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REVIEW

# Targeting mitochondrial dysfunction to intervene in liver cancer

Maomao Li[1]*, Siyao Liang[1]*, Le Chang[1]*, Bingyan Lu[1], Jiahua Cheng[1], Tian Yang[1], Ying Wu[1], Yuhong Lyu[1], Xiaochan He[1,2], Changwu Yue[1,3]

[1]Yan'an Key Laboratory of Microbial Drug Innovation and Transformation, Yan'an Medical School of Yan'an University, Yan'an 716000, China; [2]Xi'an Honghui Hospital, Xi'an Jiaotong University, Xi'an 710000, China; [3]Shaanxi Engineering and Technological Research Center for Conversation and Utilization of Regional Biological Resources, Yan'an University, Yan'an 716000, China

**ABSTRACT** The occurrence and progression of liver cancer are closely associated with mitochondrial dysfunction. Mitochondria exhibit characteristics, such as decreased oxidative phosphorylation efficiency, abnormal accumulation of reactive oxygen species in liver cancer and promoting tumor proliferation and drug resistance through the Warburg effect, as the core of energy metabolism and apoptosis regulation. Mutations in mitochondrial DNA (mtDNA) and dysregulation of mitochondrial autophagy (mitophagy) further enhance the invasive and metastatic capabilities of liver cancer. Current targeted therapeutic strategies focus on modulating the activity of respiratory chain complexes, regulating calcium homeostasis, repairing mtDNA, and activating mitochondrial apoptotic pathways. Although these approaches have shown therapeutic effects, challenges persist, such as tumor heterogeneity, insufficient drug specificity, and drug resistance. Future research needs to integrate the concept of precision medicine by focusing on breakthroughs in the molecular mechanisms underlying mitochondrial dysfunction, development of targeted delivery systems, optimization of combination therapy regimens, and screening of biomarkers to provide new pathways for individualized treatment. With advances in technology, targeting mitochondrial dysfunction is expected to become an important breakthrough for improving the prognosis of liver cancer.

**KEYWORDS** Mitochondrial targeting; liver cancer therapy; mtDNA mutations; reactive oxygen species; mitochondrial metabolic reprogramming; clinical translation

## Introduction

Hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma (iCCA), and secondary liver cancer are the three main types of liver cancer. Liver cancer is one of the most common malignant tumors worldwide. The complex pathogenesis of liver cancer poses many challenges for treatment and most patients die within 5 years after diagnosis. Notably, many HCC cells exhibit mitochondrial defects with a reduced dependence on mitochondrial function; this defect is closely associated with pathogenicity[1].

As the powerhouse of the cell, mitochondria generate adenosine triphosphate (ATP) through oxidative phosphorylation (OXPHOS) to provide energy for cellular functions. Mitochondria not only meet the basic energy requirements of cells but also reprogram metabolism to convert nutrients into precursor molecules for biosynthesis when the nutrient supply is sufficient, thereby promoting cell proliferation and tissue regeneration[2]. However, impaired mitochondrial function can lead to cellular energy metabolic disorders, decreased OXPHOS activity, and a series of metabolic disturbances[3]. In addition to a role in energy metabolism, mitochondria regulate cellular signaling through functions, such as reactive oxygen species (ROS) generation and calcium ion ($Ca^{2+}$) regulation, playing important roles in physiologic and pathologic processes, including apoptosis and autophagy. During

*These authors contributed equally to this work.
Correspondence to: Yuhong Lyu, Xiaochan He and Changwu Yue
E-mail: yuhonglyu@126.com, xiaochan.he@hotmail.com and changwuyue@yau.edu.cn
ORCID ID: https://orcid.org/0000-0003-1859-2457, https://orcid.org/0009-0002-7122-272X and https://orcid.org/0000-0003-2679-5772
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apoptosis, mitochondria release pro-apoptotic factors, such as cytochrome c (Cyt c), which activates the apoptotic cascade and leads to programmed cell death. In addition, autophagy clears damaged or dysfunctional mitochondria, thereby maintaining cellular homeostasis[4].

HCC cells can exhibit signs of mitochondrial dysfunction, indicating that HCC cells are highly dependent on mitochondrial function and are closely associated with mitochondrial abnormalities[5]. Emerging evidence suggests that mitochondrial bioenergetics, dynamics, and autophagy are closely associated with HCC metabolic reprogramming[1]. Mitophagy exhibits a dual nature in HCC. First, mitophagy can eliminate damaged mitochondria, thereby maintaining mitochondrial quality control. During this process the production of ROS is reduced, which in turn decreases the likelihood of genetic mutations and thereby suppresses the development of HCC[6,7]. For example, the thyroid hormone, triiodothyronine (T3), induces mitophagy by targeting the PINK1/Parkin pathway in a mouse model of HCC, thereby eliminating damaged mitochondria and reducing ROS levels, which in turn suppresses the progression of liver cancer[6]. Icaritin exerts its effects by activating the PINK1-Parkin signaling pathway to induce mitophagy and apoptosis in HCC cells, thereby inhibiting growth, proliferation, and migration[8]. Second, after the formation of liver cancer, activated autophagy can alleviate metabolic stress to meet the high metabolic demands of HCC cells; cancer cell growth is thereby promoted[5]. HCC cells meet growth requirements through metabolic reprogramming, in which mitochondria have a significant role.

For example, HCC cells may shift from an energy metabolism mode relying on OXPHOS to an energy metabolism mode depending on glycolysis. This shift is known as the "Warburg effect," by which tumor cells preferentially use glycolysis to produce energy even in the presence of sufficient oxygen.

Mitochondria are one of the primary sources of ROS within cells. Mitochondrial dysfunction can lead to increased ROS levels in HCC cells, which triggers oxidative stress. Oxidative stress not only damages cellular DNA, proteins, and lipids but also activates a series of pro-tumorigenic signaling pathways. For example, cyclic GMP-AMP synthase (cGAS) localized in the mitochondria inhibits the accumulation of mitochondrial ROS, thereby suppressing ferroptosis (a form of regulated cell death) and ultimately promoting the development and progression of liver cancer[9]. These processes collectively influence the development and progression of liver cancer. Therefore, in-depth investigation into the mechanisms by which mitochondria are involved in these processes will help to elucidate the pathogenesis of liver cancer and provide potential targets for the development of new therapeutic strategies.

Targeting mitochondrial intervention holds significant promise in the treatment of liver cancer. Modulating mitochondrial energy metabolism and ROS levels can suppress the proliferation and growth of HCC cells. For example, inhibiting mitochondrial OXPHOS or promoting ROS accumulation may increase oxidative stress, thereby suppressing tumor cell growth. In addition, disrupting the mitochondrial membrane potential and inducing pro-apoptotic factors can trigger apoptosis in HCC cells. Targeting mitochondria in conjunction with existing chemotherapy and immunotherapy can significantly enhance therapeutic outcomes. For example, modulating mitochondrial function can increase drug sensitivity or bolster the functionality of immune cells. More importantly, mitochondrial targeting can help overcome drug resistance developed by HCC cells during prolonged treatment, circumventing some of the limitations of traditional therapies. This characteristic provides a more durable and effective treatment option for patients with HCC.

Because mitochondria exhibit distinct characteristics in tumor cells compared to normal cells, mitochondrial-targeted interventions can improve treatment specificity, reducing damage to normal cells and minimizing side effects. This research will drive innovation and development in the field of liver cancer treatment, providing a theoretical basis and practical guidance for the development of new therapeutic drugs and methods. Mitochondrial-targeted intervention has the potential to achieve breakthroughs in the treatment of liver cancer (**Figures 1 and 2**).

## Literature search strategy and inclusion criteria

The literature search strategy and inclusion criteria were designed to systematically identify high-quality studies related to mitochondrial-targeted therapy for liver cancer. We conducted searches in English-language databases, such as Google Scholar, Web of Science, and PubMed, as well as Chinese-language databases, including China National Knowledge Infrastructure (CNKI) and Wanfang, to cover both English and Chinese literature resources.

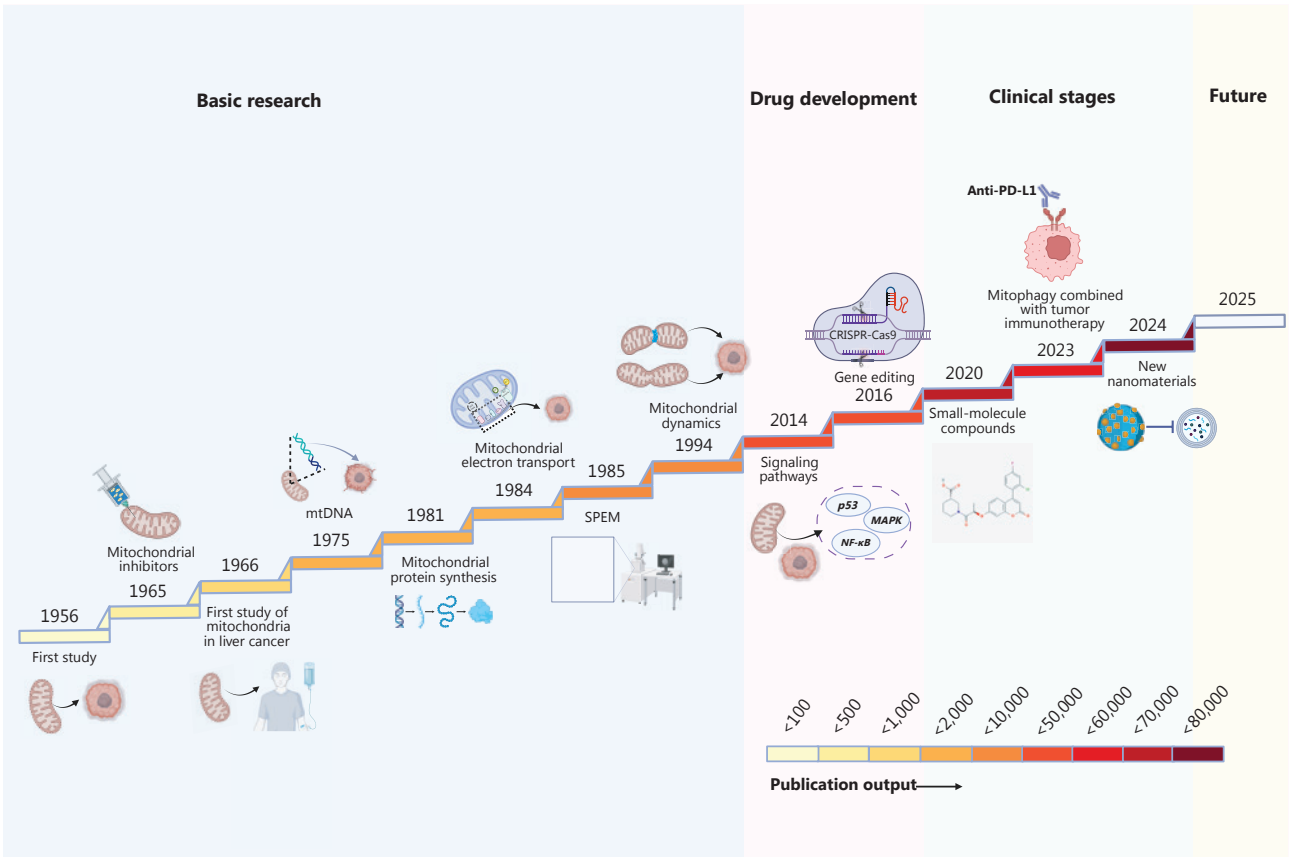



**Figure 1** Mitochondrial dysfunction with the critical node timeline of tumors. The picture describes the timeline of mitochondrial dysfunction and tumor over the years, which is divided into four parts (basic research, drug development, clinical stage, and future). Darker colors represent more published literature. The period between 1956 and 1994 is known as the basic research phase. The first paper suggesting that targeting mitochondrial dysfunction could intervene in cancer was published in 1956. Mitochondrial inhibitors were introduced in 1965. Studies showed that regulating mitochondrial function could inhibit liver cancer in 1966. Researchers discovered the importance of mitochondrial DNA in 1975. The significance of mitochondrial protein synthesis was identified in 1981. The crucial role of mitochondrial electron transfer was discovered in 1984. Research involving scanning and transmission electron microscopy began in 1985. Studies on mitochondrial dynamics were initiated in 1994. The period between 2014 and 2019 is referred to as the drug development phase. For example, research focused on MAPK and the NF-κB pathways related to tumors in 2014. Gene editing technology was explored in 2016. The clinical phase began with small-molecule drugs entering clinical use in 2020, the rise of immunotherapy occurred in 2023, and new particles were applied in 2024. Clearly, with the advances in science and technology and the continuous development of modern medicine, research into mitochondrial structure and mechanisms has deepened and new drugs and delivery methods have been continuously improved, providing a foundation for researchers to understand tumor intervention measures.

Core keywords, such as "mitochondria", "liver cancer", "targeted therapy", and "intervention" were used combined with extended terms, like "mitophagy" and "nanoparticle drug delivery systems". Logical operators (e.g., AND) were used to construct search queries. We focused on publications from the past decade (2015–2025) to ensure timeliness. Priority was given to reviews, research articles, and clinical trial reports, while incomplete documents, such as conference abstracts, were excluded.

