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Review Article

Mitochondria-related genes or proteins affect the progression of hepatocellular carcinoma: roles, mechanisms and potential treatments

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Abstract: Mitochondria-related genes or proteins can affect various functional indicators of mitochondria, encompassing ATP synthesis, the generation of reactive oxygen species, and the intricate process of mitochondrial autophagy. Numerous researches have unveiled a profound association between mitochondrial dysfunction and the onset, progression, and prognosis of hepatocellular carcinoma. In recent years, a large number of studies have conducted experiments on mitochondria-related genes or proteins to explore their roles and mechanisms in causing mitochondrial functional changes and thereby influencing the progression of hepatocellular carcinoma. Over the past five years, a plethora of studies have been meticulously conducted on mitochondria - related genes and proteins. The aim is to precisely define their functions and the underlying molecular mechanisms in triggering mitochondrial functional aberrations, thereby affecting the progression of HCC. This review is dedicated to comprehensively recapitulating the pertinent progress made in the past half - decade. Additionally, it will delve into how these factors can present feasible and prospective therapeutic modalities for the management of HCC.

Keywords: Mitochondria, hepatocellular carcinoma, mitophagy, reactive oxygen species mitophagy, reactive oxygen species

Introduction

Hepatocellular carcinoma (HCC)

Liver cancer represents the foremost driver of cancer-related mortalities in China, casting a profound shadow over public health and demanding urgent attention. Among male patients, it ranks fourth in incidence and holds the second position in mortality [1]. Hepatocellular carcinoma (HCC), which represents the predominant subtype of the primary liver cancer, constitutes 75-85% of the whole liver cancer cases [2]. The majority of patients with HCC are diagnosed at a stage that the disease has already progressed to a point of significant complexity, at which point surgical intervention is no longer a viable option. Additionally, HCC is a heterogeneous disease with limited response to radiotherapy and a high degree of resistance to chemotherapy. Furthermore, the currently available molecular-targeted therapies and immunotherapies in clinical practice are still plagued by numerous shortcomings. The prognosis for patients with HCC is generally grim. This highlights the urgency of a deeper comprehension of the molecular mechanisms that govern HCC progression and the identification of more potential treatment methods.

Mitochondria

Mitochondria, dynamic organelles that supply the energy necessary for driving key cellular processes, such as cell survival, proliferation, and migration [3]. They preserve a reservoir of deoxyribonucleoside triphosphates (dNTPs) to sustain the replication of mitochondrial DNA (mtDNA), which is responsible for encoding no fewer than 13 genes, including the unique ribosomal protein for protein synthesis [4]. Mitochondria are the main source of energy of eukaryotic cells and mainly produce ATP through oxidative phosphorylation. Accumulating

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evidence has firmly established that mitochondrial oxidative phosphorylation assumes a cornerstone role in the intricate processes of tumorigenesis and the relentless progression of tumor [5]. In addition, the primary wellspring of reactive oxygen species (ROS) within the intricate cellular landscape originates from mitochondria. Moreover, ROS are often elevated in cancer cells, serving as pivotal signaling molecules that intricately regulate tumor progression. When mitochondrial function falters, it triggers abnormal oxidative phosphorylation, heightened resistance to glycolysis as well, culminating in the reprogramming of cancer metabolism and the insidious damage of lipid oxidation [6].

Research significance

Recent investigations unequivocally revealed that the functional parameters of mitochondria are intricately associated with the progression of various types of cancers, which includes HCC. For instance, defects in mitochondrial-related genes are able to instigate the augmentation of glycolysis and lactate biosynthesis in hepatocellular carcinoma cells. This, consequentially, exerts a profound impact on orchestrating the immune-metabolic microenvironment within the tumor microcosm [7]. The modifications in this microenvironment can significantly influence the functionality of immune cells, thus potentially enabling tumor cells to evade immune surveillance and fostering their survival and proliferative capacity. Elucidating these complex relationships is of utmost significance for the formulation of highly targeted therapeutic regimens aimed at combating HCC.

Mitochondria affect the progression of HCC

Mitochondrial-related indicators in HCC cells exhibit marked disparities from those in normal hepatic cells across a wide spectrum of aspects. An extensive array of genes and proteins orchestrate the progression of HCC by exerting their influence on mitochondrial - related mechanistic pathways. This article is aimed at comprehensively expounding upon the mechanistic underpinnings of mitochondrial actions in HCC that have been unearthed or received focused attention in recent years. It will meticulously clarify the ramifications of changes in associated factors and mechanisms within this intricate process. Such an exploration is crucial for deepening our understanding of the molecular pathogenesis of HCC and may potentially lay a solid foundation for the advancement of therapeutic strategies targeting mitochondrial-related processes in the management of this recalcitrant malignancy.

