective therapeutic target for lung adenocarcinoma (Hong et al. 2021).

In summary, abnormal expression of mitochondrial genes, including both functional and non-functional genes, can lead to alterations in redox reactions, metabolic reprogramming, and dynamics. These changes contribute to the promotion of invasion and metastasis in lung cancer, suggesting that targeting mitochondrial genes may be a crucial direction for developing novel therapeutic approaches in clinical lung cancer treatment.

Mitochondria and colorectal cancer

Colorectal cancer (CRC) is one of the most common malignant diseases worldwide and has a high potential for metastasis (Siegel et al. 2020). Recent research suggests that abnormalities in mitochondrial gene expression and function, through changes in energy metabolism, regulate the occurrence of colorectal cancer. For instance, NDUFA4, encoded by the *NDUFA4* gene within mitochondrial respiratory chain complex IV, exhibits significant dysregulation in human CRC and can modulate tumor cell growth and migration, indicating its potential as a novel target for CRC intervention. Similarly, we found high expression of NDUFA4 in human CRC tumor tissues. NDUFA4 overexpression promotes the in vitro growth of human CRC tumor cells, accompanied by alterations in mitochondrial energy metabolism, while downregulation of NDUFA4 expression produces

the opposite effect (Liu 2020). Further studies by Liu Shiming et al. revealed that NDUFA4 overexpression can promote the occurrence of epithelial-mesenchymal transition (EMT) in human CRC cells (Liu et al. xxxx). Moreover, Jean Bastin et al. discovered that mitochondrial complex I (CI) is downregulated in the stromal subtype of colorectal cancer (CMS4) cells, which is associated with an increase in mitochondrial reactive oxygen species (mtROS). This suggests that modulating mtROS levels can influence the migration of human CRC cells (Bastin et al. 2023).

It is noteworthy that the changes in the expression of certain functional enzymes can also lead to alterations in mitochondrial function, thereby influencing the invasion and metastasis of colorectal cancer (CRC). For instance, as mentioned earlier, the generation of mitochondrial reactive oxygen species (mtROS) not only occurs through changes in complex I (CI) activity but is also maintained at optimal levels through the inactivation/acetylation of Superoxide Dismutase 2 (SOD2), a major mitochondrial antioxidant enzyme, affecting tumor cell migration (Bastin et al. 2023). Additionally, studies suggest that the Translocase of Outer Mitochondrial Membrane 20 (TOMM20) is overexpressed in various cancers. Sang-Hee Park et al. found that TOMM20, as a receptor for targeting mitochondrial proteins, plays a crucial role in the invasion and metastasis of CRC. Overexpression of TOMM20 increases the proliferation, migration, and invasion of colorectal cancer cells. Mechanistically, TOMM20 expression directly impacts mitochondrial function, including ATP production and membrane potential maintenance, contributing to tumor cell activities such as the regulation of the S-phase cell cycle and apoptosis (Park et al. 2019). Furthermore, Mitochondrial Lon protease (LonP1) is a multifunctional enzyme that regulates mitochondrial function, induces a shift towards glycolysis, and promoting the EMT, thereby conferring migratory and invasive capabilities to tumor cells (Gibellini et al. 2018). Gibellini et al. found that silencing LonP1 leads to severe mitochondrial damage and apoptosis in colon cancer cells. Importantly, LonP1 is virtually absent in normal mucosa, gradually increasing from aberrant crypt foci to adenomas, with the highest expression level in colon cancer. These findings suggest LonP1 is a potential new intervention target for human CRC tumors.

Furthermore, research indicates that non-coding RNAs and transcription factors also play a role in regulating mitochondrial control over the invasion and metastasis of colorectal cancer (CRC) tumor cells. For instance, Wang et al. discovered that the long non-coding RNA FEZF1-AS1 (FEZF1-AS1) is upregulated in colorectal cancer. FEZF1-AS1 regulates the expression of mitochondrial protein phosphoenolpyruvate carboxykinase (PCK2), which is crucial in regulating mitochondrial energy metabolism. This suggests that FEZF1-AS1 deficiency may facilitate the binding of ubiquitin enzymes to PCK2 and promote its degradation. FEZF1-AS1 upregulates PCK2 protein level by inhibiting proteasome-dependent degradation. Knocking out FEZF1-AS1 significantly reduces PCK2 protein level, leading to a decrease in mitochondrial energy metabolism and inhibiting the proliferation and migration of colorectal cancer cells. FEZF1-AS1 is found to increase the protein, but not the mRNA level of PCK2, indicating a post-translational regulatory mechanism (Wang et al. 2021). However, the study does not reveal whether FEZF1-AS1 interacts with PCK2 directly or indirectly, nor does it fully elucidate the mechanisms through which FEZF1-AS1 regulates PCK2 protein levels. Further exploration is needed to uncover the underlying interactions and pathways incolved. Moreover, Lin et al. find that metastatic colorectal cancer cells (SW620) express higher levels of mitochondrial transcription factor A (TFAM) and mtDNA compared to primary SW480 cells. Additionally, the oxygen consumption rate (OCR) and respiratory control ratio (RCR) are higher in SW620 cells. Therefore, it can be concluded that a higher mtDNA copy number and enhanced mitochondrial function may provide an invasion advantage for CRC (Lin et al. 2018).

In summary, aberrant expression of mitochondrial genes can regulate the invasion and metastasis of colorectal cancer, suggesting that targeting mitochondrial-related genes may be a crucial direction for future developments in clinical strategies for colorectal cancer treatment.

Mitochondria and gastric cancer

Recent studies indicate a close association between the occurrence and invasion-metastasis of gastric cancer (GC) and mitochondrial abnormalities. Sustained communication between the mitochondria and the cell nucleus ensures cellular balance and adaptation to mitochondrial stress.