The retrieved literature themes are directly related to the mechanisms underlying mitochondrial action in liver cancer or mitochondrial-targeted intervention strategies, covering basic research, clinical studies, and reviews. Priority was given to peer-reviewed articles from high-impact journals but limited to Chinese and English languages. Studies with themes deviating from the focus (e.g., involving mitochondrial research in other diseases), low-quality literature with incomplete data or poor methodology, repetitive

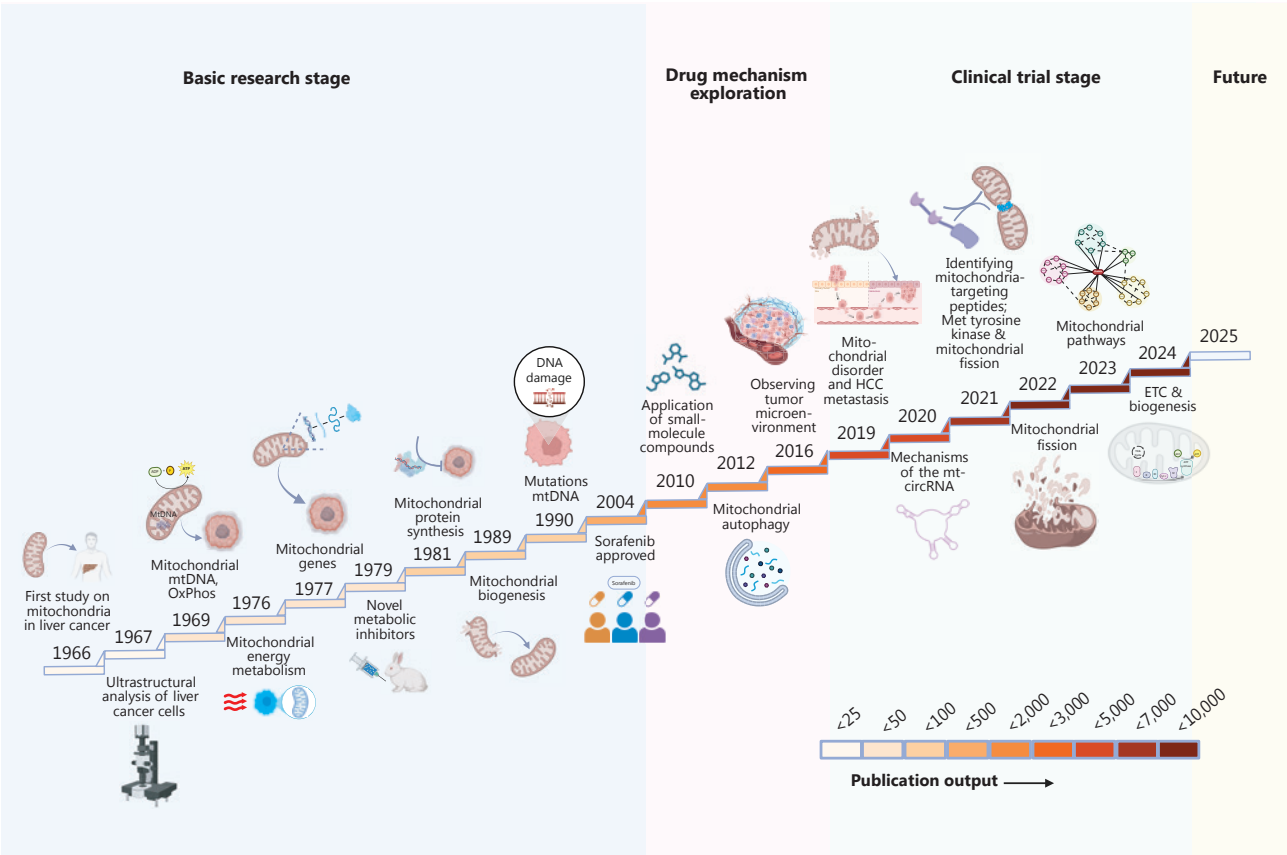



**Figure 2** Key nodal timeline of mitochondrial dysfunction and liver cancer. The picture describes the timeline of mitochondrial dysfunction and liver cancer over the years, which is divided into four parts (basic research, drug development, clinical stage, and future) in the lower right corner. Darker colors indicate more published literature. The period between 1966 and 2004 is termed the basic research stage. Targeting mitochondrial dysfunction was first shown to improve liver cancer in 1966. The application of electron microscopy enabled researchers to observe the ultrastructure of liver tumors in 1967. Mechanisms, such as mitochondrial DNA and oxidative phosphorylation, were studied in 1969. Energy metabolism of mitochondria was investigated in 1976. Gene therapy related to mitochondria was researched in 1977. New mitochondrial inhibitors were developed in 1979. Studies focused on mitochondrial protein synthesis and biosynthesis were conducted from 1981 to 1989. Mitochondrial DNA mutations were explored in 1990. Sorafenib, a first-line drug for liver cancer, was developed in 2004. The period between 2010 and 2016 is known as the mechanism exploration stage for anti-liver cancer drugs. Small-molecule compound drugs were developed in 2010. Mitophagy was studied in 2012. The tumor microenvironment was observed in 2016. The period from 2019 to 2024 is referred to as the clinical translation stage. Research first revealed the relationship between mitochondrial dysfunction and liver cancer metastasis in 2019. A new mechanism by which mitochondrial circular RNAs regulate liver immunometabolic inflammation was identified in 2020. Mitochondrial targeting peptides and the relationship between Met tyrosine kinase and mitochondrial fission were studied in 2021. Mitochondrial fission was investigated in 2022. The research mainly focused on the mechanisms of mitochondrial-related pathways and genes in liver cancer in 2023. Mitochondrial electron transport chains and biosynthesis were studied in 2024.

research, and outdated findings that have been superseded were excluded.

This strategy ensured the scientific rigor, comprehensiveness, and up-to-date nature of the review by screening from multiple dimensions, balancing the breadth and depth of the literature. The strategy provides a reliable basis for analyzing the mechanisms and applications of mitochondrial-targeted therapies.

# Mitochondrial structure and function

## Mitochondrial structure

Mitochondria are important organelles within cells that are characterized by a complex structure. The outer mitochondrial

membrane, which covers the surface, contains numerous porins that allow the passage of small molecules. The inner membrane is folded into cristae, effectively increasing the membrane surface area and providing space for the electron transport chain (ETC) for OXPHOS and ATP synthase. The mitochondrial matrix contains a variety of enzymes, proteins, mitochondrial DNA (mtDNA), and other components involved in metabolic processes.

Mitochondria serve as the cell power source and is primarily responsible for generating ATP through the process of OXPHOS, thereby supplying energy to the cell[10]. Additionally, mitochondria are involved in a multitude of metabolic processes, including lipid metabolism, $Ca^{2+}$ regulation, and amino acid metabolism[11].

The key aspects of mitochondrial energy metabolism include the tricarboxylic acid cycle [TCA cycle (also known as the citric acid cycle)], OXPHOS, lipid β-oxidation, and pyruvate oxidative decarboxylation. The TCA cycle involves the conversion of acetyl-CoA into carbon dioxide and energy carriers, such as NADH and $FADH_2$, by enzymatic catalysis. Subsequently, these energy carriers enter the ETC[12]. The ETC consists of a series of protein complexes (complexes I–IV). These complexes facilitate a series of redox reactions that transfer electrons from NADH and $FADH_2$ to oxygen during OXPHOS, ultimately reducing oxygen to water[13]. The formation of the proton-motive force (PMF) is a critical step in OXPHOS. Protons ($H^+$) are pumped from the mitochondrial matrix into the intermembrane space, generating the PMF, which in turn provides the energy required for ATP synthase to catalyze ATP production. During this process, the establishment of the PMF is a pivotal step in OXPHOS. $H^+$ are translocated from the mitochondrial matrix to the intermembrane space, resulting in generation of the PMF. This PMF drives the conversion of adenosine diphosphate (ADP) and inorganic phosphate (Pi) into ATP by ATP synthase[14]. The β-oxidation of lipids is a key process in fatty acid metabolism. Fatty acids first combine with ATP and CoA in the cytoplasm to form acyl-CoA, which then enters the mitochondria. On the inner mitochondrial membrane, the acyl group is transferred to carnitine (a key substance for fatty acids to enter the mitochondria) in a reaction catalyzed by carnitine-acyltransferase I, forming acylcarnitine. Acylcarnitine then enters the mitochondrial matrix through a transferase and the acyl group is re-transferred to CoA in a reaction catalyzed by carnitine-acyltransferase II to generate acyl-CoA. Energy is produced through the β-oxidation cycle of "dehydrogenation-hydration-dehydrogenation-thiolysis" in the mitochondrial matrix.

Mitochondrial bioenergetics also involve various regulatory mechanisms, such as fusion and fission, which influence cellular energy metabolism by altering mitochondrial mass[15]. Furthermore, multiple signaling molecules, such as AMP-activated protein kinase (AMPK) and mechanistic target of rapamycin (mTOR), regulate mitochondrial function to maintain normal cellular growth[16].

## Cell cycle and cell death

Mitochondria have a pivotal role in cell cycle progression and cell death. Regulation of the cell cycle is intimately connected to mitochondrial functionality, which influences cell cycle' advancement by modulating energy metabolism and the redox balance[17]. Mitochondria are pivotal organelles in the processes of programmed cell death and necrosis. For example, changes in mitochondrial outer membrane permeabilization (MOMP) are crucial steps in initiating apoptosis. Activation of BAX and BAK proteins leads to the release of Cyt c from mitochondria, which subsequently triggers activation of the caspase cascade[18]. Furthermore, in the context of necroptosis, activation of RIP3 and MLKL proteins leads to mitochondrial dysfunction[19]. Mitochondrial dynamics influence the susceptibility of cells to apoptosis and necrosis[20]. These studies have elucidated various mechanisms involving mitochondria within cells, thereby providing a foundation for understanding cellular processes in pathologic conditions.

## Multidimensional regulation of mitochondrial function

As the core hub of cellular energy metabolism, mitochondrial function is precisely coordinated through multidimensional mechanisms to maintain cellular homeostasis and regulate pathologic processes. At the energy metabolism level mitochondria convert nutrients into ATP *via* OXPHOS. ETC complexes I–IV drive proton transmembrane pumping to form the membrane potential ($\Delta\Psi m$). HCC cells often shift to glycolytic energy supply by activating the Warburg effect, accompanied by reduced activity of the mitochondrial oxidative respiratory chain[21]. ROS, as byproducts of energy metabolism (primarily from electron leakage in complexes I and III), also serve as key signaling molecules. Low-level ROS activate hypoxia-inducible factor 1-alpha (HIF-1α) and nuclear factor kappa B (NF-κB) to promote proliferation, while excessive ROS damage mtDNA and induce apoptosis or ferroptosis. The

antioxidant system [e.g., manganese superoxide dismutase (SOD2) and glutathione (GSH)] maintains balance by scavenging ROS[22]. Mitophagy, a core quality control mechanism, selectively degrades damaged mitochondria *via* the PINK1/Parkin pathway. Autophagy inhibits carcinogenesis by reducing ROS damage in early-stage cancer. Autophagy is hijacked as a survival strategy in advanced HCC, degrading mitochondria for energy supply and promoting drug resistance[23].

The dynamic balance between fission and fusion regulates mitochondrial morphology and function. For example, the fission protein, dynamin-related protein 1 (DRP1), mediates mitochondrial fragmentation to adapt to metabolic demands (e.g., the glycolytic shift in tumor cells), while fusion proteins [mitofusin (MFN)1/2 and optic atrophy 1 (OPA1)] maintain mitochondrial network connectivity to ensure OXPHOS efficiency. Imbalance can lead to mitochondrial swelling or functional heterogeneity[24]. $Ca^{2+}$ signaling regulates metabolism and apoptosis *via* the mitochondrial calcium uniporter (MCU). Physiologic $Ca^{2+}$ concentrations activate TCA cycle enzymatic reactions, whereas overload triggers the opening of mitochondrial permeability transition pores (mPTPs), inducing Cyt c release and apoptotic cascades[25]. Genetic mutations further exacerbate mitochondrial dysfunction. The high mutation rate of mtDNA (lacking histone protection) leads to abnormal ETC complex function (e.g., decreased complex I activity). Nuclear gene mutations, such as peroxisome proliferator-activated receptor gamma coactivator (PGC-1α) (regulating mitochondrial biogenesis) or isocitrate dehydrogenase (IDH)1/2 [affecting accumulation of the metabolite, 2-hydroxyglutarate (HG)], drive tumor progression through epigenetic or metabolic reprogramming[26].

Overall, mitochondria form a complex regulatory network through the interplay of energy metabolism, ROS regulation, autophagy–dynamic balance, $Ca^{2+}$ signaling, and genetic variations. Mitochondrial dysfunction serves as a stress-adaptive mechanism and a key therapeutic target in diseases, like HCC.

# Concept and classification of liver cancer

## The concept of liver cancer

HCC is a highly malignant tumor of hepatocellular origin and is one of the most common cancers worldwide with a very high incidence, especially in Asia and Africa[27]. Many chronic liver diseases, such as hepatitis and cirrhosis, are closely related to the onset of HCC. Due to the high recurrence and metastasis rates of tumors with a poor prognosis, the 5-year survival rate is low[28].

HCC cells have significant manifestations of metabolic reprogramming, in which mitochondria have a key role. Mitochondria are not only the cellular motility source but are also involved in regulation of apoptosis, oxidative stress, and calcium homeostasis[29]. Mitochondrial dysfunction leads to abnormal metabolic pathways in HCC, such as the Warburg effect, which promotes tumor cell proliferation, invasion, and metastasis[27]. Therefore, targeting mitochondrial dysfunction provides a novel strategy for the treatment of HCC (**Figure 3**).

## Classification of liver cancer

There are many classification methods for liver cancer. HCC can be divided into HCC, cholangiocarcinoma (CC), and mixed cancer (cHCC-CC) based on histologic features. The most common type of primary liver cancer is HCC, which accounts for 75%–85% of all liver cancers[30]. HCC usually develops in the context of chronic liver disease or cirrhosis, in which the hepatocyte of origin is HCC. CC originates from the bile duct epithelial cells, which accounts for 10%–15% of primary liver cancer. CHCC-CC is a rare liver cancer with dual features of HCC and CC[27].

HCC is classified into proliferative and non-proliferative types based on the gene expression profile and mutational characteristics. The proliferation class is characterized by high cell proliferation activity and is usually associated with *TP53* mutations and activation of the Wnt/β-catenin signaling pathway. The non-proliferative class is usually associated with *CTNNB1* mutations and altered expression of metabolism-related genes exhibiting lower cell proliferative activity[31].

Mitochondrial function is also different in liver cancer subtypes. For example, the proliferative liver cancer subtype may be more dependent on glycolysis (Warburg effect), while the non-proliferative subtype may be more dependent on mitochondrial OXPHOS[32]. Therefore, personalized mitochondria-targeted therapeutic strategies are needed for different HCC subtypes.

