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**Thrice Monthly Volume 11 Number 23 August 16, 2023**

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RESPONSIBLE EDITORS FOR THIS ISSUE
Production Editor: Hua-Ge Yu; Production Department Director: Xiang Li; Editorial Office Director: Jin-Lei Wang.
Recent progress in understanding mitokines as diagnostic and therapeutic targets in hepatocellular carcinoma

Jiang Wang, Lan-Zhu Luo, Dao-Miao Liang, Chao Guo, Zhi-Hong Huang, Xiao-Hong Jian, Jie Wen

**Abstract**

Hepatocellular carcinoma (HCC) is one of the most prevalent tumors worldwide and the leading contributor to cancer-related deaths. The progression and metastasis of HCC are closely associated with altered mitochondrial metabolism, including mitochondrial stress response. Mitokines, soluble proteins produced and secreted in response to mitochondrial stress, play an essential immunomodulatory role. Immunotherapy has emerged as a crucial treatment option for HCC. However, a positive response to therapy is typically dependent on the interaction of tumor cells with immune regulation within the tumor microenvironment. Therefore, exploring the specific immunomodulatory mechanisms of mitokines in HCC is essential for improving the efficacy of immunotherapy. This study provides a comprehensive overview of the association between HCC and the immune microenvironment and highlights recent progress in understanding the involvement of mitochondrial function in preserving liver function. In addition, a systematic review of mitokines-mediated immunomodulation in HCC is presented. Finally, the potential diagnostic and therapeutic roles of mitokines in HCC are prospected and summarized. Recent progress in mitokine research represents a new prospect for mitochondrial therapy. Considering the potential of mitokines to regulate immune function, investigating them as a relevant mole-
Wang J et al. Mitokines in HCC

Mitokines as diagnostic and therapeutic targets in hepatocellular carcinoma.

Hepatocellular carcinoma (HCC) is a primary tumor of the liver, most of which are related to hepatitis B virus or hepatitis C virus. Other related factors include alcohol, hereditary hemochromatosis cirrhosis, primary biliary cholangitis, etc. In addition, 90% to 95% of patients with HCC have a history of cirrhosis before diagnosis. HCC progresses from small nodules, and the asymptomatic period lasts for several years.[1]. HCC is one of the leading causes of cancer deaths worldwide. Currently, specific treatments for HCC are not available, resulting in a 5-year survival rate of less than 20%.[2, 3]. Immunotherapy has emerged as a promising “fourth therapy” after surgery, radiotherapy, and chemotherapy, with the potential to improve the prognosis of individuals with HCC. However, immune escape limits the efficacy of immunotherapy. Therefore, it is of great clinical significance to investigate the potential immunomodulatory mechanisms of HCC in the tumor micro-environment (TME).

The liver is one of the vital organs that control energy metabolism throughout the body. The metabolism of energy substances such as glucose, fatty acids, and amino acids occurs mainly in liver mitochondria.[4,5]. Mitochondria play several vital functions in energy metabolism and intra-cellular environmental homeostasis, including regulating cellular respiration, oxidative phosphorylation, balancing reactive oxygen species (ROS), and modulating cell death.[6]. In addition, when an abnormal mitochondrial function occurs, cancer cells lose the ability to drive anti-tumor immunity.[7].

Over the past decades, there has been a growing interest in investigating the connection between mitochondria and HCC. In response to endogenous or exogenous stimuli, mitochondria undergo stress and release mitochondrial damage-associated molecular patterns (DAMPs), such as mitochondrial DNA and mitochondrial ROS, into the cytoplasm or extracellular environment.[8]. The mitochondrial stress response is involved in tumor growth and metastasis of HCC in various ways through autophagy, ROS generation, metabolic reprogramming, and pro-divisional responses in the mitochondria of damaged hepatocytes.[9]. In mitochondrial metabolism, mitokines are soluble proteins, peptides, or hormone-like substances produced and secreted in response to mitochondrial stress. There is increasing evidence that mitochondrial DNA released into the cytoplasm or outside the cell can participate in different types of innate immune regulation by activating cellular molecular signaling pathways.[10]. In addition, it can be released into distant tissues or cells via in vivo translocation to participate in multi-tissue and intercellular interactions and systematically regulate tissue and cellular metabolism, thus playing a key role in various oncological diseases.[11].