Compared to normal cells, tumor cells preferentially undergo aerobic glycolysis to metabolize glucose, with several genes encoding enzymes involved in this process prone to alternative splicing (AS). For instance, Vasiliki Papadaki and colleagues discovered that the IQ Motif Containing GTPase Activating Protein 1 (IQGAP1), a scaffold protein, significantly influences mitochondrial respiration by regulating AS in various gene subgroups in GC cells. IQGAP1 promotes tumor development by regulating AS of specific pre-mRNAs related to the cell cycle. Their research shows that IQGAP1 affects AS of components in the electron transport chain (ETC), enhancing oxidative metabolism in GC cells, thus facilitating tumor

proliferation and invasiveness (Papadaki et al. 2023). To investigate IQGAP1's role in mitochondrial homeostasis, they examined NUGC4 and NUGC4-IQGAP1KO cells for mitochondrial DNA content, mitochondrial mass, and the expression of transcription factors involved in mitochondrial biogenesis (TFAM, PGC1α, and NRF1). They discovered that IQGAP1 depletion results in a 30% increase in cells with fragmented mitochondrial networks, compared to those with tubular or hyperfused networks. This fragmentation is marked by a decrease in the Aspect Ratio (AR) and Form Factor (FF), indicating reduced mitochondrial elongation and network complexity, along with a lower number of identified mitochondria per cell. Notably, reintroducing cMyc-IQGAP1 in IQGAP1KO cells largely reversed this phenotype. Moreover, IQGAP1 depletion led to a decrease in mitochondrial reactive oxygen species (mtROS) production, which was also restored upon cMyc-IQGAP1 expression. These findings indicate a deficiency in mitochondrial function in the absence of IQGAP1. Additionally, cancer cells generally exhibit higher levels of reactive oxygen species (ROS) compared to normal cells, suggesting that cancer cells are more sensitive to oxidative stress, and mitochondrial reactive oxygen species can accelerate the invasion of GC cells (Chen et al. 2016; Tamura et al. 2014).

In GC cells, the expression of certain nucleic acids also plays a regulatory role. For example, Wu and colleagues found that the overexpression of miR-431-5p significantly inhibits cell proliferation and induces apoptosis, leading to impaired mitochondrial function. This impairment is characterized by a reduction in mitochondrial quantity, a decrease in mitochondrial membrane potential, an increase in mitochondrial permeability transition pore (mPTP) opening, elevated ROS production, and decreased ATP level (Wu et al. 2023). Moreover, increasing evidence suggests that long non-coding RNAs (lncRNAs) can participate in tumorigenesis by regulating invasion, proliferation, and migration (Fonseca Cabral et al. 2020; Lu et al. 2021; Tan et al. 2020; Yang et al. 2022).

Furthermore, recent studies suggest that changes in the expression of certain mitochondrial proteins may impact the development of GC. For instance, NDUFA4 exhibits significantly increased expression in human GC and regulates tumor cell growth and metastasis. NDUFA4 plays a crucial role in GC development by controlling pathways such as mitochondrial oxidative phosphorylation and glycolysis, and regulating other molecules. This highlights its potential value in the prognosis and treatment of GC. To investigate NDUFA4's functions in GC cells, researchers observe its high expression in AGS and HGC27 cells and low expression in MKN45 cells. They found that.the knockdown of NDUFA4 significantly reduced the viability of AGS and HGC27 cells, whereas its overexpression enhanced cell viability in MKN45 cells. Similarly, colony formation was significantly inhibited by shNDUFA4 but promoted by overexpressed NDUFA4 (Frezza and Gottlieb 2009; Gogvadze et al. 2008; Li et al. Dec 2018; Zhang et al. 2019; Xu et al. 2022; Cheng et al. 2012). Additionally, small molecules can influence mitochondrial metabolism to regulate tumor invasion and metastasis. For example, Yuto Sasaki and colleagues discovered that asporin (ASPN) is a leucine-rich small proteoglycan mainly expressed by cancer-associated fibroblasts (CAFs), playing a crucial role in tumor progression. ASPN expression enhances GC cell resistance to oxidative stress by reducing mitochondrial ROS. ASPN induces the expression of the transcription factor HIF1α and upregulates lactate dehydrogenase A (LDHA), indicating that ASPN reprograms GC cells to undergo anaerobic glycolysis, suppressing ROS generation in the mitochondria. Overexpression of ASPN in two GC cell lines leads to increased migration and invasion capabilities (Sasaki et al. 2021).

Similarly, the changes in the expression of certain functional enzymes can regulate the invasion and metastasis of tumor cells. For example, Mi Y and colleagues confirmed a significant increase in the expression of mitochondrial creatine kinase (uMtCK) in GC tissues, which is significantly associated with poorer prognosis, especially in advanced-stage patients. Functionally, uMtCK promotes glycolysis in GC cells and enhances their migration, invasion, and liver metastasis in both in vitro and in vivo settings. Mechanistically, uMtCK enhances the occurrence and invasion-metastasis of GC through the JNK-MAPK/JUN signaling pathway, thereby reinforcing HK2-dependent glycolysis Mi et al. 2023.

In summary, the expression levels of mitochondrial functional genes are closely associated with the metastasis of GC, making them potential targets for intervention. A comprehensive understanding of these molecular mechanisms could contribute to the development of novel anti-cancer strategies targeting mitochondria.

Mitochondria and breast cancer

Breast cancer (BC) is the most common cancer among women globally, posing a significant threat to women's health. Investigating its biological mechanisms is crucial for improving patient prognosis.

The metabolic imbalance of mitochondria is closely associated with the growth and metastasis of breast cancer. In epithelial breast cancer cells, the oxidative phosphorylation (OxPhos) level is upregulated, enabling these cells to generate high levels of ATP, thereby promoting proliferation and invasive metastasis (Nayak et al.