## Clinical staging of liver cancer

Two clinical staging systems [TNM staging system and Barcelona clinical liver cancer (BCLC)], are mainly used. The TNM staging system classifies liver cancer according to tumor size (T), degree of lymph node involvement (N), and distant

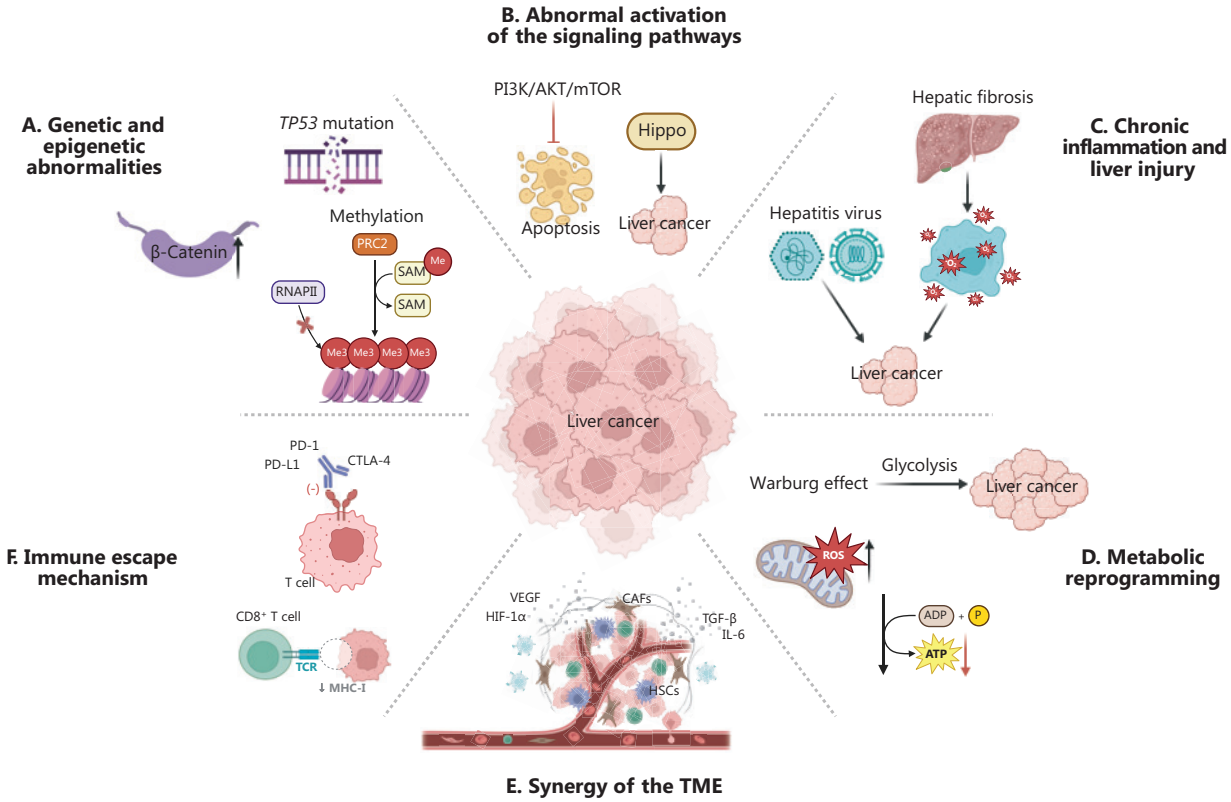



**Figure 3** The pathogenesis of liver cancer. The pathologic mechanisms of liver cancer mainly include the following six parts: (A) Genetic and epigenetic abnormalities mainly include changes, such as *TP53* mutations, β-catenin up-regulation, and methylation (e.g., regarding the molecular mechanism related to histone methylation modification and gene transcription regulation, the process by which Me3 mediated by PRC2 inhibits the transcription initiation of RNAPII). These changes drive the occurrence of liver cancer by influencing gene expression. (B) Abnormal activation of the signaling pathways, such as the PI3K/AKT/mTOR pathway, inhibits tumor cell autophagy and the abnormal Hippo signaling pathway, both of which promote the formation of liver cancer. (C) Chronic liver injury and inflammatory states, such as hepatitis virus infection and hepatic fibrosis, increase the oxidative stress of hepatocytes and ultimately lead to liver cancer. (D) Metabolic reprogramming, such as the Warburg effect, emphasize how glycolysis, mitochondrial oxidative stress, and electron transport chain abnormalities promote the development of liver cancer. (E) Synergy of the TME, including inflammatory factors, such as IL-6 and TNF-α, and growth factors, such as VEGF, regulate angiogenesis and the interaction of immune cells, thus aggravating liver cancer. (F) The immune escape mechanism, such as the immune checkpoint inhibitor, PD-L1, has a crucial role in this process. CAFs, cancer-associated fibroblasts; HSCs, hepatic stellate cells; Me3, histone H3 lysine 27 methylation; PRC2, polycomb repressive complex 2; RNAPII, RNA polymerase II; TME, tumor microenvironment.

metastasis (M), which is a common clinical staging method. In contrast, the BCLC staging system divides liver cancer from stage 0 (very early) to D stage (late) combined with the tumor characteristics, liver function status, and overall patient status. This system provides the basis for treatment decisions.

## Etiology of liver cancer

Chronic viral hepatitis, liver cirrhosis, alcoholic liver disease, and non-alcoholic fatty liver disease (NAFLD) are the main causes of liver cancer. Hepatitis A virus (HAV), hepatitis B virus (HBV), excessive alcohol consumption, cigarette smoking, obesity, aflatoxin exposure, diabetes, and genetic factors can also lead to liver cancer.

In modern society increased stress and unhealthy lifestyle habits, such as cigarette smoking, alcohol consumption, and poor diet, have further elevated the risk of liver disease[33]. A healthy lifestyle, such as a balanced diet and regular sleep patterns, is the common challenge that society needs to face. Mitochondrial dysfunction has an important role in the

development of liver cancer. For example, infections with HBV and hepatitis C virus (HCV) can cause mtDNA damage and functional disorders[34]. Alcohol metabolites can directly affect the mitochondrial membrane potential and respiratory chain function[35]. NAFLD-related liver cancer is often accompanied by mitochondrial fatty acid oxidation (FAO) disorders[36].

## Diagnosis and treatment of liver cancer

Currently, the diagnosis of liver cancer mainly involves imaging examinations (ultrasound, CT, and MRI), serum biomarkers [alpha-fetoprotein (AFP) and des-gamma-carboxy prothrombin (DCP)], and histologic features. Metabolites and gene expression profiles related to mitochondrial dysfunction may emerge as novel biomarkers for liver cancer diagnosis with increasing research on mitochondrial dysfunction. For example, some mitochondrial metabolic intermediates, such as succinate and fumarate, are significantly elevated in the serum of liver cancer patients and could serve as potential diagnostic biomarkers[27]. In addition, imaging techniques based on mitochondrial functional abnormalities, such as metabolic imaging, also hold promise for improving the diagnostic accuracy of liver cancer[37].

The traditional treatment methods for liver cancer mainly include surgical therapy (liver transplantation and hepatectomy), local therapy [radiofrequency, microwave ablation, and transarterial chemoembolization (TACE)], and systemic therapy (sorafenib, lenvatinib, and PD-1/PD-L1 inhibitors). However existing treatment methods have not fully focused on the impact of mitochondrial function on liver cancer and have not received sufficient attention[27]. For example, TACE may lead to increased mitochondrial oxidative stress in tumor cells, thereby inducing drug resistance. Targeted therapeutic agents may exert anti-tumor effects by influencing mitochondrial metabolic pathways[38]. Therefore, combining mitochondrial targeting strategies with existing therapies is expected to improve therapeutic efficacy and overcome drug resistance.

In addition, the degree and type of mitochondrial dysfunction may impact the prognosis of liver cancer. For example, the extent of mitochondrial metabolic reprogramming may be associated with the aggressiveness and metastatic potential of the tumor[39]. The activation status of the mitochondrial-dependent apoptotic pathway may influence tumor sensitivity to treatment[40]. Therefore, assessing mitochondrial functional status is expected to be a new indicator to predict HCC prognosis and guide individualized treatment.

## Future directions for liver cancer research

Future research should focus on precision medicine, novel therapeutic strategies, and translational research with the goal of achieving personalized treatment and long-term survival for patients with liver cancer. Precision medicine is a type of multi-omics research based on genomics, transcriptomics, and metabolomics and can provide a basis for precise classification and treatment of liver cancer. Precision medicine can combine the molecular characteristics of different liver cancer subtypes and the functional status of mitochondria and develop a personalized treatment plan for patients[41]. Second, new mitochondrial targeted drugs can be developed, such as mitochondrial reactive oxygen inhibitors, and agents targeting mitochondrial dynamics. Third, mitochondrial targeted therapy can be combined with the existing treatment methods to improve the efficacy of liver cancer treatment[42].

In addition, translational studies should be conducted to establish preclinical liver cancer models closer to clinical practice, such as patient-derived xenograft (PDX) models and large-scale clinical trials should be conducted to evaluate the safety and efficacy of mitochondrial-targeted therapy[43].

Because mitochondria have an important role in hepatocytes, mitochondria are currently a hot topic of interest among scholars that are expected to occupy a more important position in future research involving liver cancer and make breakthrough progress in the treatment of liver cancer.

HCC is a highly heterogeneous malignancy, the occurrence and progression of which are closely related to mitochondrial dysfunction. By gaining a comprehensive understanding of the concepts, classification, etiology, diagnosis, treatment, and prognosis of liver cancer, we can better recognize the role of mitochondrial dysfunction in liver cancer. This knowledge also provides a theoretical basis for developing novel targeted therapeutic strategies.

# Association between liver cancer and mitochondrial dysfunction

## Mitochondrial metabolic reprogramming and redox imbalance

Mitochondrial dysfunction drives tumor progression in HCC through a synergistic mechanism of metabolic network rewiring and redox homeostasis imbalance, specifically manifested as energy metabolic pattern switching,

abnormal membrane potential, and disordered ROS regulatory networks.

Mitochondrial oxidative respiratory chain ETC dysfunction serves as the starting point of metabolic reprogramming in HCC. The activity of respiratory chain complexes I (NADH dehydrogenase) and III (cytochrome bc1 complex) is significantly reduced in HCC cells, leading to decreased electron transport efficiency and reduced ATP production[44]. To compensate for energy crisis, tumor cells shift to glycolytic dependence (Warburg effect), which not only rapidly generates ATP through glucose metabolism but also provides precursors for the biosynthesis of nucleotides, lipids, amino acids, and biogenic amines to maintain the malignant proliferative phenotype[45]. This metabolic switch is accompanied by abnormal ΔΨm. Indeed, ΔΨm is driven by proton gradients and participates in ATP synthesis and apoptosis regulation in normal cells, whereas ΔΨm is often abnormally elevated in HCC cells. This elevation blocks mPTP opening, inhibits Cyt c release, and suppresses mitochondria-dependent apoptosis[46]. High ΔΨm further enhances the survival advantage of tumor cells by disrupting calcium homeostasis and metabolite transport (e.g., ADP/ATP exchange; **Figure 4**). Mitochondria serve as the main source of ROS (accounting for ~80% of total intracellular ROS) with ETC complexes I and III being the primary sites for superoxide anion ($O_2^-$) generation. Specifically, ~1%–2% of electrons leaking from the ETC combine with oxygen to form $O_2^-$, which is then converted to hydrogen peroxide ($H_2O_2$) by superoxide dismutase (SOD1/SOD2), and finally scavenged by catalase (CAT) and glutathione peroxidase (GPX)[47]. This balance is disrupted in HCC. For example, in chronic liver diseases (e.g., hepatitis and fatty liver), pathogen infections, lipid accumulation, or metabolic disorders, the mitochondrial ETC is activated to overproduce ROS. In addition, mPTP opening causes calcium overload, further stimulating mitochondrial ROS generation[48]. HCC cells exhibit downregulated SOD2 expression and reduced GPX4 activity, leading to impaired $H_2O_2$ scavenging and formation of an oxidative stress microenvironment (**Figure 4**). Excessive ROS drives HCC progression through multiple mechanisms, as follows: ① direct damage to mtDNA and respiratory chain proteins, exacerbating metabolic dysfunction; ② activation of NF-κB and HIF-1α signaling pathways, inducing proinflammatory cytokines (e.g., IL-6) and vascular endothelial growth factor (VEGF) to promote tumor invasion and angiogenesis[45]; and ③ modification of cell membranes *via* lipid peroxidation, enhancing cell motility and inducing ferroptosis resistance. Notably, low-level ROS acts as a signaling molecule to promote tumor cell adaptation to metabolic stress, while high-intensity oxidative stress drives carcinogenesis by damaging genomic stability, reflecting the "dose-effect biphasicity" of ROS. Current therapeutic strategies focus on the cross-network of metabolic reprogramming and redox imbalance, as follows: In ETC-targeted intervention, complex I inhibitors (rotenone and 3-NPA) block the ETC, depleting ATP and inducing explosive ROS generation, demonstrating single-agent antitumor activity in HCC animal models[49]. In membrane potential and mPTP regulation cyclosporine A (CsA) inhibits mPTP opening to alleviate oxidative stress damage, though balancing the immunosuppressive side effects is necessary[50]. Dual strategies of anti-oxidation and pro-oxidation involve antioxidants, like vitamin E, which reduce oxidative damage in chronic liver diseases to delay carcinogenesis. Ferroptosis inducers targeting GPX4 (e.g., RSL3) deplete GSH to amplify mitochondrial ROS and induce tumor cell death[51]. Emerging technologies, such as mitochondria-targeted nanomedicines (e.g., doxorubicin-loaded triphenylphosphine-conjugated liposomes), enhance drug enrichment in tumor mitochondria, while reducing toxicity to normal tissues. Future research should further dissect key nodes in the metabolism-oxidative stress network (e.g., the SOD2/mPTP/HIF-1α axis) and screen personalized therapeutic markers *via* multi-omics technologies to accelerate the translation of mechanistic research to clinical applications.

Innovative therapies targeting these links are expected to break through the current therapeutic bottlenecks. In the future it will be necessary to deepen mechanistic research and accelerate clinical translation.

## Apoptosis and autophagy

Mitochondria-mediated apoptosis is a "double-edged sword" for HCC cell fate. Mitochondria have a significant role in the apoptotic pathway. Mitochondria dysfunction, such as increased MOMP, can lead to the release of Cyt c into the cytosol. Cyt c binds to apoptotic protease-activating factor 1 (Apaf-1) to form the apoptosome, which activates caspase-9 and downstream effector caspases-3/7, ultimately triggering programmed cell death[40]. In addition to the classic apoptotic pathway, mitochondria also release pro-apoptotic factors, such as SMAC/DIABLO, to antagonize apoptosis inhibitors, thereby reinforcing apoptotic signals. This is a canonical mechanism of mitochondrial apoptosis.