Energy metabolism reprogramming

The metabolic disparities between normal hepatic cells and HCC cells are significant. For instance, normal hepatic cells predominantly depend on aerobic oxidation for energy production. In contrast, tumor cells, even under conditions of ample oxygen availability, predominantly generate energy and lactic acid via glycolysis. The intermediate metabolites of glycolysis further play a crucial role in facilitating biosynthesis within cancer cells, thereby enabling their rapid proliferation. This phenomenon, referred to as the “Warburg Effect”, represents a pivotal mode of metabolic reprogramming. Metabolic reprogramming represents a fundamental and essential strategy employed by tumor cells with the purpose to adapt to the microenvironment and accomplish unrestricted proliferation. The dysregulation of glycolysis within mitochondria and the perturbations in the respiratory chain of HCC cells represent critical mechanisms by which metabolic reprogramming impacts the progression of HCC. For instance, contemporary research has demonstrated that the deletion or mutation of the SDHB subunit within succinate dehydrogenase, a component of mitochondrial respiratory chain complex II, can precipitate the disruption of the tricarboxylic acid (TCA) cycle. The accumulation of succinate, the activation of the Warburg Effect, the enhancement of glycolysis, and ultimately, the facilitation of HCC cell proliferation and metastasis [8]. Beyond exerting an impact on glucose metabolism for metabolic reprogramming, mitochondrial - related factors are also capable of influencing the progression of HCC through modulating other substance metabolisms. For instance, HCC cells enhance β-oxidation (FAO) by upregulating carnitine palmitoyl transferase CPT1A located on the outer mitochondrial membrane. By doing so, they utilize fatty acids as an energy source to adapt to the nutrient-deficient microenvironment [9]. Additionally, emerging research has indicated that silencing of oxoglutarate dehydrogenase-like (OGDHL) can propel the progression of

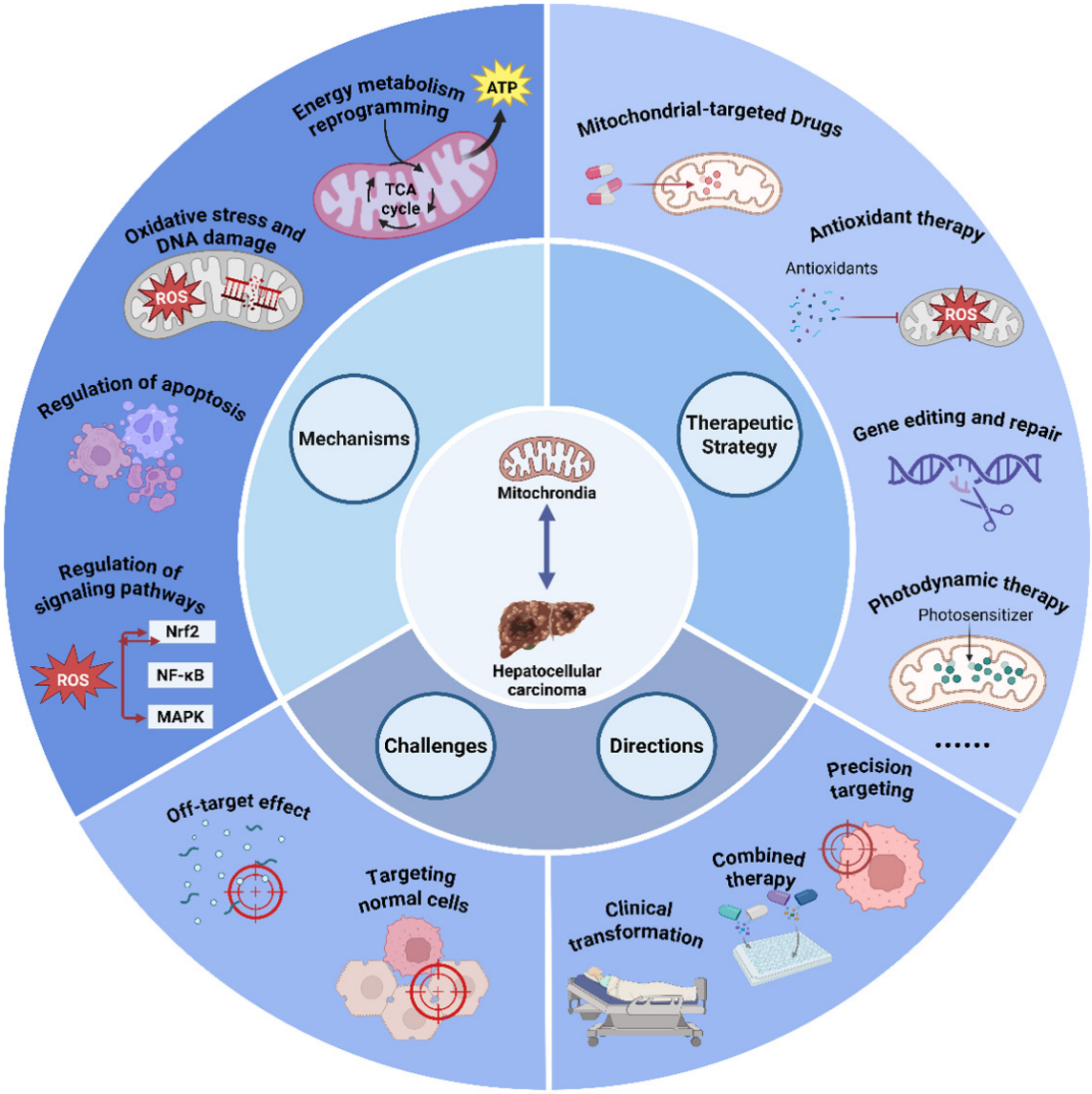

Figure 1. The schematic diagram of the overall idea of this article. This diagram illustrates the mechanisms, therapeutic strategies, challenges, and future directions of mitochondria in hepatocellular carcinoma.

hepatocellular carcinoma via reprogramming glutamine metabolism [10].