In this study, the association of the immune micro-environment with HCC was analyzed, highlighting the important role of immune regulation in the progression of this disease. Subsequently, the importance of mitochondrial function in maintaining liver function and the potential key immunomodulatory role of mitokines in HCC are outlined. Finally, the potential and challenges of mitokines as new HCC diagnostic and therapeutic targets are discussed.

Document retrieval is executed through the PubMed database using keywords “HCC”, “mitokines”, or “immunoregulation”.

The liver, a vital immune organ, contains both innate and adaptive immune cells. These immune cells are the main constituents of the immune micro-environment in HCC. This micro-environment establishes a dynamic interaction with tumor cells, which ultimately promotes tumor growth by suppressing the anti-tumor activity of immune cells.[12].

**Key Words:** Hepatocellular carcinoma; Mitochondria; Mitokine; Immune escape; Autophagy

**Citation:** Wang J, Luo LZ, Liang DM, Guo C, Huang ZH, Jian XH, Wen J. Recent progress in understanding mitokines as diagnostic and therapeutic targets in hepatocellular carcinoma. *World J Clin Cases* 2023; 11(23): 5416-5429

**URL:** https://www.wjgnet.com/2307-8960/full/v11/i23/5416.htm

**DOI:** https://dx.doi.org/10.12998/wjcc.v11.i23.5416

**INTRODUCTION**

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Over the past decades, there has been a growing interest in investigating the connection between mitochondria and HCC. In response to endogenous or exogenous stimuli, mitochondria undergo stress and release mitochondrial damage-associated molecular patterns (DAMPs), such as mitochondrial DNA and mitochondrial ROS, into the cytoplasm or extracellular environment.[8]. The mitochondrial stress response is involved in tumor growth and metastasis of HCC in various ways through autophagy, ROS generation, metabolic reprogramming, and pro-divisional responses in the mitochondria of damaged hepatocytes.[9]. In mitochondrial metabolism, mitokines are soluble proteins, peptides, or hormone-like substances produced and secreted in response to mitochondrial stress. There is increasing evidence that mitochondrial DNA released into the cytoplasm or outside the cell can participate in different types of innate immune regulation by activating cellular molecular signaling pathways.[10]. In addition, it can be released into distant tissues or cells via in vivo translocation to participate in multi-tissue and intercellular interactions and systematically regulate tissue and cellular metabolism, thus playing a key role in various oncological diseases.[11].

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**IMMUNE MICRO-ENVIRONMENT AND HCC**

The liver, a vital immune organ, contains both innate and adaptive immune cells. These immune cells are the main constituents of the immune micro-environment in HCC. This micro-environment establishes a dynamic interaction with tumor cells, which ultimately promotes tumor growth by suppressing the anti-tumor activity of immune cells.[12].
The liver requires energy for metabolic, biosynthetic, excretory, secretory, and detoxification processes in the organism. Oxidative stress is an important mechanism for a variety of liver injuries, characterized by increased production of ROS and the absence of antioxidant defense mechanisms in the body with mitochondria being the main source of intracellular ROS.

Impaired urea synthesis. Under such conditions, ammonia toxicity is mainly detoxified by the synthesis of glutamine. In normal physiological conditions, the body metabolizes ammonia through the synthesis of urea and glutamine. The first step of urea synthesis is catalyzed by glutamine synthetase in hepatocytes, leading to a decrease in intracellular glutamine levels. Abnormalities in mitochondrial structure and function are present in a variety of chronic liver diseases such as chronic HBV infection but is significantly enriched in the immune micro-environment of the liver.

An important role in the regulation of tumor progression and immune cell function[22]. In summary, the progression of HCC is inextricably associated with immune regulation resulting from crosstalk between components of the immune micro-environment. Moreover, this immune regulation can affect the prognosis of tumor patients. Therefore, exploring potential therapeutic targets that can influence the regulation of tumor immunity, such as mitokines, has important clinical implications. Overall, the findings of this study will help to more accurately predict immunotherapy response, determine immunotherapy efficacy and guide individualized treatment regimens.

MITOCHONDRIA AND LIVER FUNCTION

The liver is involved in regulating the metabolic processes of the body, including neutralizing toxic substances, storing glycogen, and producing hormones that mediate metabolism. Under physiological and pathological conditions, mitochondria in the liver exhibit altered metabolic pathways depending on their density and number. These pathways include β-oxidation, ketogenesis, tricarboxylic acid cycle, respiratory activity, and synthesis of adenosine triphosphate (ATP) through oxidative phosphorylation[23,24].