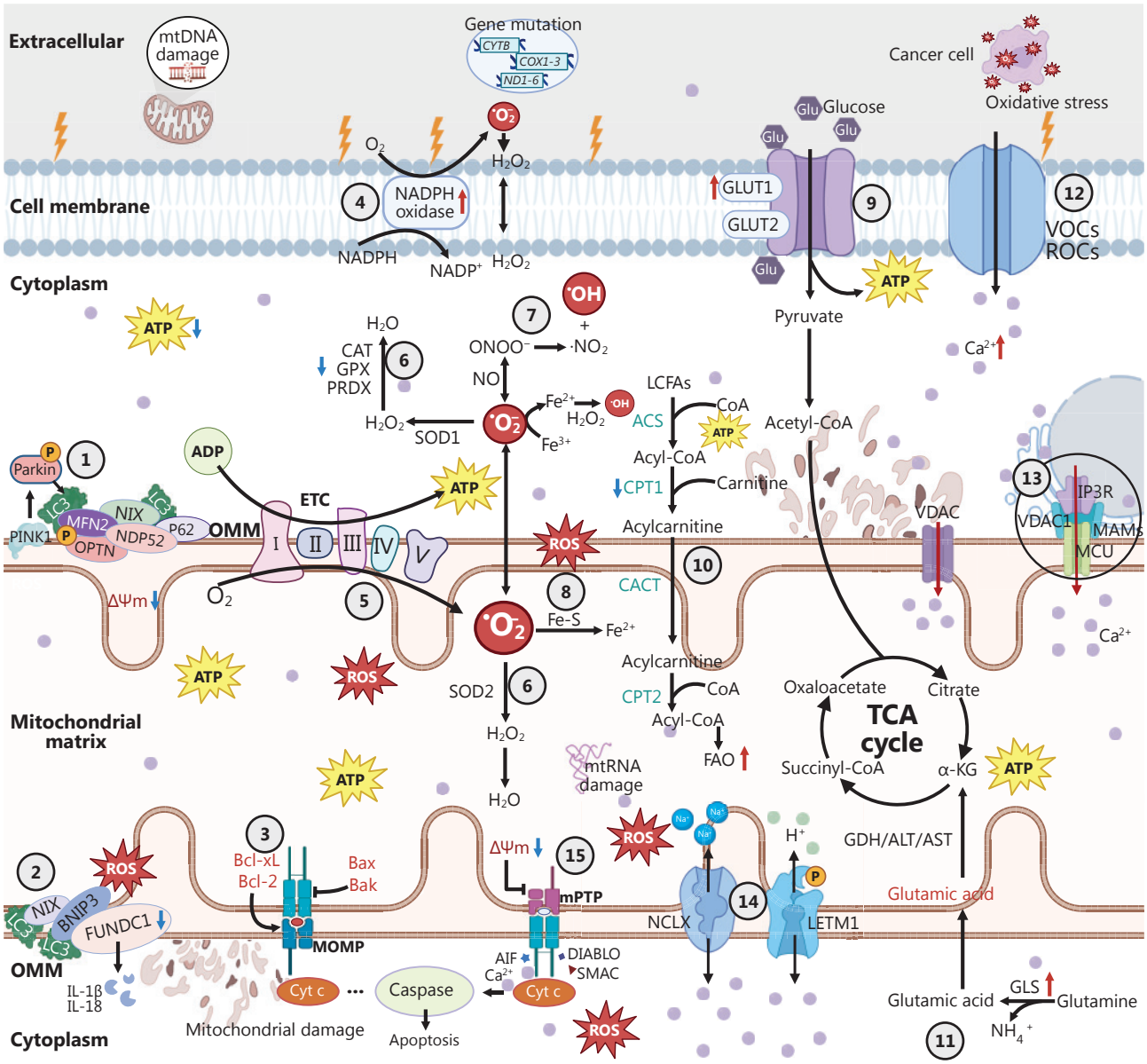



**Figure 4** The pathologic mechanism underlying mitochondrial dysfunction in hepatocellular carcinoma cells. This figure illustrates four parallel mechanisms (A–D), where each sub-step is numbered (1–15) to correspond to the signaling events and processes in the diagram. (A) Abnormal mitophagy and mitochondrial outer membrane permeability involves steps 1–3, as follows: 1. Ubiquitin-dependent mitophagy (PINK1/Parkin pathway). When mitochondrial function is impaired (e.g., loss of membrane potential), PINK1 accumulates on the OMM and undergoes autophosphorylation, thereby activating Parkin. Activated Parkin mediates ubiquitination of OMM proteins, such as MFN2 and NIX. The ubiquitinated mitochondria are then recognized by autophagic adaptor proteins (P62, NDP52, and OPTN), which bind to ubiquitin chains *via* ubiquitin-binding domains and interact with LC3 to promote autophagosome formation and encapsulation. Finally, the encapsulated mitochondria fuse with lysosomes to complete degradation. 2. Ubiquitin-independent mitophagy (BNIP3/NIX and FUNDC1 pathways). Under hypoxia or ROS stress, the OMM proteins (BNIP3 and NIX) directly interact with LC3 to induce mitophagy, cooperating with the PINK1/Parkin pathway to maintain mitochondrial quality. Loss of FUNDC1 leads to the accumulation of damaged mitochondria, activates inflammasomes, and triggers the release of pro-inflammatory cytokines (e.g., IL-1β and IL-18), exacerbating the hepatic inflammatory microenvironment. 3. Abnormal MOMP. In hepatocellular carcinoma cells, there is an imbalance between pro- and anti-apoptotic protein systems. Specifically, anti-apoptotic proteins, such as Bcl-2 and Bcl-xL, are highly expressed due to gene amplification and transcriptional upregulation, while pro-apoptotic proteins, such as Bax and Bak, lose function due to promoter methylation or accelerated degradation. This process leads to a "closing tendency" of MOMP, making MOMP difficult to open normally to initiate apoptosis. Cytochrome c in the mitochondrial

intermembrane space can still be released through non-classical pores mediated by Bax/Bak, activating the caspase cascade. However, hepatocellular carcinoma cells inhibit this process by upregulating anti-apoptotic mechanisms. Meanwhile, impaired MOMP results in the loss of $\Delta\Psi m$, which further reduces ATP synthesis and promotes ROS accumulation, forming a vicious cycle. (B) Cascade amplification of mitochondrial oxidative stress involves steps 4–8, as follows: 4. Activation of NADPH oxidase. The NADPH oxidase complex is activated by oncogenic signals in hepatocellular carcinoma cells. The NADPH oxidase complex uses cytoplasmic NADPH as an electron donor to catalyze the generation of $O_2^-$ from $O_2$. In addition, NADPH is converted into $NADP^+$ and $H^+$. $O_2^-$ is further converted into $H_2O_2$, which diffuses into the cytoplasm and initiates oxidative stress. 5. ROS generation mediated by the respiratory chain. $O_2^-$ is one of the major ROS in mitochondrial oxidative stress. Mutations in mitochondrial DNA (mtDNA) or functional defects in respiratory chain complexes (I and III) lead to electron leakage, which combines with $O_2$ to form $O_2^-$. A decrease in $\Delta\Psi m$ exacerbates electron transport blockage, further promoting ROS production, accompanied by a reduction in ATP synthesis. 6. Inactivation of antioxidant systems. The enzymatic antioxidant system is the main way to scavenge ROS in cells. Cytoplasmic SOD1 and mitochondrial matrix SOD2 convert $O_2^-$ into $H_2O_2$ in normal hepatocytes, which is then degraded into non-toxic water by CAT, GPX, and PRDX. However, the above antioxidant enzymes are downregulated due to epigenetic silencing or accelerated degradation in hepatocellular carcinoma cells, leading to ROS accumulation. 7. Vicious cycle of $ONOO^-$. Excessive $O_2^-$ reacts rapidly with NO to generate $ONOO^-$, driving the excessive accumulation of $ONOO^-$. As a highly oxidizing RNS, excessive $ONOO^-$ exacerbates mitochondrial dysfunction through oxidative and nitrosative modifications of key mitochondrial molecules, such as irreversible damage to respiratory chain complexes, destruction of mitochondrial membrane structure, and damage to mtDNA. 8. Fe-S damage. $O_2^-$ and other ROS directly oxidize iron-sulfur clusters, leading to the release of $Fe^{2+}$. Free $Fe^{2+}$ reacts with $H_2O_2$ *via* the Fenton reaction ($Fe^{2+} + H_2O_2 \rightarrow \bullet OH + OH^-$) to generate highly reactive •OH, which further damage Fe-S clusters and mitochondrial structures. This process establishes a self-perpetuating cycle ("ROS accumulation → Fe-S cluster damage → $Fe^{2+}$ release → more ROS generation"). (C) Adaptive changes in mitochondrial metabolic reprogramming involve steps 9–11, as follows: 9. Enhanced glucose transport. Glucose transport relies on the GLUTs family, with GLUT1 and GLUT2 being the main transporters. In the context of mitochondrial dysfunction, the abnormal enhancement of glucose transport primarily depends on the high expression and increased membrane localization of GLUT1. This compensatory mechanism not only represents adaptation of the cell to mitochondrial energy production defects but also serves as the metabolic basis for maintaining malignant proliferation, invasion, and metastasis. 10. Hyperactive FAO. LCFAs are activated in the cytoplasm by ACS to form acyl-CoA. Through the carnitine shuttle system (CPT1 catalyzes the combination of acyl-CoA and carnitine to generate acylcarnitine → CACT mediates trans-inner membrane transport → CPT2 regenerates acyl-CoA), acyl-CoA enters the mitochondrial matrix. Acyl-CoQ is then degraded *via* FAO to acetyl-CoA, which supplements the TCA cycle for energy supply. Hepatocellular carcinoma cells exhibit high expression of CPT1/2 and CACT, enhancing FAO to adapt to hypoxic environments. 11. Glutamine metabolic compensation. Cytoplasmic glutamine is converted to glutamic acid by GLS (which is highly expressed in hepatocellular carcinoma). Glutamic acid then enters mitochondria and is converted to α-KG *via* GDH or ALT/AST, replenishing the TCA cycle and further promoting glutamine metabolism. In addition, $NH_4^+$ generated from glutamine metabolism participate in nucleotide synthesis. (D) Calcium homeostasis imbalance and abnormal apoptosis regulation involve steps 12–15, as follows: 12. Enhanced cytoplasmic calcium influx. Abnormal activation of exogenous VOCs and endogenous ROCs leads to increased calcium ions entering the cytoplasm, which further enter the mitochondrial matrix through VADC channels. 13. Endoplasmic reticulum-mitochondria calcium transfer. MAMs form high-calcium microdomains. IP3R on the endoplasmic reticulum directly binds to VDAC1 on the outer mitochondrial membrane, efficiently transferring $Ca^{2+}$ to the mitochondrial intermembrane space, which is then transported to the matrix *via* MCU on the inner membrane. This process is enhanced in hepatocellular carcinoma cells due to abnormal MAMs structure. 14. Dysfunction of calcium exchangers. NCLX (sodium-calcium exchanger) on the inner mitochondrial membrane relies on the $Na^+$ gradient to efflux $Ca^{2+}$ from the matrix, while LETM1 (calcium-hydrogen exchanger) assists in $Ca^{2+}$ efflux depending on the proton gradient. However, the $Na^+$ gradient (due to $Na^+$-$K^+$-ATPase inhibition) and proton gradient (due to respiratory chain defects) are disrupted in hepatocellular carcinoma cells, resulting in impaired $Ca^{2+}$ efflux and matrix calcium overload. 15. MPTP opening and apoptotic escape. Matrix calcium overload and ROS accumulation jointly activate the mPTP, leading to loss of $\Delta\Psi m$, mitochondrial swelling, and release of apoptotic factors, such as cytochrome c, AIF, and SMAC/DIABLO. These factors activate the caspase cascade in normal cells, but hepatocellular carcinoma cells inhibit this process by overexpressing Bcl-2/Bcl-xL and simultaneously activate the NF-κB pathway to promote survival, achieving apoptotic escape. In conclusion, mitochondrial dysfunction in hepatocellular carcinoma cells induces ROS accumulation, ATP deficiency, and loss of $\Delta\Psi m$ through four major mechanisms (abnormal autophagy, oxidative stress, metabolic reprogramming, and calcium homeostasis imbalance). These changes further activate pathways, such as HIF-1α (which promotes angiogenesis) and NF-κB (which triggers the release of inflammatory factors). In addition, by inhibiting caspase activity and enhancing anti-apoptotic signals, the pathways ultimately facilitate tumor proliferation, invasion, and drug resistance. It can be concluded that the oxidative stress of the patient with liver cancer increases, the electron transport chain decreases, and some membrane potential changes will increase Cytochrome c and calcium ions, which will make the mitochondria lose normal function and aggravate the course of liver cancer. α-KG, α-ketoglutarate; ACS, acyl-CoA synthetase; AIF, apoptosis-inducing factor; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ATP, adenosine triphosphate; Bak, Bcl-2 antagonist/killer; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2; Bcl-xL, B-cell lymphoma-extra large; BNIP3, Bcl-2/adenovirus E1B 19 kDa protein-interacting protein 3; CACT, carnitine-acylcarnitine translocase; CAT, catalase; CPT1, carnitine palmitoyltransferase 1; CPT2, carnitine palmitoyltransferase 2; $\Delta\Psi m$, mitochondrial membrane potential;

FAO, fatty acid oxidation; $Fe^{2+}$, ferrous ion; Fe-S, iron-sulfur cluster; FUNDC1, FUN14 domain-containing protein 1; GDH, glutamate dehydrogenase; GLUT1, glucose transporter 1; GLUT2, glucose transporter 2; GLUTs, glucose transporters; GPX, glutathione peroxidase; GLS1, glutaminase 1; $H_2O_2$, hydrogen peroxide; HIF-1α, hypoxia-inducible factor 1α; •OH, hydroxyl radical; IL-1β, interleukin-1β; IL-18, interleukin-18; IP3R, inositol 1,4,5-trisphosphate receptor; LETM1, leucine zipper-EF-hand containing transmembrane protein 1; LCFAs, long-chain fatty acids; LC3, microtubule-associated protein 1 light chain 3; MAMs, mitochondria-associated endoplasmic reticulum membranes; MCU, mitochondrial calcium uniporter; MOMP, mitochondrial outer membrane permeabilization; mPTP, mitochondrial permeability transition pore; mtDNA, mitochondrial DNA; MFN2, mitofusin 2; Na+-K+-ATPase, sodium-potassium ATPase; NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB, nuclear factor-kappa B; $NH_4^+$, ammonium ion; NCLX, sodium-calcium exchanger; NDP52, nuclear dot protein 52 kDa; NO, nitric oxide; X, BNIP3-like protein; OMM, outer mitochondrial membrane; $ONOO^-$, peroxynitrite; OPTN, optineurin; $O_2^-$, superoxide anion; PINK1, PTEN-induced kinase 1; PRDX, peroxiredoxin; RNS, reactive nitrogen species; ROCs, receptor-operated calcium channels; ROS, reactive oxygen species; SOD1, superoxide dismutase 1; SOD2, superoxide dismutase 2; SMAC/DIABLO, second mitochondria-derived activator of caspases/direct IAP-binding protein with low pI; TCA, tricarboxylic acid cycle; VADC, voltage-dependent anion channel; VDAC1, voltage-dependent anion channel 1; VOCs, voltage-operated calcium channels.