From this, it is evident that energy metabolism reprogramming associated with mitochondrial function is intricately linked to the genesis and progression of HCC cells (**Figure 1**).

Oxidative stress and DNA damage

The progression of HCC is intricately intertwined with the protracted accrual of oxidative stress and the incapacitation of DNA damage repair processes. The mitochondrial electron leakage of mitochondrial electron transport chain (ETC) complexes, such as complex I and III, are prone to electron leakage, thereby acting as the principal endogenous generators of ROS within cells. In the context of tumor cells, the dysregulation of the antioxidant system, which is effectively synonymous with oxidative stress, precipitates the progressive accumulation of ROS [11]. It is thus clear that oxidative stress stands as one of the characteristic signatures of tumor cells, playing a pivotal role in the multifactorial pathogenesis of HCC. For instance, contemporary research has demonstrated that the absence of ferredoxin 1 (FDX1),

a mitochondrial - localized protein, when absent, induces an increase in ROS levels, activates mitochondrial autophagy within HCC cells, promotes tumor growth, and exerts an impact on patient prognosis [12].

Due to the absence of histone protection shielding and its close proximity to the loci of ROS generation, oxidative stress in HCC cells inflicts oxidative lesions upon mtDNA [13]. In HCC tissues, the repair efficiency of mtDNA decreases, encompassing a reduction in the efficiency of base excision repair efficiency and impairment to the mitochondrial autophagy pathway, which is responsible of the elimination of mutant mtDNA. This cascade of events culminates in the progressive accumulation of mutant mtDNA, which multifarious influence in promoting carcinogenesis. The underlying mechanism suggests that eliminating mutant mtDNA and alleviating mtDNA accumulation hold significant promise as potential therapeutic avenues for impeding the initiation and progression of HCC. This is exemplified by FUN14 domain-containing 1 (FUNDC1), a protein that actively promotes mitochondrial autophagy. To reduce the burden of mutant mtDNA, agonists of FUNDC1, such as urolithin A, effectively impede the proliferation of HCC cells via this mechanism [14]. Given the intricate interaction network existing between oxidative stress and DNA damage, strategies aimed at neutralizing or diminishing the generation of ROS to curb oxidative stress and DNA damage represent an efficacious approach of suppressing the progression HCC. Such strategies have the potential to open up novel avenues for the early intervention and targeted therapy of HCC, thereby offering new hope for patients suffering from this recalcitrant malignancy.

Apoptosis regulation

Mitochondria occupy a pivotal position as the epicenter for the regulation of apoptosis and are the decisive arbiters of the survival or demise of tumor cells. The mechanistic framework of mitochondria-mediated apoptosis can be delineated in the following manner: mitochondria induce an elevation in the permeability of their outer membrane (MOMP), which results in the liberation of pro-apoptotic effector molecules, chief among them being cytochrome c. This liberation sets in motion the Caspase-mediated proteolytic cascade. During this cascade, a diverse array of intracellular substrates are cleaved, ultimately culminating in the execution of apoptosis. Unquestionably, this sequence of events plays an instrumental role in impeding the growth and propagation of tumor cells. However, the existence of apoptosis resistance in HCC tissues is one of the important reasons for tumor progression and chemotherapy failure [15]. In recent years, research has been incessantly delving into genes associated with mitochondria-dependent apoptosis in an endeavor to unearth additional therapeutic targets. For instance, the mitochondrial enzyme immune response gene 1 (IRG1) sequesters MCL-1, an anti-apoptotic protein, thereby instigating apoptosis of liver cells, contribute to the initiation of carcinogenesis [16].

Beyond mitochondria-dependent apoptosis, contemporary investigations have gradually unveiled that mitochondria assume a multidimensional regulatory function in the death of HCC cells. Mitochondria are intricately engaged in the execution or inhibition of numerous forms of liver cancer cell death, including ferroptosis and ferroptosis-like form of copper-induced cell death, mostly known as cuproptosis, via distinct molecular mechanisms.

Mitochondria exert influence and regulation over ferroptosis within cells through multiple pathways. Firstly, considering that mitochondria contain approximately 20% to 50% of the total cellular iron content, aberrant iron metabolism within mitochondria has a direct bearing on the onset of ferroptosis. Secondly, the overgeneration of ROS by mitochondria culminates in lipid peroxidation, which to a certain degree potentiates ferroptosis. Consequently, measures such as regulating mitochondrial iron metabolism or ROS generation can be harnessed to facilitate ferroptosis in HCC cells and impede the progression of HCC. For instance, contemporary research indicates that the deficiency of the mitochondrial-enriched protein GCN5L1, which downregulates the expression of the mitochondrial iron transporter CISD1 and induces iron accumulation, increases the sensitivity of HCC cells to the ferroptosis inducer Sorafenib [17].