Mitochondria have been shown to play a crucial role in the regulation of intracellular calcium ion concentration, innate immunity, and cell death signaling[25]. Damage to mitochondrial DNA (mtDNA) and abnormal production of ROS are associated with the onset and progression of several liver diseases, including HCC[26,27]. Mitochondria are one of the sensitive organelles within hepatocytes. Abnormalities in mitochondrial structure and function are present in a variety of acute and chronic liver diseases. These organelles are closely related to the pathogenesis of liver failure, and possible pathways of action have been proposed. These include ATP depletion due to inhibition of the respiratory chain, oxidative stress, inhibition of fatty acid oxidation, and mitochondrial permeability transition, leading to apoptosis or necrosis of hepatocytes[28,29]. However, the exact mechanism of action has not been fully elucidated. Under normal physiological conditions, the body metabolizes ammonia through the synthesis of urea and glutamine. The first step of urea synthesis takes place in the mitochondria. However, damage to the mitochondria can result in a blocked ornithine cycle and impaired urea synthesis. Under such conditions, ammonia toxicity is mainly detoxified by the synthesis of glutamine[30]. Oxidative stress is an important mechanism for a variety of liver injuries, characterized by increased production of ROS and the absence of antioxidant defense mechanisms in the body with mitochondria being the main source of intracellular ROS[31].

Almost all high-energy-producing processes take place in the mitochondria, the "energy factories" of the body. The liver requires energy for metabolic, biosynthetic, excretory, secretory, and detoxification processes in the organism.
Therefore, the liver is a highly energy-dependent organ. When mitochondria are damaged, ATP production relies mainly on the glycolytic pathway\cite{32}. The synthesis of hepatic glycogen also consumes energy. Therefore, ATP deficiency due to massive mitochondrial damage will inevitably affect the energy reserves of the liver. In addition, mitochondrial damage can inhibit gluconeogenesis, leading to intrahepatic lactic acid accumulation and even lactic acidosis\cite{33}.

**MITOCHONDRIA AND IMMUNOREGULATION**

Mitochondria play multiple roles in the host immune response, such as exerting signaling and effector functions, promoting immune cell activation and antimicrobial defense, and triggering inflammatory responses when cells and tissues are damaged (Figure 1)\cite{34}.

When a host is infected by a pathogen, mitochondria induce multiple immune responses to scavenge the infected cells and have an important role in the immunity of the body against infection\cite{35}. Mitochondria are one of the primary sources of mitochondrial DAMPs\cite{36}. Deoxyribose on the inner membrane of mitochondria called mtDNA is the genetic material of mitochondria\cite{37}. mtDNA, an important DAMP, has unique structural features and properties, such as high sensitivity to oxidative damage. Moreover, mtDNA contains a large number of demethylated CpG sequences that can be recognized by Toll-like receptors\cite{38}. The mtDNA released into the cytoplasm or outside the cell has a crucial function in pathogenic infections and inflammatory disorders. It activates molecular defense mechanisms or induces damage to the organism, thereby participating in various innate immune responses. mtDNA regulates a variety of innate immune pathways, including mtDNA-TLR9-NF-xB, mtDNA-NLRP3-caspase-1, and mtDNA-GAS-STING-IRF3 signaling pathways, inducing diverse innate immune responses\cite{39}.

The innate immune system is the first line of defense of the body against pathogenic infections. The pattern recognition receptors (PRRs) of the innate immune system identify PAMPs as well as DAMPs. PAMPs contain structural components of pathogenic microorganisms, nucleic acids, and proteins\cite{40}. PRRs are categorized into four main families: Toll-like receptors, NOD-like receptors, c-type lectin receptors, and RIG receptors\cite{41}. Ligand binding activates PRRs and downstream signals such as inflammatory complexes, interferon regulatory factors, nuclear transcription factor-xB (NF-xB), and mitogen-activated protein kinases. This activation leads to the production of inflammatory cytokines, chemokines, and interferons. In addition, the interaction of mitochondrial DAMPs with the aforementioned PRRs can mediate a more efficient innate immune response\cite{42}.

**MITOKINES: AN IMPORTANT SIGNAL FOR COMMUNICATION BETWEEN THE NUCLEUS AND MITOCHONDRIA**

Mitokines are a class of peptides, cytokines, or signaling pathways generated, secreted, or triggered in response to mitochondrial stress. They have the potential to serve as new targets for clinical disease diagnosis and treatment research \cite{43}.