2018). This metabolic imbalance is often correlated with changes in the expression of related genes. For example, Wang et al. identified an upregulation of citrate synthase (ACLY) in breast cancer. ACLY is the first crucial enzyme in the production of acetyl-CoA, and its overexpression is associated with pathological grading, tumor size, and lymph node metastasis. Inhibiting ACLY can effectively suppress tumor growth (Wang et al. 2017). The expression of mitochondrial ribosomal protein L52 (MRPL52) is elevated in human breast cancer and significantly correlated with invasive clinical pathological features and higher metastatic risk. Li et al. found that MRPL52 overexpression in breast cancer is induced by hypoxia-inducible factor 1 in response to hypoxic exposure, demonstrating its role in inhibiting apoptosis and promoting migration and invasion of hypoxic breast cancer cells (Li et al. 2021).

Triple-negative breast cancer (TNBC) is an aggressive form of breast cancer. The tumor microenvironment, rich in pro-inflammatory cytokines like TNF-α, regulates cancer cells' bioenergetic capacity, immune evasion, and survival. NLRX1, a mitochondrial NOD-like receptor protein, regulates mitochondrial function during apoptosis and tissue damage. Depletion of NLRX1 impairs lysosomal function, leading to altered turnover of damaged mitochondria through mitophagy in the presence of TNF-α. The loss of NLRX1 reduces OxPhos-dependent cell proliferation and migration under TNF-α conditions, supporting the tumorigenic potential of invasive breast cancer cells by maintaining energy homeostasis and preserving organelle functio (Singh et al. 2015; Singh et al. 2019).

Dynein Light Chain Tctex-Type 1 (DYNLT1) is upregulated in breast tumors and is upregulated in breast tumors and is a crucial component of the motor complex that transports cellular cargo along microtubules. DYNLT1 co-localizes with Voltage-Dependent Anion Channel 1 (VDAC1) on the mitochondria, regulating essential metabolic and energy functions, thereby promoting proliferation, migration, invasion, and mitochondrial metabolism of breast cancer cells in vitro, and facilitating the development of breast tumors *in vivo* (Huang et al. 2023). Epidermal Growth Factor-Like 9 (EGFL9) is significantly upregulated in basal-like breast cancer cells and is associated with the metastatic progression of breast tumor samples. EGFL9 is both necessary and sufficient to enhance cancer cell migration, invasion, and distant metastasis (Meng et al. 2019). NDUFA4 is also overexpressed in breast cancer, leading to enhanced oxidative phosphorylation and increased ATP consumption (Li et al. 2020).

Changes in gene expression can lead to alterations in signaling pathways and mitochondrial dynamics. For example, Li et al. found that mitochondrial ribosomal protein L52 (MRPL52) enhances epithelial-mesenchymal transition, migration, and invasion of hypoxic breast cancer cells by activating the ROS-Notch1-Snail signaling pathway (Li et al. 2021). Another study revealed a significant upregulation of mitochondrial fission protein Dynamin-related protein 1 (DRP1) in human invasive breast cancer and lymph node metastasis. Compared to non-metastatic breast cancer cells, metastatic cells exhibited more fragmented mitochondria, higher levels of total and active DRP1, and lower expression of mitochondrial fusion protein 1 (Mfn1). Silencing DRP1 or overexpressing Mfn1 led to mitochondrial elongation or clustering, respectively, significantly inhibiting the metastatic ability of breast cancer cells (Zhao et al. 2013). Human MARCH 5, a mitochondria-localized E3 ubiquitin ligase, promotes the growth and metastasis of breast cancer cells in vitro and in vivo.,mainly mediated through increased mitochondrial fission and subsequent ROS production (Tang et al. 2019).

In summary, the studies mentioned above have revealed the crucial role of mitochondria in the growth and metastasis of breast cancer cells. This provides a significant foundation for further developing clinical treatment strategies targeting specific genes within the mitochondria for breast cancer.

Mitochondria and liver cancer

Recent studies have found that many mitochondria-related proteins can influence the growth and metastasis of liver cancer cells, participating in the development of hepatocellular carcinoma (HCC). For instance, mitochondrial transcription elongation factor (TEFM) is a novel nuclear-encoded factor involved in mitochondrial genome transcription. Fei et al. found that both protein and mRNA expression levels of TEFM were significantly upregulated in HCC tissues compared to non-cancerous liver tissues (Zy et al. 2020). Additionally, TEFM mRNA expression levels were significantly associated with vascular invasion. Further analysis revealed that high expression levels of TEFM were associated with poor prognosis in HCC patients. Wan et al. also found that TEFM partially exerted its tumor-promoting effects by increasing ROS production and subsequently activating the ERK signaling pathway. Increased TEFM expression in HCC tissues was mainly attributed to the downregulation of miR-194-5p. TEFM upregulation was associated with poor prognosis in HCC patients (Wan et al. 2021). Recently, phosphodiesterase 2A (PDE2A) has been found to be involved in the regulation of mitochondrial function andclosely associated with the progression of various types of tumors. For example, Chen et al. found that overexpression of

PDE2A could inhibit proliferation, colony formation, migration, and invasion of two HCC cell lines, while inhibition of PDE2A had the opposite effect. The mechanism of action of PDE2A on HCC cells is attributed to changes in mitochondrial morphology and ATP levels (Chen et al. 2022).

Similarly, changes in the expression of some mitochondrial functional proteins can also affect tumor development. For instance, Zhang et al. found high expression of the mitochondrial translocator protein (TSPO) in HCC, which is associated with poor prognosis. Mitochondrial TSPO promotes the growth, migration, and invasion of HCC cells by inhibiting ferroptosis (A type of regulated cell death characterized by excessive ROS-mediated lipid peroxidation, which eventually leads to plasma membrane damage and cell death (Stockwell 2022).)and anti-tumor immune responses (Zhang et al. 2023). Notably, the expression of NDUFA4 complex molecule NDUFA4L2 is abnormal in HCC and plays a role in regulating tumor cell growth and metastasis (Lai et al. 2016; Tello et al. 2011).