Mitochondria assume a significant role during the cuproptosis process. To put it simply, the central mechanism of cuproptosis involves the

intracellular accumulation of copper ions. These copper inon bind to mitochondrial proteins that contain lipoic acid moieties. This leading event precipitates widespread protein aggregation, ultimately culminating cell death. Mitochondria have approximately two regulatory nodes in this process: one is that the copper ion carrier FDX1 promotes Cu^{2+} entry into mitochondria and targets lipoic acid-containing proteins (such as DLAT). The other is that defects in the mitochondrial lipoic acid synthesis pathway (LIAS) enhance copper toxicity. Research has demonstrated that tumors characterized by high levels of FDX1 and lipoic acid-containing proteins exhibit sensitivity to cuproptosis [18]. In HCC cells, the pronounced expression of FDX1 suggests that HCC cells possess enhanced susceptibility to cuproptosis. As such, the strategy of promoting cuproptosis through the modulation of mitochondrial function represents a viable approach for ultimately inhibit the progression of HCC. In recent years, certain copper ion carriers, like Elesclomol, have advanced to clinical trials and have registered notable progress [19].

Signal pathways

Mitochondria serve as pivotal orchestrators in the genesis, progression, and metastasis of HCC, intricately intertwined with a multitude of signaling pathways. These pathways engage in dynamic cross-talk, weaving an elaborate network that synergistically governs mitochondrial functionality and propels the advancement of HCC. A profound exploration of these signaling cascades not only unravels the enigmatic pathogenesis of HCC but also unveils innovative targets and strategic paradigms for the diagnosis and therapeutic intervention of liver cancer.

Among the signaling pathways in association with energy metabolism, the AMPK/mTOR pathway and PI3K/Akt pathway plays a principal role [20]. When mitochondrial dysfunction occurs, resulting in inadequate cellular energy supply, AMPK would be activated [21, 22]. Upon activation, the signaling pathway is capable of regulating cellular glycolysis through multiple mechanisms, thereby inhibiting the malignant phenotype of HCC [23]. Furthermore, studies have found that AMPK/mTOR-dependent autophagy activation promotes the invasion and migration of HCC [24], demonstrating the potential of this pathway as a therapeutic target for the intractable disease. Similar to the AMPK signaling pathway, the PI3K/Akt signaling pathway regulates cellular glycolysis through mitochondrial-related mechanisms. For instance, after the activation of the PI3K/Akt pathway, it can facilitate the attachment of the glycolytic enzyme HK2 to VDAC in the mitochondria [25]. In addition, PI3K/Akt and AMPK can interact with each other through regulation of the expression of glycolytic enzymes [26], which exerts extremely important role in the growth control of cancer cells and glucose metabolism.

Oxidative stress and the mitochondrial ROS-related signaling pathway network constitute one of the most classical and intricate mechanism networks involved in the growth and development of HCC, encompassing key pathways such as Nrf2, MAPK, and NF-κB. Nrf2 undoubtedly plays a pivotal role in facilitating the survival and proliferation of tumor cells and mediating tumor immune evasion [27]. As excessive ROS generation by mitochondria causes oxidative stress, Nrf2 is activated and induces the expression of detoxification enzymes and antioxidant enzymes, regulating mitochondrial-related metabolism, such as the metabolism of glucose and glutamine. As a result, it successfully mitigate oxidative damage and enhance the survival capacity of HCC cells, facilitating their proliferation in adverse circumstances [28, 29]. Nrf2 also influences the immune microenvironment by suppressing the release of inflammatory factors, assisting HCC cells in evading immune surveillance of the body [27, 30, 31]. In addition, ROS generated by mitochondria can oxidize and activate the Ras protein, subsequently triggering the activation of the Raf-MEK-ERK signaling cascade. During the development of HCC, aberrant activation of the MAPK signaling pathway may result in enhanced proliferation, migration, and invasive capabilities of tumor cells [32]. For instance, a tropolone derivative called β-Thujaplicin induces apoptosis in human HCC through ROS-mediated MAPK signaling [33]. Not only that, the MAPK signaling pathway can also feedback-regulate mitochondrial function. For instance, a research has demonstrated that some natural prenylated isoflavonoid exerts anti-cancer effects through oxidative stress