Mitochondria can release some beneficial signaling molecules under mild stress. These molecules are released into the cell via in vivo transport to regulate the cellular state and complete the information exchange between the mitochondria and the nucleus\cite{44}. In addition to acting as a signaling molecule for information exchange between mitochondria and the nucleus, mitokines can be released into distal tissues to exert systemic immunomodulatory effects. Nucleus-derived mitokines such as irisin, fibroblast growth factor 21 (FGF21), adropin, and growth differentiation factor 15 (GDF15) are secreted to mediate the immune response of the organism\cite{45}. The mitochondrial genome is responsible for encoding mitochondria-derived peptides (MDPs) and the mitochondrial unfolded protein response (UPRmt). They upregulate molecular chaperone, protease, and antioxidant gene expression and enhance mitochondrial immunomodulatory properties with retrograde signaling\cite{11}.

**MITOKINES-MEDIATED IMMUNE REGULATION IN HCC NUCLEUS-DERIVED MITOKINES FGF21**

FGF21, the first identified member of the FGF family, belongs to the FGF19 subfamily. It is primarily expressed in the liver and can regulate glucometabolism, modulate inflammatory responses, inhibit oxidative stress, and ameliorate liver injury\cite{46}.

FGF21 has a low expression level in the liver under normal physiological conditions. Long-term injection of FGF21 in a rat model of diethylnitrosamine (DEN)-induced HCC inhibited hepatic oxidative stress and, thus, the onset of HCC\cite{47, 48}. Fasting and starvation can increase FGF21 expression in the liver via peroxisome proliferator-activated receptor a/retinoid X receptor a signaling, thereby altering fatty acid levels\cite{49-52}. The regulation of FGF21 expression can vary depending on specific conditions prevailing at the time. These factors include carbohydrate response element binding protein, farnesoid X receptor /retinoid X receptor alpha, peroxisome proliferator-activated receptor gamma, and liver X receptor\cite{53-56}. In addition, the expression of FGF21 in the liver is also regulated by p53 and signal transducer and activator of transcription 3 (STAT3). p53 and STAT3 can upregulate the expression of FGF21 under various cellular stress conditions, such as ER stress, mitochondrial stress, and oxidative stress. Furthermore, upregulation of p53 and STAT3 expression can promote liver injury and HCC progression by regulating FGF21\cite{57, 58}.
FGF21 forms a stable FGF21/KLB/FGFR complex via β-Klotho (KLB) and FGF receptor (FGFR) to activate downstream related signaling molecules, exerting biological effects and fulfilling corresponding specific functions. The binding of KLB to FGFR4 induces apoptosis and inhibits tumor cell proliferation[59,60]. As the concentration of FGF21 increases, KLB mRNA expression increases, and KLB protein content also increases in a consistent manner. Therefore, during DEN-induced carcinogenesis in LO2 hepatocytes, FGF21 can prevent hepatocarcinogenesis by promoting the upregulation of KLB mRNA expression and increasing the level of its specific receptor KLB[61]. FGF21 acting on DEN-induced LO2 hepatocytes can promote KLB expression, reduce the phosphorylation level of AKT and intracellular oxidative stress level, and inhibit HCC to some extent[62]. FGF21 regulates immune responses by targeting macrophages[63]. In the liver, FGF21 is highly expressed in response to pathogenic metabolic disorders. In addition, FGF21 inhibits lipid overload and steatosis, thereby preventing the progression of steatohepatitis and fibrotic damage that may lead to chronic HCC[64]. The loss of systemic FGF21 exacerbates hepatic steatosis and steatohepatitis[64].

Figure 1 Mitochondrial distribution and immune regulation in the liver. ROS: Reactive oxygen species; MDPs: Mitochondria-derived peptides.

DOI: 10.12998/wjcc.v11.i23.5416 Copyright ©The Author(s) 2023.
The aforementioned studies provide an abundant theoretical basis for FGF21 to treat liver diseases and inhibit HCC. FGF21, as a newly discovered hepatocyte cytokine or a biomarker indicating the functional status of hepatocytes, may resist inflammation and cancer metabolism through important intrinsic defense mechanisms. However, the molecular mechanism of the inhibitory effect of FGF21 on HCC and the optimal dose still needs to be further investigated.