Certainly, dysregulation of mitochondrial dynamics is closely associated with tumorigenesis. For example, Tian et al. found that the extracellular matrix-related protein CCBE1 promotes mitochondrial fusion in HCC. They observed a significant downregulation of CCBE1 expression in tumors compared to non-tumor tissues, which was attributed to the high methylation of the CCBE1 promoter in HCC (Ga et al. 2023). Furthermore, overexpression of CCBE1 or treatment with recombinant CCBE1 protein significantly inhibited the proliferation, migration, and invasion of HCC cells both in vitro and in vivo. Huang et al. discovered that increasing mitochondrial division by forced expression of DRP1 or knockdown of MFN1 promotes the survival and invasion of HCC cells in vitro and *in vivo* (Huang et al. 2016). Moreover, Glia Maturation Factor-β (GMFB) is known as a growth and differentiation factor for glial cells and neurons. In the study by Wan Sun et al., GMFB expression was significantly upregulated in HCC patients and positively correlated with tumor node metastasis (TNM) stage and histological grade of HCC. Deletion of GMFB in cancer cells significantly inhibited proliferation, migration, and invasion of cancer cells, downregulated the expression levels of some matrix metalloproteinases (MMPs), and increased mtDNA copy number and loss of mitochondrial transmembrane potential (Sun et al. 2021).

In general, abnormal expression of mitochondrial-related genes may lead to changes in oxidative-reduction reactions, metabolic reprogramming, and mitochondrial dynamics, thereby promoting the invasion and metastasis of liver cancer. This suggests that targeting mitochondrial genes or proteins, and further elucidating their mechanisms, could provide a new perspective for mitochondria-targeted therapy in liver cancer.

Mitochondria and other cancers (esophageal, thyroid, pancreatic, prostate, cervical)

Prostate Cancer (PCa) is the most common malignant tumor in the male reproductive system. In addition to mtDNA mutations/deletions found in cancer cells, mutations in nuclear-encoded mitochondrial enzymes are also associated with tumorigenesis (Thompson 2009). These findings suggest that tumorigenesis occurring in mitochondria involves not only defects in mitochondrial energy production but also changes in mitochondrial biogenesis and metabolism. Regarding PCa, the invasive phenotype of cancer cells is related to metabolic shifts toward aerobic glycolysis, citrate oxidation, and loss of zinc accumulation (Shiraishi et al. 2015). CAFs are a major cellular stromal component in many solid tumors. CAFs establish a metabolic symbiosis with PCa cells, enhancing cancer invasiveness through lactate shuttle mechanisms (Ippolito et al. 2019). Importantly, metabolites are not only exchanged from CAFs to cancer cells in soluble form but also via exosome shuttle. In this scenario, amino acids and TCA cycle intermediates can upregulate glycolysis while downregulating OxPhos, contributing to tumorigenesis and invasion (Zhao et al. 2016). Furthermore, mutations in mitochondrial-encoded respiratory complex I are significantly associated with PCa. Mutations in respiratory complex I can lead to decreased expression levels of the corresponding complex in prostate cancer, increased expression of MFN1, MFN2, and PINK1, and decreased expression of MT-TFA, thereby promoting PCa cell cycle progression and invasiveness. Philley et al. suggest that mutations in complex I are associated with increased mitochondrial fusion (Philley et al. 2016).

Pancreatic cancer is the third leading cause of cancer-related deaths. Increasing evidence suggests that mitochondrial metabolites may act as second messengers, inducing epigenetic changes in the nucleus (Frezza 2017; Shaughnessy et al. 2014). Acetyl-CoA is one of the most extensively studied signaling molecules. Recent work has reported that overexpression of ACLY leads to elevated levels of acetyl-CoA in the cytoplasmic/nuclear, which promotes the invasiveness of pancreatic cancer (Carrer et al. 2019). Depletion of DRP1 in pancreatic cancer cells has been shown to reduce oxygen consumption rates and ATP production levels, leading to decreased tumor growth and metastasis *in vivo* (Yu et al. 2019). Studies have shown that pancreatic tumors exhibit metabolic heterogeneity and contain cancer stem cell subpopulations with high metastatic and tumorigenic potential, which rely on OxPhos (Viale

et al. 2015). Recently, studies have found that NDUFA4 is upregulated in pancreatic cancer tissues, and its high expression levels are negatively correlated with patient survival rates. Zhang Y further discovered that downregulation of NDUFA4 induces G1 phase arrest, reducing proliferation in human pancreatic cancer cells. This downregulation of NDUFA4 significantly inhibits tumor growth and invasion *in vivo* (Zhang et al. 2022).

Cervical cancer is the fourth most common cancer in women. When diagnosed early and treated effectively, it is one of the most treatable cancers. Xin et al. found that ACLY is upregulated in cervical cancer, which can enhance the proliferation and invasion of cervical cancer cells (Xin et al. 2016). Recent research has identified Double C-2 like domain beta (DOC2B) as a tumor suppressor, exhibiting anti-proliferative, anti-migratory, anti-invasive, and anti-metastatic functions in cervical cancer. Divya Adiga et al. confirmed the tumor growth-regulating function of the DOC2B-mitochondrial axis in cervical cancer. They found that DOC2B expression induces changes in mitochondrial morphology, accompanied by a decrease in mitochondrial DNA copy number, mitochondrial mass, and mitochondrial membrane potential. In the presence of DOC2B, intracellular and mitochondrial levels of Ca_2^+, intracellular $O.^-_2$, and ATP are significantly increased, while glucose uptake, lactate production, and mitochondrial complex IV activity are reduced. AMPK signaling is also activated. These changes ultimately promote the invasion and metastasis of cervical cancer (Adiga et al. 2023).