and regulation of the MAPK signaling pathway, and depolarize the mitochondrial membrane potential in HCC cells via the MAPK pathway, thus inhibiting mitochondrial respiration [34]. In addition to these two signaling pathways, the NF-κB signaling pathway is also a classical one that exerts an effect on the progression of HCC through a close connection with ROS. Briefly interpretating, the excessive generation of mitochondrial ROS in hepatocytes promotes inflammatory factors like IL-1, IL-6, and TNF-α expressing. The expression of these factors can stimulate the activation of NF-κB, and the activated NF-κB, in turn, causes an increase in inflammatory factors like IL-1, IL-6, and TNF-α and the accumulation of ROS, forming a positive cyclic cascading interaction relationship, aggravating hepatocyte damage and inducing the occurrence of HCC [35-37]. It is noteworthy that the enhanced mitochondrial fission in HCC cells can facilitate autophagy and liver cancer cell survival via the ROS-mediated regulation of the NF-κB pathway [38]. In recent years, numerous factors have been demonstrated to exert influences via NF-κB pathway, either promoting or inhibiting. For instance, overexpression of mitochondrial proteins CR6-interacting factor 1 (Crif1) and Human TFB2M (mitochondrial transcription factor B2) in HCC cells induces the ROS/NF-κB pathway in HCC, facilitating growth and metastasis [39, 40].

Some other signaling pathways exert their influence on HCC by regulating the related circumstances of mitochondrial dynamics. The Wnt pathway can regulate mitochondrial homeostasis and be involved in the occurrence of tumors such as colon cancer and liver cancer [31, 41]. Among the anti-cancer-related signaling pathways in the human body, large tumor suppressor 2 (LATS2) regulates the expression of DRP1 via the Wnt/β-catenin pathway. DRP1 increases mitochondrial fission, a progress marked by mitochondrial dysfunction, encompassing reduced mitochondrial membrane potential, downregulation of mitochondrial respiratory complexes, and initiation of mitochondrial apoptosis. Eventually, this inhibits the progression of HCC and exerts its anti-cancer effect [31].

Naturally, the content mentioned above merely expounds the relationship between various signaling pathways and mitochondria in a certain dimension, along with their influence on HCC. In reality, the majority of signaling pathways typically regulate mitochondrial functions through multiple dimensions, propelling the continuous progression of HCC. For instance, The PI3K/AKT pathway can profoundly influence the development of HCC through regulating mitochondrial metabolism, apoptosis, dynamics and ROS balance. New research has shown that the down-regulation of FDX1 can activate mitochondrial autophagy and the PI3K/AKT signaling pathway, promoting the proliferation, invasion and growth of HCC cells both in vitro and in vivo [12]. Likewise, the fatty acid receptor CD36 also makes use of the PI3K/AKT pathway. It mediates metabolic reprogramming via the Src/PI3K/AKT/mTOR signaling pathway, thereby exerting a stimulatory effect on the growth and metastasis of HCC [42].

These signaling pathways constitute a complex and extensive network in HCC, mutually checking and balancing each other. Any anomaly of any molecule in any of these pathways may affect the functions of other pathways, and subsequently influence the biological behaviors of HCC, including its occurrence, development, invasion and metastasis. For the simplest case, various signaling pathways that can mediate the generation of ROS in mitochondria often eventually give rise to a cascade effect with the NF-κB signaling pathway. Anyway, further researches on the interrelationships of these signaling pathways are conducive to a comprehensive recognization of the pathogenesis of HCC and offer a theoretical basis for the precise treatment of the disease.

The potential of mitochondria as therapeutic targets for HCC

Mitochondrial - targeted drugs: Some drugs are designed to specifically accumulate in mitochondria and disrupt their functions. For instance, the liposolubility of betulinic acid (BA) enables it to more easily pass through the mitochondrial membrane, increase mitochondrial membrane permeability and generate ROS, thereby exerting its anti-cancer effect [43]. Resveratrol (RSV), an antioxidant compound present in red grapes, has been demonstrated to cause apoptosis in HCC cells via mechanisms including promoting mitochondrial depolarization and the activation of caspase-3

release [44]. Recent research progress based on the results of this study indicates that the nano-drug co-loaded with Curcumin can synergistically treat HCC, decrease the required drug dosage, and improve therapeutic efficacy [45]. Apart from exerting anti-tumor effects through the regulation of mitochondrial membrane potential and ROS generation levels, there exist drugs like a coumarin-Pt(IV) prodrug, named Bromocoumarinplatin that target mtDNA. Such drugs induce apoptosis by impairing mtDNA integrity, thereby effectively mitigating the resistance of cancer cells to the conventional chemotherapeutic agent Cisplatin [46]. In addition to the chemotherapy drugs mentioned above, drugs that exhibit anti-cancer effects via this mechanism have found widespread application in photodynamic therapy (PDT) and photothermal therapy (PTT) [47].

Antioxidant therapy: Although oxidative stress can contribute to cancer development, in some cases, cancer cells are more vulnerable to excessive ROS than normal cells [48, 49]. Therefore, using antioxidants to modulate the ROS level in cancer cells can be a strategy [50]. There are various drugs that are in the experimental stage up to now, including antibody drugs, exosome drugs, nanocarrier drugs, aptamer drugs and polysaccharide drugs [51]. It is believed to furnish novel hope to the clinical treatment of patients with HCC. For instance, dietary curcumin (CUR) has been shown to suppress the proliferation of various hepatoma cell lines and induce apoptosis in HepG2 cells through promoting the production of ROS [52, 53]. Likewise, resveratrol (RSV), a natural polyphenolic mixed with antioxidant properties found in numerous plants, exhibits preventive or inhibitory effects on the development of liver cancer [54]. Upon these foundation, a new formulation was created to provide an innovative strategy for HCC therapy. A SP94-mediated Nanoparticles (NPs) allowed a large amount of CUR and RSV to accumulate in HCC tissue, which demonstrated satisfactory therapeutic efficacy while minimizing potential side effects [45].