GDF15

GDF15, a member of the TGF-β superfamily, is primarily expressed in the placenta and prostate under normal physiological conditions. However, in pathological states such as inflammation and malignancy, GDF15 expression levels are significantly elevated in affected tissues and blood and are strongly associated with tumor metastasis[65,66]. GDF15 has been identified as a UPRmt-related cellular non-autonomous mitogenic factor. It has a role in regulating systemic energy homeostasis and the nutritional behavior of an organism[67-69]. In addition, GDF15 has the potential to serve as a diagnostic biomarker for mitochondrial disease. The expression of GDF15 can be induced by the activation of transcription factor 4 and C/EBP Homologous Protein (CHOP) in both humans and mice under conditions of mitochondrial stress and dysfunction[70-72].

Several studies have found that GDF15 is a "double-sided agent". Specifically, GDF15 can act as both a tumor suppressor and a carcinogen, depending on the tumor type[73,74]. GDF15 has anti-tumor activity in glioblastoma cells[75] and exerts anti-tumor effects by promoting apoptosis in human rectal cancer cells[76]. However, in oral squamous cell carcinoma, GDF15 expression was positively correlated with tumor malignancy, suggesting that it may promote tumor cell proliferation[77]. Experimental data collected by Wang et al[78] demonstrated that GDF15 promotes the proliferation, invasion, migration, and angiogenesis of HepG2 cells. Therefore, GDF15 may be a risk factor for HCC and a serum marker for HCC diagnosis.

Based on the association between mitochondrial dysfunction and liver damage, GDF15 is now recognized as a biomarker for several liver disorders[79]. The expression of GDF15 is upregulated in the tumor tissues of individuals with HCC, and there is a positive correlation between GDF15 expression and the progression of HCC[80]. According to Zhou et al[81], GDF-15 promotes the growth, multiplication, and migration of HepG2 cells and is considered a possible risk factor for HCC. In addition, overexpression of GDF15 enhanced the proliferation and invasive ability of HCC[82]. In animal models of HCC, knockdown of the GDF15 gene inhibited tumor formation, growth, and invasion[81,83]. Chemotherapy or hypoxic environments can significantly increase GDF15 in HCC cells. The specific mechanism of this phenomenon may be related to chemotherapy-induced DNA damage and hypoxia-induced activation of signaling pathways such as p38 mitogen-activated protein kinase, c-Jun N-terminal kinase, as well as extracellular signal-regulated kinase 1/2[84]. In a study investigating risk factors for HCC, it was discovered that GDF15 induced the formation of collagen in hepatic stellate cells, resulting in an escalation of liver fibrosis[85]. GDF15 was positively correlated with an increase in Treg cells among patients with HCC[65]. Specifically, GDF15 can interact with the T-cell receptor CD48 to promote the production and improve the function of Treg cells, thus creating an immunosuppressive environment associated with HCC[65]. Consistently, GDF15 knockdown in hepatic stellate cells reduced liver tumor size induced by a steatohepatitis-based tumorigenesis model[66].

Based on the above data, GDF15 could be a potential target for effective treatment of HCC. However, the in-depth immunomodulatory role of GDF15 in HCC needs to be further explored.

IRISIN

Irisin, a novel cytokine, was discovered by the Bostrom team at Harvard University in 2012[86]. Irisin is formed by proteolytic hydrolysis of the fibronectin type III domain-containing protein 5 (FNDC5). Irisin increases thermogenesis and regulates energy metabolism by promoting the conversion of white adipocytes to brown adipocytes. Specifically, peroxisome proliferator-activated receptor-γ coactivator-1 promotes the expression of several muscle gene products upon stimulation, including a gene encoding the type I membrane protein FNDC5. Furthermore, the peptide hormone secreted into the bloodstream by FNDC5 after proteolysis and processing is irisin[87].

Irisin is expressed at significantly higher levels in HCC tissues and cell lines than in paraneoplastic tissues, promoting HCC cell proliferation and migration while inhibiting apoptosis[88]. Irisin is upregulated in the liver tissues of individuals with HCC and is closely associated with the expression of genes involved in inflammation[89]. Irisin plays an important immunomodulatory role in chronic inflammation. In addition, irisin expression is increased in the chronic inflammatory setting of HCC[89]. Irisin interacts with macrophages and promotes their phagocytic activity. Furthermore, irisin can regulate leukocyte migration in inflammation and exerts a biological role[90].