Thyroid cancer is a malignant tumor originating from the follicular epithelial cells of the thyroid gland or parafollicular cells and is the most common malignant tumor in the head and neck region. Although evidence suggests a correlation between mutations in mtDNA and nDNA, Notably, approximately 20% of patients exhibit mitochondrial gene mutations without concurrent nuclear gene mutations, indicating that some mtDNA mutations may be involved in carcinogenesis (Yuan et al. 2020). Correlations between mitochondrial and nuclear mutation burdens have been observed in various types of cancers, including an increase in thyroid cancer. Furthermore, deleterious mitochondrial mutations are associated with the overexpression of genes involved in cancer signaling pathways, such as the TNFα pathway, OxPhos, and protein secretion pathways (Yuan et al. 2020). Papillary thyroid carcinoma (PTC) is the most common malignant tumor of the thyroid gland. Bojie Chen et al. detected cyclin D1 and mitochondrial complex IV in PTC patients with tumor lymph node metastasis (LNM) samples. They found that downregulation of mitochondrial function negatively affects tumor progression and LNM through the PI3K/Akt/FoxO1/Cyclin D1 pathway (Chen et al. 2022).

Esophageal cancer originates from the squamous epithelium and columnar epithelium of the esophagus and is a common malignant tumor of the digestive tract. In China, esophageal squamous cell carcinoma (ESCC) is the most common type. Recent research has found that the expression level of NDUFA4 in ESCC tissues is significantly lower than that in adjacent non-cancerous tissues. The expression of NDUFA4 is closely associated with the clinical stage, depth of infiltration, histological grade, and lymph node metastasis of ESCC patients. Studies have shown that NDUFA4 regulates tumor cell growth and metastasis in ESCC through the interactions with other molecules. For example, Tang et al. found that NDUFA4 is a direct target of miR-147b. The expression of NDUFA4 in ESCC tissues is negatively correlated with the expression of miR-147b. Inhibitors of miR-147b significantly increase the expression of NDUFA4 in ESCC EC1 and EC9706 cells, inhibiting the proliferation and invasion ability of ESCC, and altering the distribution of the cell cycle (Tang et al. 2018).

In conclusion, the regulation of mitochondrial gene expression plays a crucial role in the development and progression of cancer, highlighting its potential value in prognosis assessment and treatment of cancer. (Fig. 2.)

Advances in research and clinical practice of mitochondrial drug therapy

Over the past decade, significant progress has been made in the study of mitochondrial-targeted drugs. In cancer cells, alterations in mitochondrial signaling and metabolic pathways are frequently observed, contributing to cancer development and progression. These changes render cancer cells more susceptible to mitochondrial-targeted therapies. Loss of functional mitochondria can lead to stagnation of cancer progression or cell death.

Currently, research on drugs targeting mitochondria mainly focuses on several key aspects. Among them, the biguanide class of antidiabetic drugs (such as metformin and phenformin) is one of the most extensively studied. Although their mechanisms are not fully understood, it is confirmed that these drugs inhibit electron transport chain complex I (NADH dehydrogenase) (Ashton et al. 2018; Chae and Kim 2018; García Rubiño et al. 2019; Andrzejewski et al. 2018; Luengo et al. 2014). These drugs may affect the survival capability of cancer cells by inducing mitochondrial respiratory dysfunction, reducing ATP synthesis, and mediating ROS-induced apoptosis. A recent study on pancreatic cancer reported that metformin is toxic to undifferentiated tumor cells with high mitochondrial content. This toxicity is attributed to the bioenergetic stress caused by the inability of cells to