Mitochondrial gene therapy: This approach aims to correct mitochondrial gene mutations or dysfunctions in cancer cells. It can involve the delivery of normal mitochondrial genes into cancer cells to restore their normal functions or the use of gene-editing technologies to repair mutant mitochondrial DNA. Currently, there are relatively few approved drugs directly utilized for the therapy of HCC based on the mechanism of mitochondrial gene therapy. Nevertheless, there are certain related drug delivery approaches and medications in the research phase. Mitochondrial transcription-specific inhibitors (IMTs) suppress the transcription of mtDNA by targeting human mitochondrial RNA polymerase (POLRMT). This causes a significant reduction in the basal respiration of tumor cells, inhibition of cell proliferation, and a decrease in cell viability. Furthermore, this strategy demonstrates excellent tolerability in mice, with no observable effects on normal liver tissue and minimal side effects [55]. In addition, there is another mitochondrial gene editing technology Mito-TALENs. Studies have designed Mito-TALENs targeting specific mutation sites in mtDNA to specifically recognize and cleave the mutated mtDNA, correct mitochondrial gene mutations, and restore normal mitochondrial functions [56]. If it is introduced into liver cancer cells to regulate mitochondrial functions, it might promote the apoptosis of HCC cells. Although it is still in the theoretical stage, it offers novel ideas and directions for the treatment of HCC.

Autophagy modulation: Mitochondrial autophagy, or mitophagy, is a process by which damaged mitochondria are selectively removed from cells. In cancer, the dysregulation of mitophagy can affect cell survival and proliferation [57]. Some therapeutic strategies focus on modulating mitophagy. For instance, a traditional Chinese medicine called Digoxigenin (DIG) has been proved that it induces autophagy by modulating the PI3K/AKT/mTOR pathway and inhibits developing of subcutaneous xenograft tumors in vivo studies, representing a potential therapeutic modality for HCC [58].

As one of the first line treatment drugs of HCC, Lenvatinib is capable of upregulating the mitochondrial-related protein STOML2 and mediating mitochondrial autophagy via its downstream pathways [59, 60]. The combined therapy of Lenvatinib and hydroxychloroquine thereby promotes HCC metastasis and modulates the inhibitory effect of HCC on primary tumor growth and lung metastasis, which is far superior to the individual administration of

either drug [60]. In an identically uniform manner, Sorafenib is the most widely used first-line drug for advanced HCC [61] while Artesunate significantly enhanced the inhibitory effect of Sorafenib on resistant cells and tumors by inducing excessive mitochondrial autophagy [62]. Overall, targeting mitochondrial autophagy-related factors such as CD24 and vaccinia-related kinase 2 (VRK2) to regulate the equilibrium between autophagy and apoptosis and restrain the further growth and development of HCC constitutes a potential strategy for overcoming the resistance to first-line drugs in the treatment of HCC [63, 64].

Photodynamic therapy (PDT): PDT involves the use of a photosensitizer that can be preferentially taken up by cancer cells and accumulate in mitochondria. When exposed to specific wavelengths of light, the photosensitizer generates ROS, which causes damage to mitochondrial proteins and membranes, which leads to mitochondrial dysfunction and subsequent cell death [65-67]. Experimental investigations have demonstrated that PDT can effectively eliminate HCC cells and shrink tumor tissues. In clinical studies, it has prolonged the survival rate of patients affected by inoperable HCC and improved their quality of life [68-70].

This therapeutic approach has been constantly evolving in recent years, indicating its substantial potential in the treatment of HCC. A research team successfully integrated the photosensitizer porphyrin and the chemotherapy drug Sorafenib into a single nanoscale platform, enabling the combination of multiple therapeutic modalities. This innovative strategy ultimately exhibited a significant synergistic tumor-suppressive effect in a subcutaneous mouse model [71]. This work heralds a favorable prospect for the integration of biomedical nanomedicine with clinical treatment modalities such as PDT. Furthermore, there are studies that have made further explorations to overcome the limitations of PDT. The limitation of PDT lies in that when tumors are hypoxic, the ROS it induces will decrease, failing to achieve the expected therapeutic effect [72]. In response to this, various oxygen delivery (NOD) strategies based on novel nanomaterials have been constructed and combined with PDT, reducing the constraints of PDT to a certain extent [73-75]. It is encouraging that the continuous construction of cell bionic carriers (CBV) can well solve the problems of low oxygen delivery efficiency, oxygen leakage and uncontrollable oxygen release of traditional NOD [76]. For example, a new bionic oxygen delivery system has been constructed in recent years, targeting HCC and achieving controlled release of oxygen, which has achieved good therapeutic effects both in vitro and in vivo [77].