In addition to promoting the growth and invasion of HCC, Irisin has also been correlated with the onset and progression of various types of tumors[91]. Irisin enhances the sensitivity of cancerous cells to the chemotherapeutic drug doxorubicin, inhibits the proliferation of breast cancer MDA231 cells, and mediates apoptosis[92]. In addition, Irisin inhibits the ability of human lung adenocarcinoma A549 cells and human small cell lung cancer NCI-H446 cells to proliferate, migrate and invade by suppressing epithelial-mesenchymal transition[93]. Irisin also inhibits the proliferation of human prostate adenocarcinoma LNCaP, DU145, and PC3 cells[94]. According to Kong et al[95], Irisin inhibits the proliferation and invasive ability of osteosarcoma U2OS and MG-63 cells. However, Irisin has no significant effect on the proliferative ability of esophageal cancer TE13 and OE33 cells, endometrial cancer KLE and RL95 cells, colon cancer HT29 and MCA38 cells, and thyroid cancer SW579 and BHP7 cells[96].
Unlike studies of abnormal irisin expression in cancer cells themselves, some scientific teams have shifted their focus to serum levels of irisin. According to Provatopoulou et al. [97], irisin serum levels were significantly lower in individuals with breast cancer. Moreover, these levels were positively correlated with tumor stage, suggesting the oncogenic effect of irisin on breast cancer. Another study found significantly lower serum irisin levels in patients with colorectal cancer and significantly higher levels in patients with renal cancer compared to healthy controls [98]. These studies suggest that serum irisin levels may serve as a novel diagnostic biomarker for cancer.

The above studies on irisin in tumors suggest its crucial role in tumorigenesis and progression [99, 100]. The effect of irisin on cell proliferation capacity and its regulation of inflammation has been confirmed by numerous researchers as a key link in tumor progression. However, its impact on HCC and its mechanisms need to be further explored. The characteristics of irisin associated with multiple tumors provide new ideas for its use as a therapeutic target for HCC and other metastatic tumors.

**ADROPIN**

Very few studies have been reported on the direct association of adropin with HCC. Current studies on adropin in the liver are primarily focused on lipid metabolism.

Adropin, a class of secretory proteins encoded by the energy homeostasis gene Enho, was identified by Kumar et al’s team in 2008 when studying obesity and nutrient homeostasis in mice. It consists of 76 amino acid residues and has a role in regulating lipid metabolism and maintaining insulin sensitivity [101]. Adropin reduces macrophage infiltration and thus improves inflammation by reducing fat accumulation [102]. Its deficiency is associated with a decrease in Treg cells and can lead to autoimmune diseases [103]. Adropin downregulates the expression of the hepatic adipogenic gene and promotes the production of peroxisome proliferator-activated receptor γ in adipose tissue. Peroxisome proliferator-activated receptor γ plays a crucial role in regulating adipogenesis and further affects intrahepatic lipid levels [104, 105]. Adropin downregulates the expression of liver X receptor α and sterol regulatory element binding protein 2. The former is a key protein in cholesterol metabolism, and regulation of the latter by the former leads to increased fatty acid synthesis [106]. Adropin treatment attenuates diet-induced hepatic steatosis or insulin resistance in obese rats [107]. Hyperlipidemia upregulates pro-inflammatory factors such as tumor necrosis factor-alpha and interleukin 6, etc., which further leads to liver tissue damage. Adropin treatment modulates the expression of inducible nitric oxide synthase in liver tissue and further decreases the level of pro-inflammatory cytokine mRNA. The above findings suggest that adropin may be one of the candidates for improving hyperlipidemia and reducing liver tissue damage [108].

Miyao et al. [109] demonstrated through a mouse model that hepatic sinusoidal endothelial cell injury is associated with elevated intrahepatic vascular resistance in the early stages of nonalcoholic fatty liver disease, which activates Kupffer cells and hematopoietic stem cells. This mechanism, in turn, leads to the continuation and progression of chronic liver impairment. Adropin pretreatment attenuates endothelial barrier dysfunction in rats [107], which implies that adropin may function as a potential target for enhancing the functional barrier of the vascular endothelium.

In conclusion, adropin is essential for maintaining metabolic homeostasis, especially for maintaining insulin sensitivity and preventing abnormalities in lipid metabolism. Adropin could be an important potential target for adjuvant therapy of HCC due to its outstanding ability to regulate lipid metabolism [110]. However, the current understanding of adropin is still poor, and further research and exploration are needed.