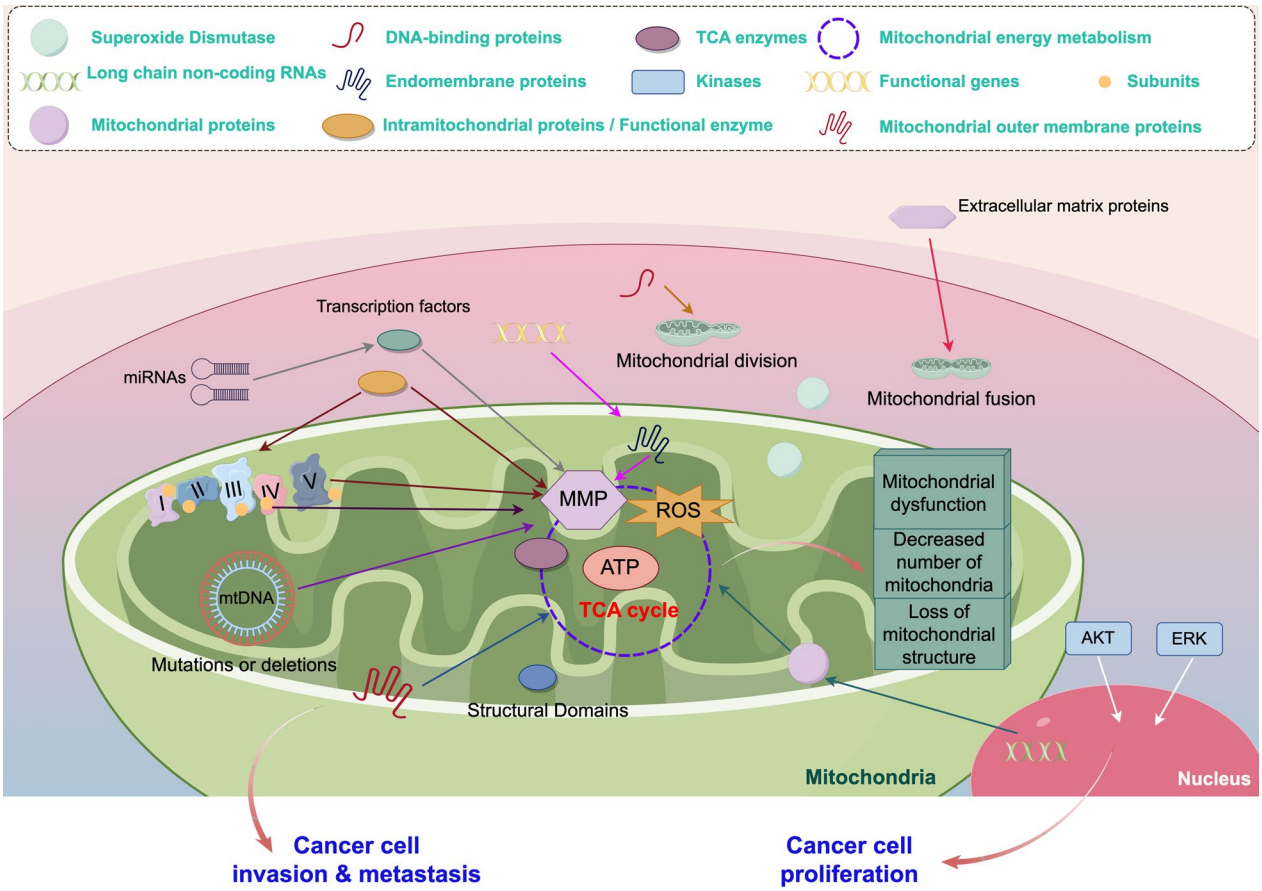


Fig. 2 Mitochondrial cancer-related mechanisms. Mitochondrial energy metabolism and mitochondrial dynamics and alterations in mitochondrial structure, number, and function ultimately lead to tumor invasion and metastasis. (By Figdraw.)

activate glycolysis after OxPhos inhibition (Deschênes-Simard et al. 2019). Additionally, metformin can inhibit the self-renewal ability and tumorigenicity of osteosarcoma stem cells by directly targeting mitochondria, resulting in reduced ATP synthesis and ROS-mediated apoptosis (Zhao et al. 2019). In other types of cancer, metformin can increase sensitivity to chemotherapy drugs, reduce the migratory ability of drug-resistant cells, decrease the number of cancer stem cells, and inhibit tumor proliferation and angiogenesis (Bishnu et al. 2019; Markowska et al. 2018). However, some types of cancer cells may develop resistance, necessitating combination therapy or the use of more potent inhibitors. Studies have shown that treatment of breast cancer cells with low concentrations of metformin may induce metabolic reprogramming in cancer stem cells by increasing glycolysis to acquire drug resistance. Nevertheless, such metabolic changes also offer opportunities for other therapeutic approaches (Banerjee et al. 2019). Such as conjugating the lipophilic cation triphenylphosphonium (TPP+) with metformin can selectively target mitochondria in animal models of pancreatic cancer, thereby enhancing therapeutic efficacy (Kalyanaraman et al. 2018).

In addition to the biguanide class of antidiabetic drugs, other compounds targeting mitochondrial complexes include menadione and Pirvinium pamoate (Diehn et al. 2009; Lamb et al. 2015). These drugs induce the generation of ROS and help prevent cancer cells from developing resistance. Furthermore, resveratrol, through its actions on complexes I and IV, reduces growth rates and invasion potential in various cancer cell lines (Lopes Costa et al. 2014; Wang and Moraes 2011). Additionally, this molecule induce mitochondrial dysfunction, cytochrome c release, and caspase activation in pancreatic cancer (Xu et al. 2015).

Furthermore, drugs like oligomycin and resveratrol have demonstrated inhibitory effects on cancer cell growth and invasion. Oligomycin is a well-known inhibitor of ATP synthase. Although its toxicity precludes its use as a single therapy for cancer treatment, it shows efficacy when used in combination with drugs like 2-DG or nicotinamide against cancer stem cells in glioblastoma,

ovarian cancer, and breast cancer cells (Yo et al. 2012; Wang et al. 2013). Salinomycin, on the other hand, is a K^+ ionophore and uncoupling agent that inhibits OxPhos. It reduces the percentage of tumor-initiating cells (TICs) both in vitro and in vivo across various types of cancer (Naujokat and Steinhart 2012; Jangamreddy et al. 2015; Jiang et al. 2018). Moreover, salinomycin overcome drug resistance and sensitizes tumor cells to radiotherapy (Hermawan et al. 2016; Ko et al. 2016; Qi et al. 2022; Dewangan et al. 2017; Magrath et al. 2020).

In clinical trials, mitochondrial drugs are typically used in combination with traditional cancer treatment such as chemotherapy and radiotherapy. Additionally, the combined use of uncoupling agents and other mitochondrial-targeted drugs is being evaluated. These studies aim to enhance tumor cell sensitivity to treatment and reduce treatment therpy (Zhang et al. 2014; Jara et al. 2014; Zhang et al. 2015). Lapatinib, a dual inhibitor of epidermal growth factor receptor (EGFR) and ErbB2, with antiproliferative effects, has been used to treat metastatic breast cancer patients with ErbB2 overexpression (Burris 2004).

Overall, the advancements in mitochondrial drug therapy research provide new directions and hope for cancer treatment. However, further research is still needed to understand the mechanisms of mitochondria in cancer development to develop more effective treatment drugs and strategies.

Summary and prospects

Metabolic changes play a crucial role in the growth and metastasis of tumor cells, Meanwhile, mitochondria serve as the primary organelles for energy metabolism. Studies have demonstrated the intimate association between mitochondrial functional gene reprogramming, alterations in respiratory chain transmission, and dynamic anomalies with tumor occurrence. This research underscores the significance of mitochondrial metabolism in tumor biology, highlighting the complexity of tumor metabolic remodeling and emphasizing mitochondria as a critical new target for future clinical intervention in tumors.