HCC cells often thwart MOMP by upregulating the expression of anti-apoptotic Bcl-2 family members, such as Bcl-2, Bcl-xL, and MCL-1, or evade apoptosis by downregulating the expression of pro-apoptotic factors, including Bax, Bak, and Bim[52]. ΔΨm disruption and the exacerbation of reactive ROS accumulation further enhance resistance to apoptosis, which has become a key mechanism for chemoresistance in HCC[53]. BH3 mimetics, such as ABT-737 and navitoclax, induce MOMP by antagonizing anti-apoptotic members of the Bcl-2 family. Mitochondrial-targeted drugs, such as Mito-CP, selectively accumulate in mitochondria, directly triggering the release of Cyt c[40]. In addition, combining radiotherapy or chemotherapeutic agents (e.g., sorafenib) synergistically enhances mitochondrial apoptosis sensitivity[54].

Under physiologic conditions, mitophagy mediated by the PINK1/Parkin pathway maintains metabolic homeostasis by clearing damaged mitochondria and prevents genomic instability caused by excessive accumulation of ROS[55]. However, autophagy can be hijacked as a pro-survival mechanism in HCC. Specifically, the hypoxic microenvironment activates HIF-1α, which induces BNIP3/NIX-dependent mitophagy. This process clears dysfunctional mitochondria to maintain energy supply and supports the survival of tumor cells under stress conditions[56]. When mitochondrial damage exceeds the repair threshold, persistent activation of autophagy may promote the death of HCC cells through "autosis" or crosstalk with apoptotic signaling, such as the interaction between Beclin-1 and Bcl-2)[57]. For example, rapamycin analogs induce protective autophagy by inhibiting mTORC1, while combination with autophagy inhibitors, such as chloroquine, can block lysosomal degradation, leading to the accumulation of autophagosomes and triggering apoptosis[58].

Selective inhibition of pro-survival autophagy (e.g., targeting ULK1 or ATG5) can enhance chemosensitivity. Conversely, inducing excessive autophagy [e.g., using the mitochondrial uncoupler, carbonyl cyanide n-chlorophenylhydrazone (CCCP)] may overcome the tolerance threshold of HCC cells. The level of autophagy needs to be dynamically regulated in combination with tumor stage and microenvironmental characteristics[59]. Apoptosis-related proteins, such as caspases cleaving ATG proteins, can inhibit autophagy, while autophagy-related proteins, such as p62/SQSTM1, indirectly regulate apoptotic signaling by degrading ubiquitinated substrates[60]. Factors released by mitochondria, such as apoptosis-inducing factor, can participate in both apoptotic and non-apoptotic cell death programs. Combining apoptosis induction (e.g., using BCL-2 inhibitors) with autophagy modulation (e.g., using HDAC inhibitors) can overcome the limitations of single-pathway targeting[61]. For example, inhibition of protective autophagy by MCL-1 while blocking protective autophagy significantly enhanced cell death in sorafenib-resistant HCC[57].

In the future it will be necessary to focus on an analysis of spatial and temporal dynamic regulatory network, develop personalized mitochondrial targeted therapy based on patient stratification, and provide new dimensions for the treatment of liver cancer. For example, a highly specific mitochondrial-targeted delivery system was developed to reduce off-target toxicity[62]. Exploring biomarkers of mitochondrial pathway dynamics in HCC heterogeneity [e.g., mtDNA mutation and transcription factor A mitochondrial (TFAM) expression][63]. Deciphering the paracrine regulation of mitochondrial function by the TME (e.g., cancer-associated fibroblasts) expands potential targets for combination therapies[64].

## Genic mutation

mtDNA lacks histone protection, has a weak repair mechanism, and is exposed to a high ROS environment. As a result, the mutation rate is 10–100 times higher than nuclear DNA[65]. Common mutations in liver cancer include mutations in genes encoding subunits of the OXPHOS complexes, such as ND1-6, CYTB, and COX1-3, leading to dysfunction of the ETC[66,67]. Mutations in the D-loop region (a key area controlling mtDNA replication and transcription) can affect the copy number of mtDNA and mitochondrial biogenesis[68]. Mutations in genes within mtDNA that regulate mitochondrial function, such as *SDHB*, *IDH1/2*, fumarate hydratase (*FH*), and *TFAM*, can indirectly impair mitochondrial function through epigenetic modifications or metabolic reprogramming[69]. For example, mutations in IDH1/2 lead to an increase in 2-HG, which competitively inhibits α-ketoglutarate-dependent enzymes, such as ten-eleven translocation (TET) enzymes and histone demethylases. This inhibition disrupts epigenetic regulation and mitochondrial metabolism, contributing to the pathogenesis of cancers associated with IDH1/2 mutations[70]. Mutations in the subunits of the succinate dehydrogenase (SDH) complex, such as SDHB, lead to the accumulation of succinate, which inhibits prolyl hydroxylase. This inhibition stabilizes HIF-1α, thereby promoting glycolysis and angiogenesis[71].

Mutations in mtDNA lead to dysfunction of ETC complexes, such as complexes I and III, reducing ATP generation and forcing HCC cells to rely on the Warburg effect (aerobic glycolysis) for energy supply. At the same time, the NADH/NAD + ratio imbalance activates the SIRT 1/AMPK pathway, promotes FAO and glutamine hydrolysis, and maintains metabolic plasticity. Dysfunction of the ETC increases electron leakage, resulting in excessive production of ROS, such as $O_2^-$, which attack nuclear DNA and induce oncogenic mutations (e.g., *TP53* and *CTNNB1* mutations)[72]. In addition to the direct effects of mtDNA mutations on mitochondrial function, these mutations can also indirectly impact tumor immunity by activating the TLR9/STING pathway. Specifically, mtDNA mutations lead to the release of damage-associated molecular patterns (DAMPs), such as mtDNA fragments, which activate the TLR9/STING pathway. This activation creates a pro-inflammatory microenvironment that facilitates tumor immune evasion[73-75] Mitochondrial dysfunction triggers calcium signaling (e.g., *via* the MCU channel), metabolic reprogramming mediated by metabolites [e.g., acetyl-CoA and α-ketoglutarate (α-KG)], and ROS, leading to nuclear transcriptional reprogramming. Activation of the NF-κB/STAT3 pathway promotes cell proliferation and anti-apoptosis. Stabilization of HIF-1α enhances glycolysis and angiogenesis. Upregulation of the MYC/mTORC1 axis drives anabolic metabolism and protein translation[76].

Mutations in mtDNA lead to altered levels of TCA cycle intermediates, such as α-KG, succinate, and fumarate), which affect the activity of histone/DNA-modifying enzymes, such as histone deacetylases (HDACs) and TETs. This results in global DNA hypomethylation or local hypermethylation (e.g., silencing of tumor suppressor gene promoters)[74]. The specific mutational spectrum of liver cancer includes high-frequency mutation genes, as follows: the D-loop region of mtDNA (approximately 30%–50% of liver cancer patients); NADH dehydrogenase 5 (ND5); Cyt b; and nuclear genes, such as *IDH2* and *SDHB*[77]. The mutation burden and prognosis are as follows: mutations in the D-loop region of mtDNA are positively correlated with poor prognosis in HBV-related HCC. HCC with IDH1 mutations show a poor response to immune checkpoint blockade (ICB) therapy. The content and mutations of cell-free mtDNA (cf-mtDNA) in the plasma of HCC patients (e.g., ND1 G3460A) can assist in early diagnosis and therapeutic monitoring, outperforming traditional AFP[78].

Intervention strategies targeting mitochondrial gene mutations mainly include three approaches: targeting metabolic vulnerabilities; gene-editing technologies targeting mutated mtDNA; and antioxidant and anti-inflammatory therapies.

Inhibitors targeting metabolic vulnerabilities primarily include ETC complex and IDH mutation inhibitors. Complex I inhibitors, such as metformin, selectively target HCC subpopulations dependent on OXPHOS. IDH mutation inhibitors, such as enasidenib (AG-221), target *IDH2* mutations to reduce 2-HG levels and restore epigenetic stability[79]. Gene-editing technologies targeting mutated mtDNA include two main approaches. The first approach is the mtZFN/TALEN technology, which specifically cleaves mutated mtDNA (e.g., ND4 G11778A) to promote preferential replication of wild-type mtDNA[80,81]. The second approach is the mito-CRISPR technology, which involves delivering CRISPR-Cas9 to mitochondria using lipid nanoparticles. However, this technique is still in the experimental stage[82]. Antioxidant and anti-inflammatory therapies mainly include two types. The first type is mitochondrial-targeted antioxidants, such as MitoQ and SkQ1, which scavenge mitochondrial ROS and block mutation-driven genomic instability[83]. The second type is STING

pathway inhibitors, such as H-151), which inhibit chronic inflammation induced by the release of mtDNA[84].

In the future there will be an urgent need to address the challenge of tumor heterogeneity. HCC cells exhibit intratumor heterogeneity in mitochondrial mutations, which requires the combined use of single-cell sequencing and spatial multiomics for detailed analysis. It is also critical to develop dynamic monitoring technologies, such as highly sensitive mtDNA mutation detection platforms that combine droplet digital PCR with next-generation sequencing. To achieve precision treatment, personalized combination therapies should be designed based on mutation types. For example, combining IDH inhibitors with ICB can be a promising strategy[44].

## Calcium homeostasis imbalance

The imbalance of $Ca^{2+}$ homeostasis is closely related to the development and progression of malignant tumors. Within the cell, the endoplasmic reticulum (ER), mitochondria, lysosomes, and other organelles, as well as the plasma membrane, work together to form a $Ca^{2+}$ regulatory network that maintains intracellular $Ca^{2+}$ balance[85]. The mitochondrial calcium uniporter (MCU), which is situated on the mitochondrial inner membrane, functions as the principal pathway for calcium ion influx into the mitochondria. The MCU is essential for maintaining mitochondrial calcium homeostasis and has a critical role in energy metabolism, reactive ROS production, and apoptosis[86]. $Ca^{2+}$ can enter mitochondria through various pathways, such as the voltage-dependent anion channel (VDAC) or the MCU, and can also be transported to mitochondria from the ER *via* inositol trisphosphate receptors (IP3Rs). These pathways collectively contribute to the maintenance of intracellular $Ca^{2+}$ homeostasis[87]. The mitochondrial sodium/calcium exchanger (NCLX), a protein located on the inner mitochondrial membrane, regulates mitochondrial calcium homeostasis by facilitating sodium-dependent calcium efflux from the mitochondria. This process has a crucial role in the maintenance of intracellular $Ca^{2+}$ homeostasis and cellular viability[88].

During the progression of cancer, the concentration of $Ca^{2+}$ and the spatiotemporal signaling patterns in the extracellular space, cytoplasm, ER, and mitochondria are frequently disrupted due to genetic mutations, dysregulated expression, imbalanced regulation, and alterations in the subcellular localization of $Ca^{2+}$ transport proteins. Disruption of $Ca^{2+}$ homeostasis leads to improper regulation of signaling effectors that depend on $Ca^{2+}$. This imbalance further exacerbates the pathophysiologic features of cancer, such as promoting cell proliferation, enhancing cell survival, and increasing invasiveness[89]. Thus, maintaining $Ca^{2+}$ homeostasis is essential for suppressing the aberrant behavior of cancer cells.

## Dynamics

Mitochondrial dynamics refer to the fission and fusion processes of mitochondria within the cell, which are crucial for maintaining cellular energy balance and overall cell homeostasis. Mitochondrial fission is the process by which mitochondria divide into smaller, ring-like structures within the cell, typically mediated by mitochondrial dynamin-related proteins, such as DRP1. In contrast, the process of mitochondrial fusion involves the merging of two or more mitochondria into a larger structure, a process that is facilitated by mitochondrial fusion proteins, such as MFN2 and OPA1. Imbalances in these processes can lead to mitochondrial morphologic abnormalities, dysfunction, and apoptosis, thereby impacting liver health[90].

Changes in mitochondrial dynamics are closely associated with the development of metabolic diseases in the liver, such as NAFLD. For example, mitochondrial dynamics become imbalanced due to various factors in NAFLD. The levels of MFN1, MFN2, and OPA1 protein expression in the hepatocytes of patients with NAFLD, which are involved in mitochondrial fusion, are decreased compared to normal hepatocytes, while the levels of fission mitochondrial 1 (FIS1) and DRP1 protein expression, which are associated with mitochondrial fission, exhibit an upward trend. This change results in impairment of mitochondrial fusion and augmentation of mitochondrial fission. Mitochondrial dynamics imbalance can alter the normal morphologic structure of mitochondria, disrupt the tubular mitochondrial network, leading to mitochondrial fragmentation, swelling, and transformation into short rod-like or spherical shapes. This imbalance is accompanied by a decrease in mitochondrial membrane potential and disruption or loss of cristae structures (**Figure 5**). These changes inhibit cellular metabolism, impair mitochondrial function, and accelerate cell death[91].

# Mechanisms and strategies for targeting mitochondrial dysfunction to intervene in HCC

As research into tumor cell metabolism and organelle function continues to deepen, mitochondria, as the core organelles

of cellular energy metabolism, are increasingly recognized for critical roles in tumor initiation and progression. Therapeutic strategies targeting mitochondria offer new ideas and directions for the precision treatment of HCC. By intervening in mitochondrial metabolism, function, and related signaling pathways, it is possible to break through the limitations of conventional therapies and bring new hope to patients with liver cancer (**Figure 6**).

### Drug intervention

Drug intervention represents the most common therapeutic approach targeting mitochondria at present. Drugs can act on key mitochondrial proteins or pathways, such as improving mitochondrial function, inhibiting mitochondrial fission, and promoting mitophagy. Additionally, some antioxidants can alleviate oxidative stress, thereby suppressing the growth of HCC cells.

## Targeting mitochondrial oxidative stress and energy metabolism

Therapeutic strategies for HCC targeting mitochondrial energy metabolism and oxidative stress have gradually emerged as research hotspots in recent years. The core lies in inhibiting tumor growth and progression by intervening in mitochondrial metabolic pathways to regulate cellular energy balance[92]. Dysregulated mitochondrial energy metabolism and elevated oxidative stress represent critical pathologic features of HCC cells[93]. The mitochondrial ETC, a central hub of cellular energy metabolism, is responsible for OXPHOS, ATP synthesis, and ROS production. ETC-targeted therapies primarily suppress HCC cell growth and proliferation by inhibiting ETC complex activity, increasing intracellular ROS levels, and inducing apoptosis[94]. AMPK has a pivotal role in regulating mitochondrial function. Activating AMPK suppresses HCC cell proliferation and further inhibits tumor progression by modulating downstream signaling pathways (e.g., AKT/ERK)[95]. Studies have shown that GCN5L1 mediates glutamine metabolism by regulating glutaminase (GLS)1/2 acetylation, thereby altering enzyme conformation and activity, and ultimately regulates HCC development by activating the mTORC1 signaling pathway[96]. Additionally, novel nanomaterial technologies, such as "O2-PFH@CHPI NPs," induce mitochondria-dependent cell death (including cuprotosis and ferroptosis) by loading the photosensitizer indocyanine green (ICG) and oxygen-saturated perfluorohexane (PFH). These nanoparticles reduce GSH levels in tumor cells, induce oxidative stress, and disrupt redox balance to achieve antitumor effects[97]. Another example is MitoCAT-g, a mitochondria-targeted oxidative stress amplifier that specifically targets mitochondria, depletes GSH, enhances ROS damage, and induces cancer cell apoptosis[98].