**MITOCHONDRIA-DERIVED MITOKINES MDPs**

MDPs, a class of small bioactive peptides expressed by mitochondrial DNA-encoded genes, primarily include humanin, 12S rRNA-c mitochondrial open reading frames (MOTS-c), and small humanin-like peptides (SHLPs) [111].

Humanin has potential cardioprotective functions. In an ischemia-reperfusion model, humanin protects left ventricular function from ROS injury by promoting the expression of nitric oxide synthase in endothelial cells [111]. In addition, humanin exerts an anti-atherogenic effect by decreasing the uptake of oxidized low-density lipoprotein by foam cells derived from macrophages and by increasing cholesterol efflux [112]. Humanin is a class of polypeptides encoded by the 16S rRNA region of mitochondria, and researchers have identified six members (SHLP1-6) of this class [113]. SHLP2 exhibits biological characteristics similar to humanin in terms of antioxidant, anti-apoptotic, and pro-mitochondrial production [114]. MOTS-c, a 16-amino acid peptide encoded by the 12S rRNA mitochondrial open reading frame, is translocated to the nucleus by metabolic stress and acts as a retrograde signaling molecule to regulate adaptive nuclear gene expression [115]. In addition, MOTS-c reduces downstream signaling activation of NF-kB-induced inflammatory factor expression and protects hepatocyte function by inhibiting mitogen-activated protein kinases activity [116]. Therefore, it is believed that lower levels of endogenous MOTS-c are associated with the impairment of hepatocyte function [117].

As the first MDP to be identified, humanin has been shown to have a role in improving body metabolism, such as reducing visceral fat, increasing glucose-stimulated insulin release, and improving glucose tolerance [118]. MOTS-c and SHLPs further support the role of MDPs in cellular metabolism [119]. The protective mechanisms of MDPs in the onset and progression of HCC have been gradually recognized in recent years [115]. In vitro, studies have shown that SHLP2 can improve mitochondrial metabolism by increasing oxygen consumption rate and ATP production [116].
Despite the relatively few studies on the direct association of MOTS-c and SHLPs with HCC, they still have potential as diagnostic and therapeutic targets for HCC due to their important functions in metabolic regulation.

**UPRmt**

Although a clear association between UPRmt and HCC has not been established, understanding its biological function and current research advances in disease regulation can still expand the research ideas of HCC.

UPRmt is a key signaling pathway that regulates the homeostasis and quality control of mitochondrial proteins. Under normal physiological conditions, proteins encoded by the nucleus are transported from ribosomes to mitochondria, where they undergo proper folding and assembly[120]. During mitochondrial stress, the entry of precursor proteins into the mitochondria is slowed down due to a decrease in intracellular ATP levels or transmembrane potential, resulting in a significant accumulation of misfolded proteins or protein precursors in the cytoplasm[121]. At this point, the corresponding mitochondrial proteasome activates and initiates UPRmt, which in turn induces the upregulation of molecular chaperones, proteases, and antioxidant genes, ultimately leading to the restoration of mitochondrial function[111]. In proliferating cells, sustained UPRmt maintains stable mitochondrial function while promoting glycolysis[122]. In mitotic cells, UPRmt inhibits the expression of genes related to the tricarboxylic acid cycle and mitochondrial oxidative phosphorylation, resulting in a reduction of the metabolic burden and the production of the secondary product ROS. It also increases the expression of genes involved in glycolysis and amino acid catabolism to meet cellular energy demands by producing ATP[123]. Pharmacological enhancement of hepatic UPRmt ameliorates mitochondria and repair dysfunction in mice with liver injury[124]. Furthermore, choline may improve hepatocyte functional recovery by regulating UPRmt[125]. Excessive prolongation or inadequate regulation of UPRmt may contribute to the accumulation of dysfunctional mitochondria[126].

UPRmt is one of the important regulatory pathways of mitochondrial protein quantity control. When mitochondrial function is compromised, the corresponding mitochondrial proteasome activates and initiates UPRmt to promote cell survival and recovery of mitochondrial function[127]. Recently, the involvement of UPRmt in amyloid-beta polymerization and Alzheimer’s disease progression has been increasingly studied. In addition, UPRmt inhibits amyloid-beta polymerization toxicity by coordinating signaling between the nucleus and mitochondria, enhances mitochondrial protein stability, reduces amyloid aggregation in cells and animal livers, and forms a conserved mitochondrial stress response process[128].