Research challenges and directions

In the research on mitochondrial-targeted therapy for HCC, the main challenges lie in the high difficulty of research and the safety of therapeutic strategies caused by the complexity of mitochondrial functions. Due to the highly interwoven functional network of mitochondria, a single molecule often involves multiple regulatory mechanisms and pathways. Intervening in its related factors alone can easily lead to off-target effects, which requires continuous practical research. Additionally, mitochondria are widely present in all cells, and targeted strategies may cause toxicity to normal tissues and damage normal liver cells. Therefore, it is necessary to control the dosage or explore combined drugs in the research to alleviate or avoid such damage and promote the precise regulation of targeted drugs.

In the future, research on this topic should focus on precise targeting and combined strategies. On the one hand, it is necessary to continuously develop specific molecular intervention tools and make full use of gene editing technologies such as CRISPR/Cas9 to precisely target mitochondrial-related molecules to inhibit the progression of HCC. On the other hand, the combination of immunotherapy and mitochondrial metabolic regulators, along with the application of nanotechnology to enhance drug delivery efficiency, is of paramount importance in the continuous development of HCC treatment drugs. Moreover, current research should not merely remain at the conceptual proof and explanation stage of the influence of multiple mitochondrial-related molecules on HCC, but also require more studies to continuously promote the transformation of mitochondrial-targeted therapy from basic research to clinical application.

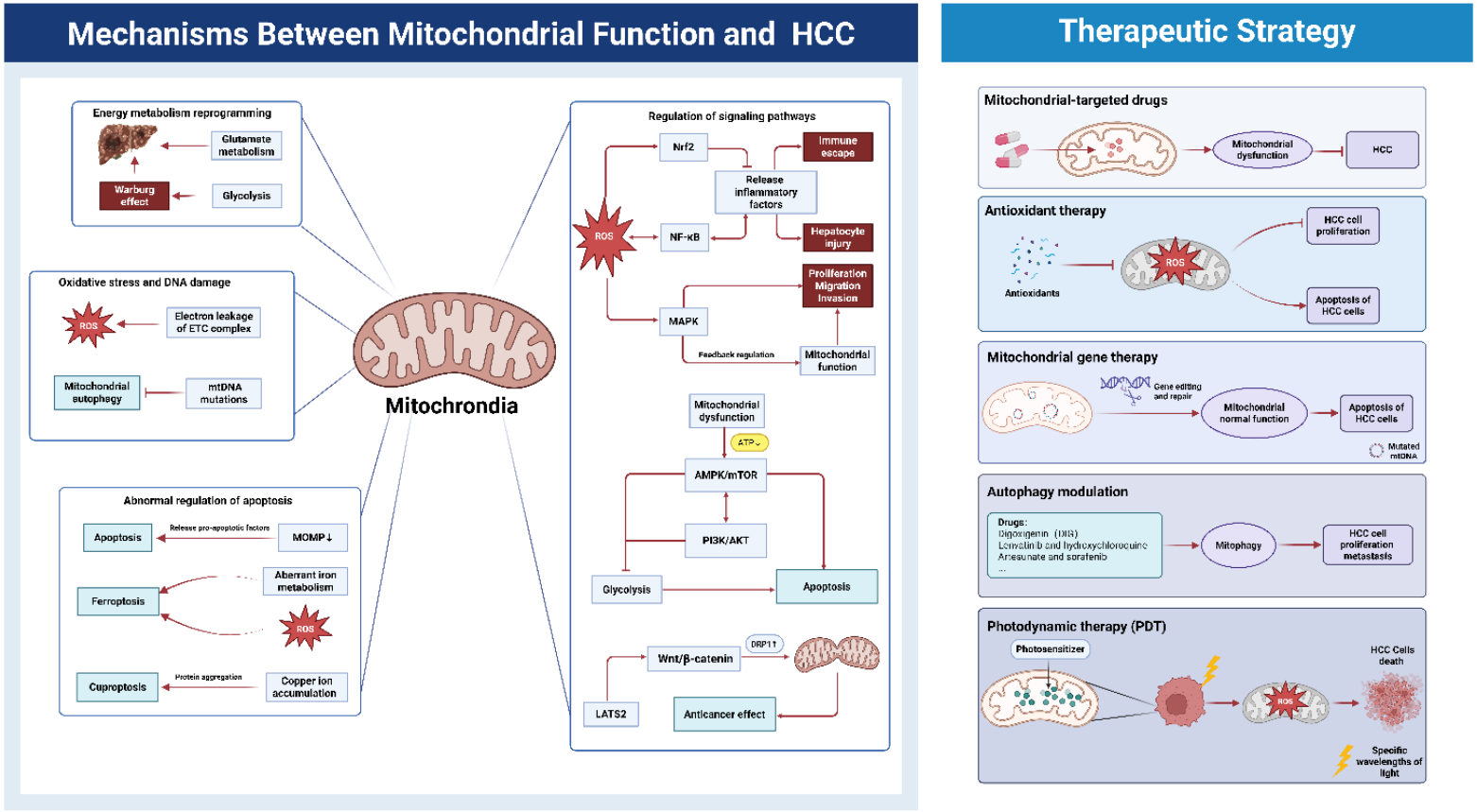
Mechanisms Between Mitochondrial Function and HCC
Energy metabolism reprogramming
Glutamate metabolism
Warburg effect
Glycolysis
Oxidative stress and DNA damage
ROS
Electron leakage of ETC complex
Mitochondrial autophagy
mtDNA mutations
Abnormal regulation of apoptosis
Apoptosis
Release pro-apoptotic factors
MOMP↓
Aberrant iron metabolism
Ferroptosis
ROS
Cuproptosis
Protein aggregation
Copper ion accumulation
Mitochrondia
Regulation of signaling pathways
Nrf2
Immune escape
Release inflammatory factors
ROS
NF-κB
Hepatocyte injury
Proliferation Migration Invasion
MAPK
Feedback regulation
Mitochondrial function
Mitochondrial dysfunction
ATP↓
AMPK/mTOR
PI3K/AKT
Glycolysis
Apoptosis
DRP1↑
Wnt/β-catenin
LATS2
Anticancer effect
Therapeutic Strategy
Mitochondrial-targeted drugs
Mitochondrial dysfunction
HCC
Antioxidant therapy
HCC cell proliferation
Antioxidants
ROS
Apoptosis of HCC cells
Mitochondrial gene therapy
Gene editing and repair
Mitochondrial normal function
Apoptosis of HCC cells
Mutated mtDNA
Autophagy modulation
Drugs:
Digoxigenin (DIG)
Lonvatinib and hydroxychloroquine
Artesunate and sorafenib
...
Mitophagy
HCC cell proliferation metastasis
Photodynamic therapy (PDT)
Photosensitizer
HCC Cells death
ROS
Specific wavelengths of light
Research Challenges and Directions
Challenges
Off-target effect
Targeting normal cells
Directions
Precision targeting
Clinical transformation
Combined therapy
Targeted strategy
Hepatocyte
HCC cell
Created with BioRender Poster Builder