However, novel mitochondrial-based strategies for tumor intervention still face several key issues that urgently need clarification:

First, further studies on the precise mechanisms of mitochondrial mtDNA gene expression are urgently needed. The regulation of mitochondrial gene expression differs from that of nuclear genes. Abnormal mitochondrial gene expression can lead to changes in redox reactions, metabolic reprogramming, and dynamics. It remains to be claried which mitochondrial genes directly impact ATP synthesis and potentially regulate processes like cancer invasion and metastasis. Furthermore, the mechanisms underlying changes in mitochondrial gene copy numbers remain to be elucidated. It is essential to investigate whether alterations in copy numbers are associated with cancer invasion and metastasis. Finally, the exact relationship among changes in mitochondrial dynamics, gene expression and cell migration, as well as related signal transduction pathways affect this process, also requires further study.

Second, the relationship between mitochondrial metabolic reprogramming in tumor cells and other metabolic processes, the complex relationship among carbohydrate, lipid, protein, nucleic acid metabolism with mitochondrial metabolism, needs further elucidation. For example, synergistic or competitive relationships between glycolysis and mitochondrial oxidative phosphorylation in the sugar metabolism pathway may affect the cell's energy utilization. Furthermore, abnormalities in lipid metabolism may also affect mitochondrial function and metabolic pathways, thereby affecting cell growth and metastatic potential (Shao et al. 2024). Therefore, research on the interactions and regulatory mechanisms will enhance our understanding of tumor cell metabolism, offering new avenues and insights for developing therapeutic strategies targeting tumor metabolism.

Finally, the relationship between changes in mitochondrial function and tumor growth and metastasis needs further investigation. For instance, recent discoveries have linked cell ferroptosis to tumor cell growth and metastasis, with changes in mitochondrial iron pools participating in ferroptosis. However, the intrinsic connection between this process and changes in mitochondrial metabolism,as well as the relationship between ferroptosis and tumor growth and metastasis, still requires exploration. Additionally, tumor stem cells play a crucial role in tumor growth and metastasis, and understanding the relationship between mitochondrial metabolic abnormalities and tumor stem cells, along with the underlying mechanisms, is essential for further investigation. (Fig. 3.)

In conclusion, the emerging applications of mitochondrial-targeted drugs in clinical trials, highlight the promising potential of mitochondria-targeted therapy. Recent technological advancement have greatly improved our understanding of mitochondria and their role in tumor biology. High-throughput sequencing has enabled a comprehensive analysis of mtDNA mutations, increasingly recognized as critical factors in cancer development (Hong et al. 2020). Live-cell imaging techniques have provided real-time insights into mitochondrial dynamics, such as fusion and fission, within living cells (Alieva et al. 2023; Dou et al. 2023). Furthermore, the CRISPR/Cas9 system has genetic editing, allowing for targeted manipulation of mitochondrial