## Targeting mitochondrial apoptosis and autophagy

Mitophagy is a specific type of selective autophagy. Mitophagy mainly gets rid of damaged or non-functional mitochondria *via* the autophagosome-lysosome system. In so doing, mitophagy stops the build-up of mtDNA mutations and helps keep the quality of mitochondria in good condition. In hepatocytes the mitochondria represent between 13% and 20% of the cell volume[99]. Mitophagy has a dual role in the development and progression of HCC. Mitophagy maintains cellular homeostasis by clearing damaged mitochondria, thus preventing the accumulation of mtDNA mutations. In contrast, mitophagy can promote cancer cell survival and drug resistance, which may negatively impact cancer treatment[100]. Therefore, therapeutic strategies targeting mitophagy need to comprehensively consider the mechanisms of action under different pathologic conditions. Studies have shown that sorafenib, a first-line treatment for advanced HCC, can sensitize HCC cells to glucose starvation-induced cell death by impairing mitophagy[101]. A research team has shown that HOTAIR knockout enhances sorafenib-induced apoptosis in HCC cells and improves sorafenib sensitivity in sorafenib-resistant advanced cases[102]. Icaritin inhibits PINK1-PRKN-mediated mitophagy, leading to the accumulation of damaged mitochondria and apoptosis in HCC cells, thereby demonstrating potent anti-tumor activity and the potential to overcome drug resistance[99]. Studies have found that thioredoxin-related transmembrane protein 2 (TMX2) promotes karyopherin β1 (KPNB1) nuclear export and transcription factor EB (TFEB) nuclear import, thereby facilitating autophagy. Moreover, TMX2 forms an interaction with voltage-dependent anion channel (VDAC)2 and VDAC3. This interaction aids in guiding PRKN towards malfunctioning mitochondria. As a result, under conditions

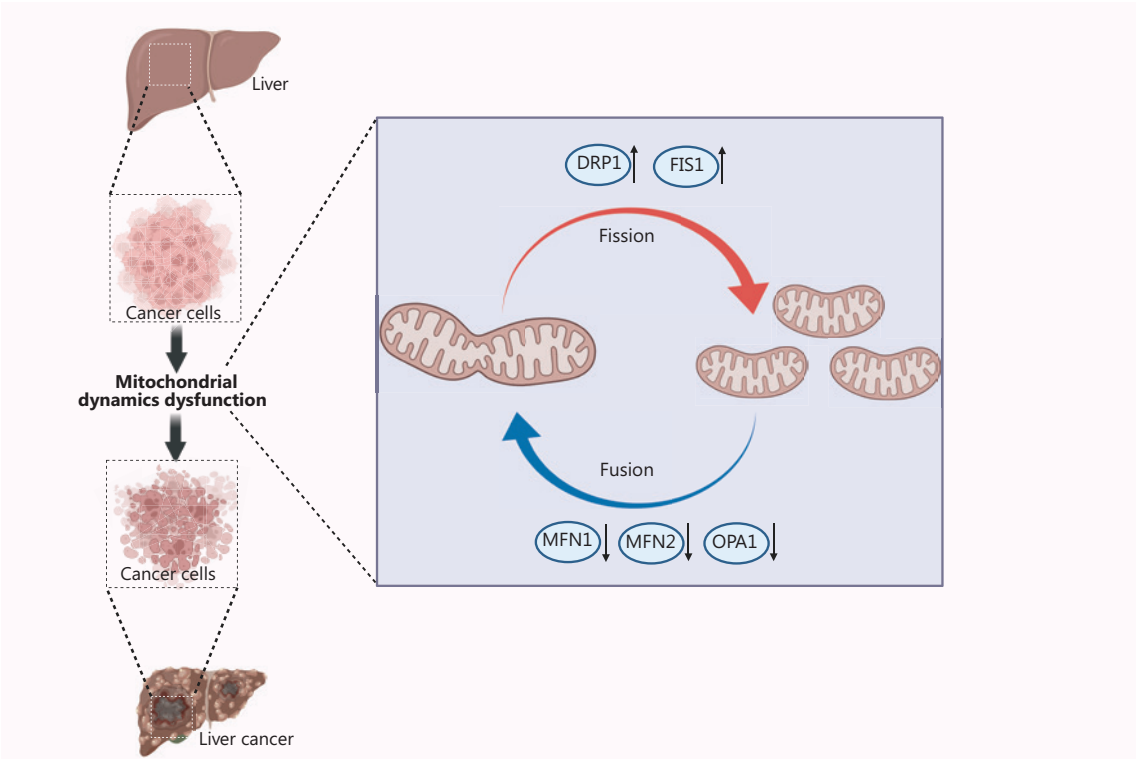



**Figure 5** Targeting mitochondrial dynamics for liver cancer intervention. This figure illustrates the mechanisms underlying mitochondrial dynamic disorders during the progression from normal liver-to-liver cancer. The left part presents the pathologic evolution of liver tissue undergoing malignant transformation due to mitochondrial dynamic imbalance, while the right part focuses on the dynamic cycle of mitochondrial fusion and fission. During fission, upregulation of DRP1 and FIS1 proteins drives mitochondria to divide into multiple smaller mitochondria. During fusion, downregulation of MFN1, MFN2, and OPA1 proteins inhibits mitochondrial fusion, disrupting the normal dynamic balance. DRP1, dynamin-related protein 1; FIS1, mitochondrial fission 1 protein; MFN1, mitofusin 1; MFN2, mitofusin 2; OPA1, optic atrophy 1.

of oxidative stress, TMX2 facilitates the occurrence of cytoprotective mitophagy[103].

## Targeting mtDNA

mtDNA is a critical target for carcinogenic factors. Excessive free radical production and an inability of the defense system to promptly clear the damage can lead to oxidative damage of mtDNA when mitochondria are damaged. Abnormalities in mtDNA can further exacerbate mitochondrial oxidative stress and cause damage to hepatocytes.

Abnormalities in mtDNA include deletions, point mutations, duplications, and insertions. The frequency of mtDNA mutations is significantly increased in HCC[104], The frequency of mtDNA mutations is higher in poorly differentiated HCC. Mutations and deletions in mtDNA lead to mitochondrial dysfunction in HCC cells, promoting cell survival, invasion, and metastasis, inhibiting apoptosis, and inducing the expression of mesenchymal proteins and stem cell markers, ultimately contributing to drug resistance in HCC[105]. Mitochondria-targeted chemotherapy has been proven to be one of the most effective strategies. Mitochondria-targeted chemotherapy kills cancer cells by damaging mtDNA and inducing apoptosis[106]. Studies have identified a small molecule inhibitor [inhibitor of mitochondrial transcription (IMT)1B], which specifically targets human mitochondrial RNA polymerase. This compound inhibits mitochondrial transcription, leading to a significant reduction in ATP production within mitochondria[107].

## Targeting mitochondrial calcium homeostasis

Mitochondrial calcium homeostasis is of great significance for both mitochondrial function and its effects on the cell. Situated on the inner mitochondrial membrane, the MCU functions as

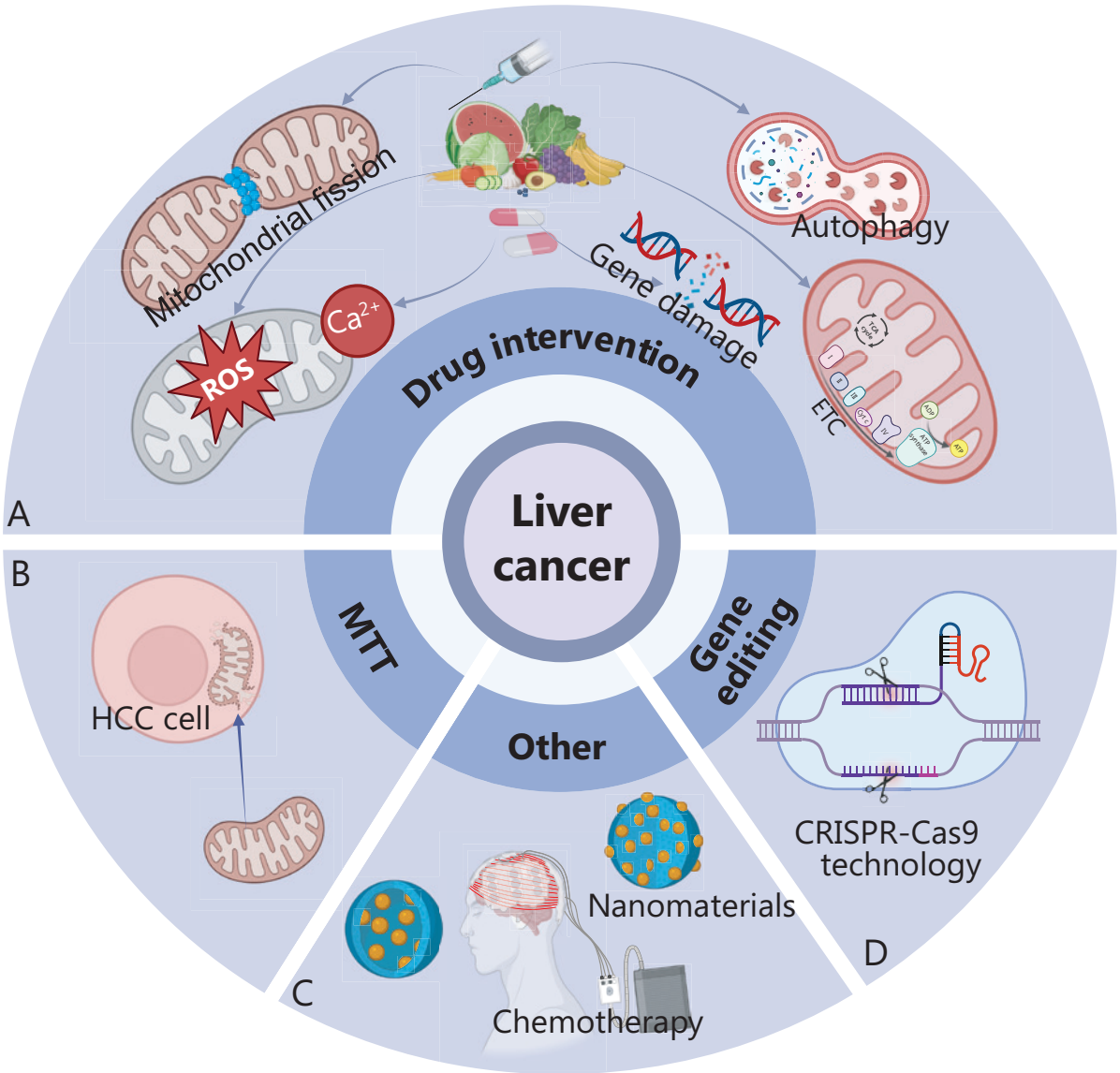



**Figure 6** Strategies for targeting mitochondrial dysfunction in liver cancer. Centered on "liver cancer," this diagram systematically presents the therapeutic mechanisms of liver cancer from four dimensions (A–D): A (drug intervention) intervenes in key mitochondrial targets, such as $Ca^{2+}$ homeostasis, ROS regulation, mitochondrial fusion/fission, genes, and OXPHOS. A is one of the core therapeutic approaches. B MTT attempts to repair dysfunctional mitochondria and reshape cellular metabolism and function by supplementing mitochondria into HCC cells. C (other treatments) encompasses diverse methods, like chemotherapy (chemotherapy) and novel nanomaterials (nanomaterials), expanding the therapeutic strategies for liver cancer. D (gene editing) relies on gene-editing techniques, such as CRISPR-Cas9, to precisely regulate liver cancer-related genes and intervene in the disease process at the molecular level. Overall, D constructs a coordinated liver cancer intervention framework of "drug - mitochondrial - multi-technology - gene editing," reflecting the integrated application of mechanism research and interdisciplinary therapeutic strategies. ETC, electron transport chain; HCC, hepatocellular carcinoma MTT, mitochondrial transplantation technology; OXPHOS, oxidative phosphorylation.

the main channel for the uptake of calcium by mitochondria and is essential in maintaining the stability of mitochondrial calcium levels[108]. Studies have shown that absence of the MCU in HCC reduces the mitochondrial calcium buffering capacity and increases the accumulation of cytoplasmic calcium. This increase in cytoplasmic calcium concentration activates $Ca^{2+}$/

calmodulin-dependent protein kinase II (CAMKII), which promotes hepatic lipolysis, gluconeogenesis, and mitochondrial oxidation. These findings highlight the crucial roles of cytoplasmic calcium and CAMKII in the regulation of mitochondrial metabolism, as well as the potential impact of MCU deficiency on the development of HCC[86]. Mitoxantrone represents a newly developed inhibitor of the MCU. Mitoxantrone functions by obstructing the influx of $Ca^{2+}$ that is mediated by the MCU[109]. One can effectively interfere with mitochondrial calcium homeostasis by modulating the activity of pivotal proteins, including the MCU, TMX2, NCLX in the inner mitochondrial membrane, and mitochondrial calcium uptake 1 regulator (MCUR1). Consequently, this interference can impede the proliferation and metastasis of HCC cells.

# Targeted mitochondrial dynamics (fusion/fission)

Mitochondrial dynamics is the process by which mitochondria maintain a dynamic equilibrium within the cell through fusion and fission. These dynamic changes not only affect the morphology and function of mitochondria but are also closely related to cellular metabolism, proliferation, apoptosis, as well as the occurrence and development of tumors[110]. FUN 14 domain-containing 2 (FUNDC2) reacts with the GTPase domain of the mitochondrial fusion protein, MFN 1, to inhibit the activity. This interaction suppresses mitochondrial fusion, leading to mitochondrial fragmentation and metabolic reprogramming, which in turn promotes hepatocarcinogenesis[111]. The extracellular matrix protein, collagen and calcium-binding EGF domain-containing protein 1 (CCBE1), inhibits the TGF-β signaling pathway and DRP1 phosphorylation, thereby promoting mitochondrial fusion in HCC. This process suppresses tumor cell proliferation, migration, and invasion, providing a potential new therapeutic target for HCC treatment[112].