Figure 2. A detailed image illustrating the key content of each part of this article. It includes the classic and newly discovered echanisms by which mitochondria influence HCC progression, therapeutic strategies targeting mitochondria for HCC treatment, as well as the challenges and opportunities that the field will face in the future.

Summary

This review expounds on the fundamental and regulatory roles of mitochondrial-related genes and proteins throughout the multistage progression of HCC, while concurrently appraising emerging and potential therapeutic interventions (**Figure 2**). Mitochondrial homeostasis and functionality are intrinsically intertwined with the pathogenesis and progression of HCC. Evidences are chiefly reflected in multiple oncogenic processes, including the metabolic reprogramming of energy metabolism, which fuels tumor cell proliferation; oxidative stress-induced genotoxic stress and subsequent DNA damage; the dysregulation of cell death modalities such as apoptosis, ferroptosis, and necroptosis; and the intricate crosstalk among diverse oncogenic and tumor-suppressive signaling pathways.

Current therapeutic armamentarium against HCC primarily revolves around two key axes: targeted modulation of metabolic reprogramming machinery and regulation of mitochondrial dynamics. Multiple pharmacological agents, such as the combination of metformin and Sorafenib, elesclomol-an inducer of ferroptosis and necroptosis, USP1 inhibitors, and Mdivi-1, have demonstrated promising pre-clinical and, in some instances, clinical efficacy, underscoring their potential as novel therapeutic candidates.

Despite these advance, this field confronts substantial hurdles. The inherent complexity of mitochondrial biology and its intricate crosstalk with cellular metabolism pose formidable challenges to research endeavors. Moreover, ensuring treatment safety while maximizing therapeutic efficacy remains a persistent and unmet clinical need. In the future, multi-omics technologies, including proteomics, genomics, transcriptomics, and metabolomics, in tandem with single-cell profiling, will be indispensable for elucidating the molecular mechanisms underpinning mitochondrial dysfunction in HCC. The development of nanotechnology - enabled precision drug delivery systems, along with rationally designed combinatorial treatment regimens, holds great promise for enhancing therapeutic efficacy. Gene-editing tools, such as CRISPR/Cas9, offer unprecedented opportunities to modulate mitochondrial function and facilitate the translation of basic research findings into clinical applications. Simultaneously, deciphering the bidirectional interaction between mitochondria and the microenvironment of tumor - comprising fibroblasts and extracellular matrix components in association with the cancer - represents a crucial avenue for the discovery of novel diagnostic and prognostic biomarkers.

In conclusion, mitochondrial dysfunction represents a linchpin in the pathogenesis of HCC, offering a fertile ground for the development of innovative and targeted therapies. In the future, the research should focus on unraveling the spatiotemporal dynamic of mitochondrial-tumor microenvironment interactions. By integrating precision oncology principles with cutting-edge multi-disciplinary technologies, we can potentially revolutionize the current treatment landscape for HCC and improve patient outcomes.

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Disclosure of conflict of interest

None.

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