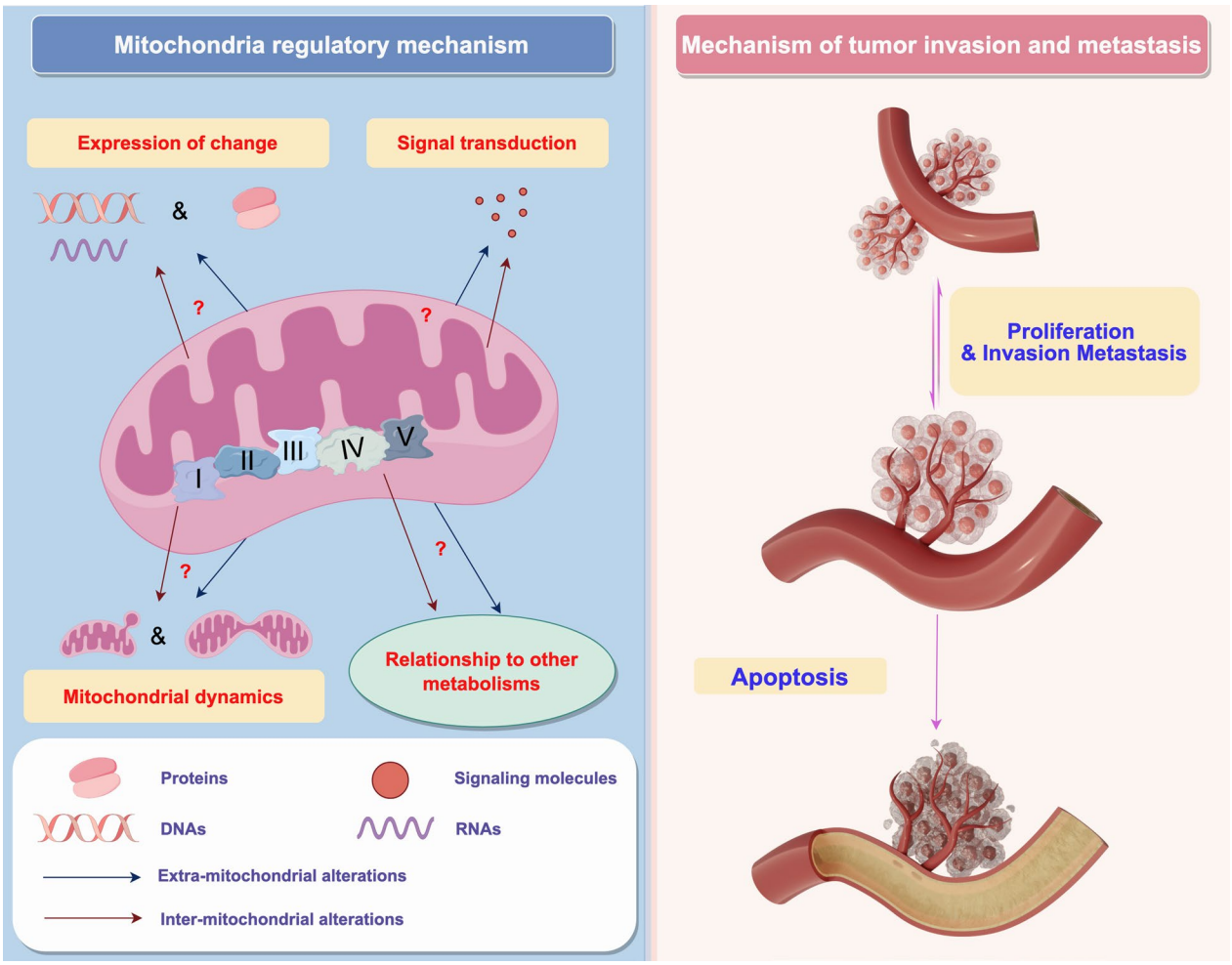


Fig. 3 Prospects of mitochondrial explorations. Focusing on 4 mitochondria related to tumor invasion and metastasis for outlook to target mitochondria to control tumor apoptosis. (By Figdraw.)

genes to study their effects on tumor development (Liu et al. 2023; Wang et al. 2022; Dekkers et al. 2020). These technologies have opened new avenues for investigating the intricate relationship between mitochondria and cancer. With the rapid advancement of molecular and cellular biology technologies, including single-cell sequencing, spatial transcriptomics, spatiotemporal transcriptomics, and metabolomics, we can further elucidate the relationship between mitochondria and tumor development as well as the underlying mechanisms. This will provide robust support for the development of novel strategies targeting mitochondria for tumor gene therapy, ultimately improving clinical treatment outcomes for tumors. Through in-depth research into the role of mitochondria in tumor development, we can better understand the biological characteristics of tumors, offering moreopportunities for personalized and precision medicine.

Abbreviations

AS	Alternative splicing
APAO	Ataxia and polyneuropathy, adult-onset
BC	Breast cancer
CAFs	Cancer-associated fibroblasts
CMHI	Cardiomyopathy, infantile hypertrophic
CRC	Colorectal cancer
DOC2B	Double C-2 like domain beta
DYNLT1	Dynein Light Chain Tctex-Type 1
EGFL9	Epidermal Growth Factor-Like 9
EGFR	Epidermal growth factor receptor
EM	Energy metabolism
EMT	Epithelial-mesenchymal transition
ETC	Electron transport chain
ESCC	Esophageal squamous cell carcinoma
FEZF1-AS1	Long non-coding RNA FEZF1-AS1
FSP1	Fibroblast-specific protein-1
GC	Gastric cancer
GMFB	Glia Maturation Factor-β
HCC	Hepatocellular carcinoma
HMGB1	High Mobility Group Box 1
IMS	Intermembrane space
IQGAP1	IQ Motif Containing GTPase Activating Protein 1

LAC	Lung adenocarcinoma
LC	Liver cancer
LDHA	Lactate dehydrogenase A
Leigh Syndrome (LS)	Leigh syndrome
LHON	Leber hereditary optic neuropathy
LonP1	Mitochondrial Lon protease
lncRNAs	Long non-coding RNAs
mPTP	Mitochondrial permeability transition pore
MRPL52	Mitochondrial ribosomal protein L52
MPc1	Mitochondrial pyruvate carrier 1
mtDNA	Mitochondrial DNA
mtROS	Mitochondrial reactive oxygen species
MT-CYB	Mitochondrial complex V deficiency, mitochondrial 1 (MC5DM1)
MLASA3	Myopathy, lactic acidosis, and sideroblastic anemia 3
MELAS	Mitochondrial encephalomyopathy with lacticacidosis and stroke-like episodes
NAP	Neuropathy, ataxia, and retinitis pigmentosa
MIBSN	Mitochondrial infantile bilateral striatal necrosis
NDUFA4	NADH dehydrogenase 1 alpha subcomplex 4
NDUFA4L2	NDUFA4 mitochondrial complex 2
NDUFS2	Mitochondrial complex I subunit NADH dehydrogenase (ubiquinone) Fe-S protein 2
OCR	Oxygen consumption rate
OM	The outer membrane
PAAD	Pancreatic adenocarcinoma
PCK2	Mitochondrial protein phosphoenolpyruvate carboxykinase
PINK1	PTEN-induced kinase 1
PTC	Papillary thyroid carcinoma
RCC	Renal cell carcinoma
SOD2	Superoxide Dismutase 2
STAT3	Signal transducer and activator of transcription 3
TBS	Triple-negative breast cancer
TefM	Mitochondrial transcription elongation factor
TFAM	Mitochondrial transcription factor A
TGCA	The Cancer Genome Atlas
TPP+	Triphenylphosphonium
TICs	Tumor-initiating cells
TOMM20	Translocase of Outer Mitochondrial Membrane 20
TSPO	Mitochondrial translocator protein
uMtCK	Mitochondrial creatine kinase
VDAC1	Voltage-Dependent Anion Channel 1

Author contributions
Conceptualization, Ya Zhou and Quanling Zhou; writing—original draft preparation, Quanling Zhou; writing—review and editing, Tingping Cao, Fujun Li, Ming Zhang, Xiaohui Li, Hailong Zhao; visualization, Ya Zhou.; supervision, Ya Zhou.; project administration, Ya Zhou.; funding acquisition, Ya Zhou. All authors have read and agreed to the published version of the manuscript.

Funding
This work was supported by the National Natural Science Foundation of China (Grant No. 82160503) and the Project of the Guizhou Provincial Department of Science and Technology (Grant No. QKH-JC-ZK-2022–624).

Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Institutional review board statement
Not applicable.

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Received: 8 June 2024 Accepted: 14 August 2024
Published online: 23 August 2024

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