# Immunotherapeutic strategies for targeting the mitochondria

Although mitochondria provide energy to hepatocytes, mitochondria can promote cancer cell survival and immune evasion in the hypoxic TME environment. Many scientists have gained a deep understanding of immunity, metabolism, and cancer, highlighting the important role of mitochondria in regulating tumor immune escape and metabolism and activation of immune cells. Recent evidence indicates that targeting mitochondria-related pathways by anticancer drugs can enhance the recognition ability of immune cells to recognize cancer cells, improve tumor antigen presentation, and enhance the antitumor function of immune cells, thus initiating cancer cell killing[113].

The compound, ae-mito-tpp, disrupts the mitochondria, leading to the release of large amounts of mtDNA, activation of the cGAS-STING pathway, reshaping the TCM, and significantly enhancing the antitumor immune response to sensitivity[114]. High translocator protein (TSPO) expression is considered a potential therapeutic target in HCC and has a critical role in tumor progression and immune evasion. By inhibiting the function of TSPO, the sensitivity of HCC cells to iron apoptosis is enhanced and the antitumor function of $CD8^+$ T cells is restored. This finding provides a new strategy for the treatment of liver cancer[115].

## Mitochondrial transplantation

Termed "mitochondrial transplantation", this emerging research field shows promise in *in vitro*, *in vivo*, and various clinical applications, offering benefits, such as preventing cell death, reducing inflammation, and restoring cellular metabolism and oxidative balance[116]. Mitochondrial transplantation involves multiple techniques, including co-culture, electroporation, microinjection, magnet-mediated transfer, photothermal nanoknife, and exosome-encapsulated delivery, to achieve directional transplantation of mitochondria into HCC cells. Enrichment efficiency in tumor tissues is enhanced *via* TOM20-targeted peptide modification[117]. For donor mitochondrial screening, high-activity mitochondria derived from M1 macrophages or normal hepatocytes are preferred to avoid genetic mutations in tumor cell mitochondria (e.g., ND1 gene deletion). Researchers first proposed targeting the transplantation of mitochondria from M1 macrophages into M2 tumor-associated macrophages (TAMs) to induce M2 TAMs to shift toward glycolytic metabolism, thereby reprogramming the immunophenotype of M2 TAMs, reversing the tumor immunosuppressive microenvironment, and enhancing cancer ICB therapy[118]. Nanotube connections established between bone marrow stromal and T cells serve as channels for transplanting stromal cell mitochondria into $CD8^+$ T cells. $CD8^+$ T cells receiving mitochondrial transplantation exhibit enhanced adaptive metabolism, improved

tumor-killing ability, and reduced exhaustion, overcoming the barrier of mitochondrial loss and dysfunction-driven T cell exhaustion after CAR-T therapy[119]. *In vitro* and animal models have confirmed that mitochondrial transplantation significantly inhibits tumor growth by arresting the cell cycle and inducing apoptosis[120]. Despite its promise, mitochondrial transplantation faces challenges, as follows: 1) Immunological rejection of mitochondria may trigger NLRP3 inflammasome activation by allogeneic mtDNA, which can be mitigated by HLA typing for donor screening or using autologous fibroblast mitochondria. 2) Degradation of exosome carriers by matrix metalloproteinase (MMP)-9 in the tumor microenvironment can be addressed by modifying exosome membranes with polyethyleneimine to enhance stability. 3) Insufficient targeting efficiency and low mitochondrial fusion efficiency in HCC cells can be improved *via* translocase of outer mitochondrial membrane (TOM)20 peptide modification combined with an ultrasound-targeted microbubble delivery system. Future strategies may also adopt combination therapy, such as concurrent use with mitochondria-targeted drugs (e.g., MitoQ), to reduce tumor recurrence through dual inhibitory effects.

## Gene therapy

In the field of gene therapy for HCC, multiple strategies have been synergistically developed to address disease challenges. At the level of tumor suppressor gene restoration, *p53* gene replacement therapy delivers wild-type *p53* gene *via* an AAV9 vector, activating the Bax/caspase-9 pathway and significantly increasing the HepG2 cell apoptosis rate. *PTEN* gene repair uses CRISPR-Cas9 technology to correct *PTEN* mutations, inhibiting the PI3K/Akt/mTOR pathway and effectively reducing tumor angiogenesis[121]. Novel lipid nanoparticle-encapsulated CTNNB1 siRNA (LNP-CTNNB1) has exhibited significant antitumor effects in multiple immunocompetent mouse models of β-catenin-mutated HCC[122]. To further enhance efficacy, combination therapy strategies have become a research hotspot.

Combination gene therapy and immunotherapy involve using AAV to deliver the *OX40L* gene for $CD8^+$ T cell activation, which when combined with ICB therapy and *in situ* tumor vaccine therapy, elicits synergistic antitumor immune responses. Stereotactic body radiation therapy combined with sorafenib improves clinical outcomes in HCC patients, particularly those with major vascular invasion, extending the median overall survival (OS) by 3.5 months and median progression-free survival (PFS) by 3.7 months, while enhancing quality of life[123]. Additionally, emerging research explores the integration of the ultrasound-activated artificial enzyme, P-Por-Os, with precision gene therapy (PGT), in which external ultrasound stimulation regulates artificial enzyme activity to generate ROS for precise HCC ablation[124]. In animal model validation, a gene therapy inducing endogenous microRNA-22 (miR-22) production successfully treated mice with HCC, demonstrating good safety and efficacy. However, clinical translation of gene therapy faces multiple bottlenecks. Non-specific expression in normal hepatocytes causes hepatotoxicity, which can be mitigated by introducing an AFP promoter for HCC-specific expression. Immunologic rejection induced by viral vectors can be alleviated by alternating multiple serotype AAVs (e.g., AAV8→AAV9). Exosome carriers are easily cleared by Kupffer cells, resulting in insufficient delivery efficiency, which can be improved *via* macrophage depletion pretreatment (clodronate disodium liposomes). These challenges and countermeasures provide directions for subsequent research.

## Intercellular mitochondrial transfer and therapeutic intervention

Mitochondrial transfer, defined as the intercellular transmission of mitochondria or their components, was first discovered in 2006 when mesenchymal stem cells (MSCs) were shown to transfer functional mitochondria into mtDNA-deficient (ρ0) cells, restoring the OXPHOS capacity. A 2023 consensus statement standardized terminology, defining the natural process of intercellular mitochondrial transmission as "mitochondrial transfer," while "mitochondrial transplantation" refers to the therapeutic application of exogenous mitochondria.

Mitochondrial transfer relies on diverse structural bases, primarily achieved *via* tunnel nanotubes (TNTs), cell fusion, gap junctions, and extracellular vesicles[125]. The mitochondrial Rho GTPase (Miro) family has a central role in regulatory mechanisms. Miro1 localizes to the outer mitochondrial membrane, mediating connections between mitochondria and microtubule motor proteins. Endoplasmic reticulum-mitochondria contact sites (ERMES) and the mitochondrial inner and outer membrane organizing system (MICOS) synergistically mediate non-vesicular transport of phosphatidylserine, with lipid transfer proteins, like ORP5/8 and VPS13D, also participating. Mitochondrial transfer in the TME exhibits bidirectional effects. Stromal-to-cancer cell transfer promotes tumor progression, such as glioblastoma acquiring astrocyte

mitochondria *via* growth-associated protein 43 (GAP43)-dependent junctions, which enhances oxidative metabolism and tumorigenicity[126]. Conversely, mitochondrial transfer can exert antitumor effects, as occurs in osteocyte-to-metastatic cancer cell transfer triggering cGAS/STING-mediated antitumor immune responses[127].

Selectively enhancing mitochondrial transfer in MSCs may optimize stem cell therapy for tissue repair in therapeutic applications, while inhibiting cancer cells from hijacking mitochondria *via* cancer-associated fibroblasts (CAFs) or immune cells in the TME emerges as a novel antitumor strategy. Studies have shown cancer cells transfer mitochondria carrying mtDNA mutations to tumor-infiltrating lymphocytes (TILs) *via* TNTs and small extracellular vesicles (sEVs), inducing metabolic dysfunction, senescence, and loss of antitumor efficacy in T cells. This mechanism not only enables tumor immune evasion but also induces resistance to ICB therapy[128]. Molecules, like USP30, have key roles by mediating mitochondrial resistance to autophagy and homotypic replacement[73]. Overall, mitochondrial transfer occurs in physiologic/pathologic contexts, especially under oxidative stress from excessive ROS, though the exact triggers and regulatory mechanisms require further study[129]. Current technical limitations (e.g., difficulty in precisely tracking and visualizing mitochondrial transfer in living tissues) have limited direct evidence of *in vivo* mitochondrial transfer in humans. Nevertheless, targeting mitochondrial transfer represents a promising therapeutic strategy, poised to drive innovative changes in organ treatment models for regenerative medicine, oncology, and other fields.

### Other treatments

In addition to pharmacologic and gene therapies, other treatment modalities include photodynamic therapy and nanotechnology. Photodynamic therapy uses light of specific wavelengths to activate photosensitizers within mitochondria, generating ROS that kill cancer cells. Nanotechnology, in contrast, uses nanoparticles as carriers to deliver drugs directly to mitochondria, enhancing the targeting and efficacy of the drugs. Nanoparticle drug delivery systems can precisely deliver drugs to mitochondria, enhancing therapeutic efficacy while reducing toxicity. For example, researchers have designed a mitochondria-targeted system based on mesoporous silica nanoparticles. By modifying the nanoparticle surface with triphenyl phosphonium and folic acid, stepwise targeting of mitochondria in tumor cells was achieved[130].

Despite significant advances in laboratory studies of mitochondrial targeting for HCC, many challenges face clinical application. For example, the specific mechanism underlying mitochondria in HCC should be further explored and more targeted drugs should be developed.

## Clinical transformation

Natural products and compound drugs exhibit distinct research trends and potentials in interventions against HCC *via* targeting mitochondrial dysfunction.

As shown in **Figure 7**, natural products targeting mitochondrial dysfunction in HCC primarily focus on energy metabolism and oxidative stress mechanisms, which are highly correlated with the compositional characteristics of natural products. Among natural product components, phenolics (52 compounds) account for the highest proportion, likely due to the strong antioxidant and anti-inflammatory properties of polyphenolic compounds (e.g., resveratrol and green tea extracts). These properties are crucial for improving mitochondrial dysfunction, which is intimately linked to HCC development. Abnormal energy metabolism and oxidative stress represent key manifestations of mitochondrial dysfunction. Flavonoids (36 compounds) and terpenoids (34 compounds) follow sequentially. For example, flavonoids, like quercetin, act on oxidative stress mechanisms *via* antioxidant effects, while terpenoids may exert anti-HCC effects by regulating apoptosis or energy metabolism, further highlighting the rationality of energy metabolism and oxidative stress as research priorities for natural product-based HCC therapy.

Mechanistically, phenolic/flavonoid compounds achieve dual effects of reducing ROS generation or inducing tumor cell energy crisis by inhibiting electron leakage from mitochondrial complexes I/III, activating the Nrf2 antioxidant pathway, or competitively binding to the ubiquinone site of complex I to block the ETC[131]. For example, nano-delivered epigallocatechin gallate (EGCG) synergizes with chemotherapy to reduce tumor volume in mouse xenograft models[132]. Terpenoids, such as oridonin, activate the mitochondrial apoptotic pathway, inducing mitochondrial damage and ROS production, thereby deeply intervening in tumor metabolic reprogramming and demonstrating significant regulatory capacity over mitochondrial metabolism[133].

At the clinical translation level, early-stage research (112 in the discovery phase + 10 in the preclinical stage) dominates, indicating that most studies remain in drug discovery

or preliminary experimental stages with untapped clinical translation potential. The relatively high number of phase II trials (30) suggests that some drugs enter efficacy verification after initial safety validation (phase I). The sharp decline in phase III trials (12) may reflect drug elimination due to insufficient efficacy or toxicity issues after phase II. The prominent number of phase IV trials (40) may include post-marketing surveillance of approved drugs (e.g., adjuvant therapy with natural products), though caution is needed for data classification errors (e.g., misclassifying observational studies as phase IV).

In summary, interventions targeting oxidative stress and energy metabolism have become the most clinically translatable directions in mitochondrial-targeted HCC therapy, supported by clear mechanistic relevance and abundant natural product resources. With the development of delivery technologies and precision medicine, natural products are expected to advance from "antioxidant/metabolic regulators" to "precision anticancer drugs."

Despite the promising prospects, the field must overcome two major bottlenecks: 1) target specificity, by developing mitochondria-targeted delivery systems (e.g., TPP-modified nanoparticles) to avoid oxidative damage or energy interference in normal tissues by natural products; and 2) biomarker guidance based on screening patient subgroups sensitive to oxidative stress/energy metabolism interventions by detecting mtDNA mutations (e.g., ND1 G3460A) or ROS levels and achieving precise "mechanism-population" matching.

Current compound drugs targeting mitochondrial dysfunction for HCC intervention exclusively focus on the single mechanism of oxidative stress across different research phases. In the field of compound drugs, a total of 276 related drugs have been collected. The development stage is significantly unbalanced and the clinical conversion rate needs to be improved. Approximately 64.1% of drugs (177 compounds) remain in basic research (20) or preclinical stages (157), indicating the field is still in the early exploration phase with most compounds yet to enter human trials. The clinical phase exhibits a "funnel-shaped" gap. Only 35.1% of compounds (97) enter clinical trials, including 1 in phase I, 8 in phase II, and 2 in phase III. The conversion rate from preclinical to clinical stages is as low as 5.6% with most drugs eliminated in early clinical trials due to insufficient efficacy or off-target toxicity.

This "early clustering, clinical disconnection" highlights the high risk of research and development for mitochondrial targeted therapy in liver cancer. Core challenges include the complexity of mitochondrial functions (e.g., metabolic compensation and cellular heterogeneity) and off-target toxicity, as evidenced by only 11 drugs (≈4%) advancing to phase I/II/III combined. It is worth noting that there are 86 drugs in clinical phase IV, suggesting that the strategy of using old drugs for new use, such as repositioning marketed metabolites and antioxidants, can effectively shorten the research and development cycle.

Future research and development directions should focus on three aspects (deepening mechanisms, exploring combination therapies, and developing biomarkers). Deepening mechanisms prioritize the advancement of drugs in the preclinical stage that have clear mechanisms and strong targeting capabilities, such as those that specifically regulate mitochondrial membrane potential or autophagy pathways. Exploration of combination therapies involves combining immune checkpoint inhibitors or chemotherapeutic drugs to enhance therapeutic efficacy through synergistic effects.

Development of biomarkers is accomplished by screening for mitochondrial function biomarkers that predict drug response, such as mtDNA mutations and ROS levels, to facilitate the design of precision stratified clinical trials (**Figure 8**).

To enhance the practical value and impact of clinical translation, we conducted a comprehensive and in-depth evaluation of ongoing clinical trials and therapeutic strategies. This information was primarily sourced from the ClinicalTrials.gov database and the latest research literature.

Detailed analyses were performed on current promising drugs. For example, MitoQ has demonstrated significant efficacy in clinical trials (e.g., NCT03514875). The MitoQ mechanism of action involves antioxidants reducing ROS, thereby increasing nitric oxide (NO) availability, improving endothelial function, and alleviating endothelial dysfunction to enhance carotid blood flow. MitoQ significantly improved endothelial function and cerebrovascular blood flow in patients in multiple trials with adverse reactions remaining within manageable limits. EGCG exerts effects through dual mechanisms, as follows: inhibiting glycolysis/fatty acid synthesis to protect mitochondria *via* antioxidant activity; and suppressing indoleamine 2,3-dioxygenase 1 (IDO1) to improve tryptophan metabolism-related immunosuppression and reduce cell-free mitochondrial DNA (cf-mtDNA)-mediated immune evasion[134]. However, the clinical trial results of EGCG (NCT03978052) highlight the limitations. Specifically, monotherapy with EGCG improves cognitive impairment but the effect subsides after discontinuation, whereas combining

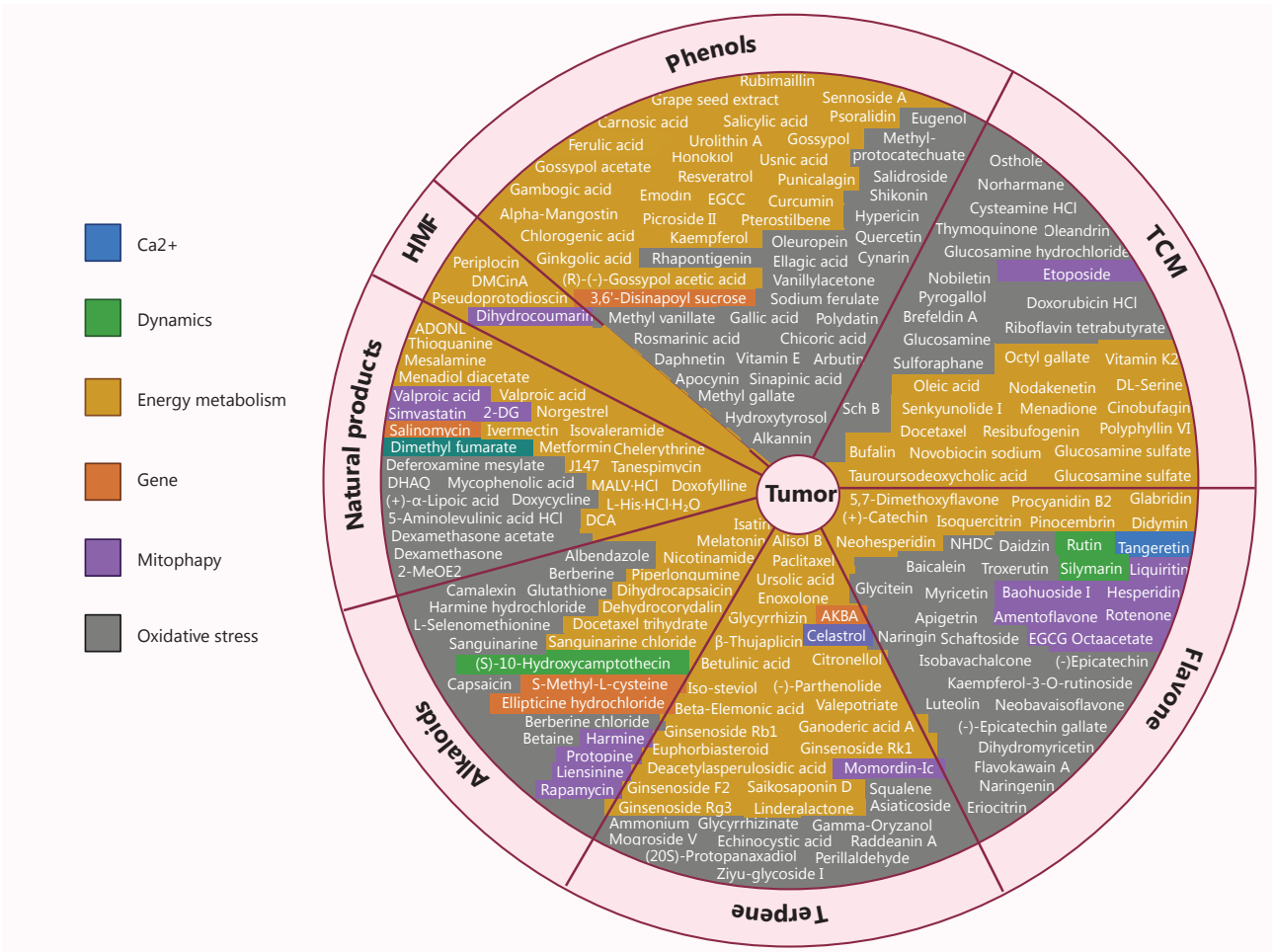



**Figure 7** Natural products targeting mitochondria. By collecting anticancer natural products from various databases, these drugs are categorized into phenolic compounds, traditional Chinese medicine, flavonoids, terpenes, alkaloids, natural products, and Chinese medicine with both medicinal and HMF. Different colored blocks indicate the regulation of various mitochondrial mechanisms, which primarily include calcium ion homeostasis, biosynthesis, mitochondrial dynamics, energy metabolism, mDNA, mitochondrial fusion and fission, mitochondrial autophagy, mitochondrial OXPHOS, and oxidative stress. These drugs offer new insights for clinical translation. TCM, traditional Chinese medicine; HMF, food properties; mtDNA, mitochondrial DNA; OXPHOS, oxidative phosphorylation.

EGCG with cognitive function training sustains the effect. This may relate to the *in vivo* metabolic processes, warranting further investigation.

In terms of biomarkers for patient stratification, cf-mtDNA has emerged as a pivotal theme in current research, serving as a novel biomarker with potential value in patient stratification and prognostic assessment. Studies have shown that cf-mtDNA levels correlate closely with disease severity and progression[19,135]. In addition, metabolic phenotypes are gaining attention by analyzing patient metabolic characteristics (e.g., changes in carcinoembryonic antigen [CEA] levels), research (NCT01373047) using designer T cell methods modify cells *in vitro* to recognize tumor antigen CEA and enabling better identification of patient subgroups suitable for specific treatment regimens.

Dr. Ding from Wuhan, China is leading a study (NCT06653062) evaluating cf-mtDNA as a biomarker for monitoring HCC recurrence (CCGLC-015). Dr. Ding emphasized the close association between cf-mtDNA levels and tumor occurrence/prognosis. Additionally, the DELFI model based on whole-genome fragmentation characteristics of cell-free DNA (ctDNA) demonstrated 88% sensitivity in detecting early-stage HCC (BCLC 0/A), which significantly outperformed traditional AFP testing[136]. The

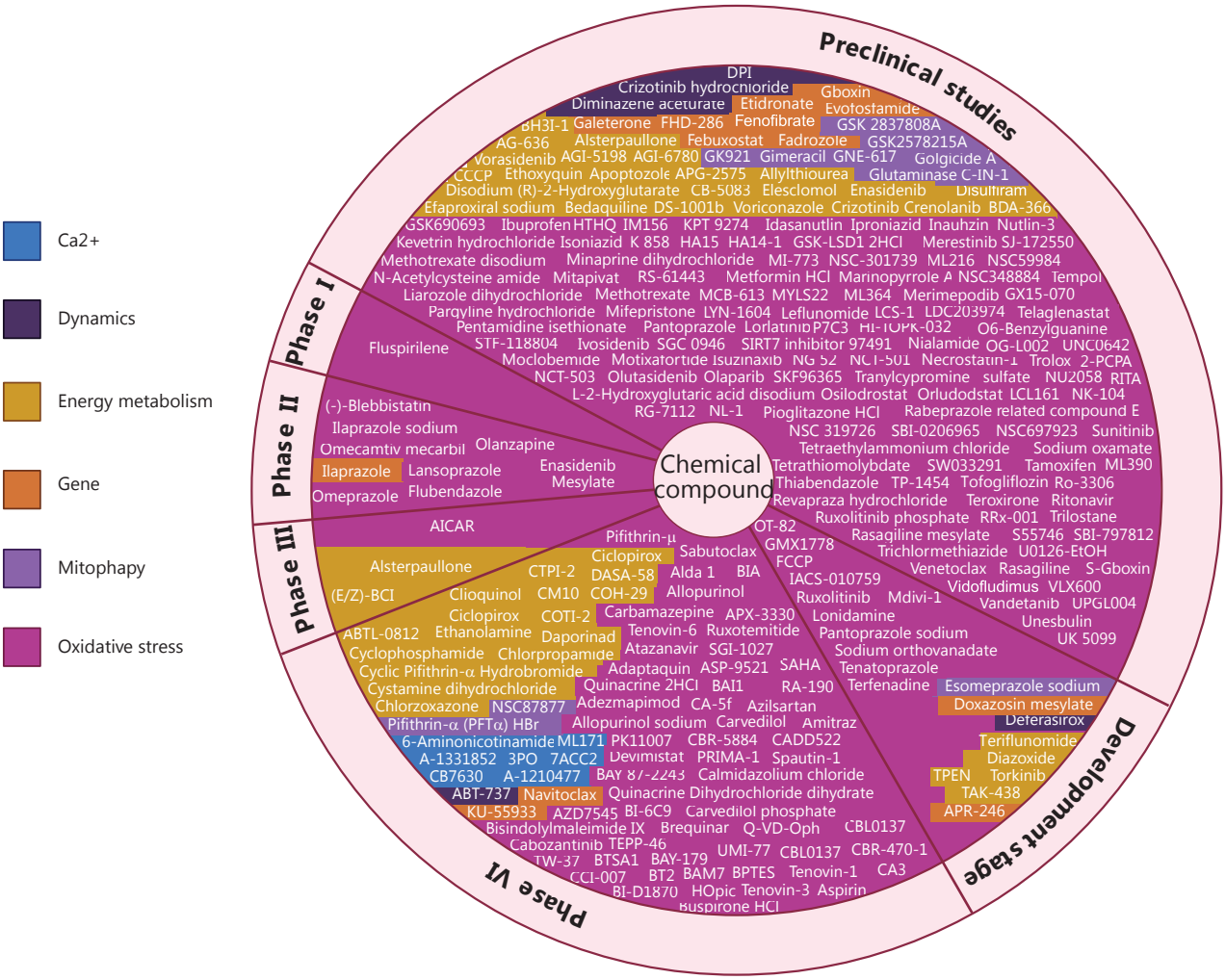



**Figure 8** Mitochondria-targeted drugs for HCC. The image is primarily divided into six stages based on different clinical phases, including the research and development phase, preclinical phase, phase I, phase II, phase III, and phase IV. Different color blocks represent various mechanisms of targeting mitochondria. Oxidative stress has a significant role in this process. A large proportion of drugs are still in the preclinical stage. HCC, hepatocellular carcinoma.

methylation patterns of cf-mtDNA also show high utility in distinguishing HCC from liver cirrhosis or chronic hepatitis. For example, detecting methylation combinations of genes, like *AK055957* and *DAB2IP*, significantly improves diagnostic specificity[137].

The development of mitochondrial targeted drugs for liver cancer shows the characteristics of "early clustering and clinical disconnection," reflecting the high risks and translational bottlenecks in this field. Future efforts should focus on mechanistic innovation, optimization of clinical translation strategies, and interdisciplinary technical integration to overcome current challenges.

# Challenges and future prospects

## Challenges

In the research on targeting mitochondrial dysfunction to intervene in HCC, specificity, drug resistance, and personalized treatment are the main challenges. First, most of the drugs targeting mitochondria lack tumor specificity and are prone to damage normal tissues. Therefore, there is an urgent need to develop an efficient, low toxic, and mitochondrial targeted delivery system with HCC specificity. Second, HCC cells are prone to developing resistance to mitochondria-targeted

drugs. The mechanisms are complex and involve multiple aspects, such as metabolic reprogramming and enhanced antioxidant defenses. A deep investigation into these resistance mechanisms and the development of effective strategies to overcome the resistance mechanisms are of vital importance.

Finally, because HCC is highly heterogeneous, there is a significant variation in patient responses to mitochondria-targeted therapies. Therefore, establishing a reliable biomarker system to drive the development of personalized precision treatment is an important direction for the future.

### Future prospects

With the in-depth research on mitochondrial biology and the metabolic mechanisms underlying HCC, more potential mitochondrial targets will be revealed, laying a solid theoretical foundation for the development of novel targeted drugs. In addition, several mitochondrial treatments are combined to form a new and more efficient therapeutic strategy, which is expected to overcome the limitations of monotherapy and significantly improve the therapeutic effect. In addition to the unique advantages of nanotechnology in drug delivery, which provide new tools for the treatment of HCC, nanotechnology can enhance the specificity, stability, and bioavailability of mitochondria-targeted drugs, thereby optimizing therapeutic outcomes. In summary, targeting mitochondrial dysfunction to intervene in HCC shows great potential. With the continuous progress of research and technology this area may bring new hope for liver cancer patients despite the need to overcome many challenges.

## Conclusions

Targeting mitochondrial dysfunction to intervene in HCC has made significant progress in recent years as an emerging therapeutic strategy. The central role of mitochondria in metabolism, proliferation, and apoptosis regulation of HCC cells make HCC cells highly promising therapeutic targets. Although current research has developed various mitochondria-targeted drugs and intervention strategies that have shown good antitumor effects in preclinical studies, many challenges remain. For example, the specificity of drug delivery is insufficient, HCC cells readily develop drug resistance, and the high heterogeneity of tumors leads to significant individual differences in responses to mitochondrial-targeted therapies. These issues urgently need to be addressed to further advance the clinical application of mitochondria-targeted interventions in HCC. By deeply exploring mitochondrial-related molecular mechanisms, developing efficient targeting delivery systems, such as nanotechnology, optimizing combination therapy strategies (e.g., combining with immunotherapy or targeted therapy), and establishing precise biomarker systems, there is hope to further promote the clinical application of mitochondria-targeted interventions in HCC in the future. In summary, with the in-depth understanding of mitochondrial biology and the pathogenesis of HCC, mitochondria-targeted therapies will offer more effective and personalized treatment options for HCC patients with broad clinical application prospects.

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## Conflict of interest statement

No potential conflicts of interest are disclosed.

## Author contributions

Wrote the original manuscript and the survey data: Maomao Li, Siyao Liang.
Conceptualization: Le Chang, Bingyan Lu, Jiahua Cheng, Tian Yang, Ying Wu.
Supervision and were involved in the manuscript reviewing and editing process: Yuhong Lyu, Xiaochan He, Changwu Yue.

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