Increased ROS-induced proteotoxicity and oxidative stress can result in the accumulation of unfolded or misfolded proteins in the matrix of mitochondria, which can activate UPRmt[129]. The transcription factor CHOP is responsible for regulating UPRmt. CHOP leads to increased expression of mitochondrial chaperones and proteases, which include heat shock protein 60 and casein hydrolysis mitochondrial matrix peptidase protein hydrolysis subunit[121]. The mitochondrial chaperones and proteases play a key role in regulating the homeostasis of mitochondrial proteins[130, 131]. Activating transcription factor 5 is a direct mammalian homolog of ATFS1 and has been shown to function downstream of CHOP[132, 133]. In addition, JUN signaling promotes the expression of CHOP in response to the accumulation of unfolded proteins in the matrix of mitochondria, thereby reducing cellular stress[134]. Sirtuin 3 (SIRT3), the mitochondrial NAD-dependent sirtuin deacetylase, also regulates UPRmt. Moreover, the SIRT3-UPRmt axis activates forkhead box O3, which in turn increases antioxidant function by activating superoxide dismutase 2[129, 135]. Despite the overexpression of superoxide dismutate 2 in non-invasive cells, the SIRT3-UPRmt axis increases cell invasiveness[136]. Activation of the SIRT3-UPRmt axis is positively correlated with tumor invasion and metastasis and is associated with mitochondrial heterogeneity[137].

**PROSPECTS FOR THE DIAGNOSTIC AND THERAPEUTIC POTENTIAL OF MITOKINES IN HCC - DIAGNOSTIC POTENTIAL**

The application of mitokines in the diagnosis of HCC remains challenging. Clinical diagnosis requires biomarkers with high specificity and high sensitivity in the short term. FGF21 and GDF15 have been validated in animal models and patient populations, suggesting their use as biomarkers of mitochondrial metabolic diseases[138, 139]. The detection of mitokines levels allows the assessment of the risk level of HCC or the prediction of the outcome of patients with HCC after treatment.

However, there are general limitations to these studies. The spatiotemporal localization of tissue damage by mitokines is challenging. Although these limitations limit a more precise diagnosis of HCC, the protective effect of mitokines on the liver is certain[140, 141].

**THERAPEUTIC POTENTIAL**

Current research on mitochondrial metabolism in HCC has focused on preclinical investigations of signaling mechanisms during mitochondrial stress. Mitokine, an important cytokine in mitochondrial stress, plays an essential role in the dynamic intracellular, intercellular, and inter-tissue homeostasis during mitochondrial stress.
Mitokines are released by tumor-associated macrophages and cancer cells in the TME. Mitokines such as FGF21 and GDF15, which are induced by mitochondrial stress, have been associated with a poor prognosis in individuals with HCC. Despite many reports of mitokine-dependent effects in cancerous cells, the effects are complex, diverse, and inconsistent. Therefore, the mitokine-dependent role in the onset and progression of HCC needs to be further investigated (Table 1). In addition, the development of mitokine-targeted drugs with high specificity and sensitivity is the future direction for the treatment of HCC.

## CONCLUSION

The interaction between mitochondrial dysfunction and HCC is receiving widespread attention. Herein, the association of mitochondrial metabolism and immune regulation of liver tumors is reviewed. In addition, the progress of research on the relevant mechanisms mediated by mitokine in HCC is summarized. Although the mechanisms of immune regulation mediated by mitochondrial stress have not yet been fully identified, available data have pointed to the involvement of mitokines in the immune response. Mitokine research advances represent a new prospect for mitochondrial therapy. Based on the potential of mitokines in immune regulation, screening mitokines as relevant molecular targets could be a promising approach for diagnosing and treating HCC. However, there are still limitations in existing mitokine studies. There is a need to more accurately elucidate the direct response of mitokines to inflammatory or immune stimuli and identify the immune cells involved in the response. In addition, the biological significance of mitokines in HCC morbidity and mortality should be evaluated. In summary, the research progress of mitokine offers novel insights into the diagnosis and treatment of HCC. However, the attainment of survival benefits for patients requires further mechanistic and clinical exploration.

## FOOTNOTES

**Author contributions:** Wang J and Luo LZ contribute equally to this study, they share co-first author; Wang J wrote the paper; Luo LZ and Liang DM did the literature review; Guo C and Huang ZH did the data analysis; Jian XH conceived and coordinated the study; Wen J revised the paper; Jian XH and Wen J contribute equally to this study, they share co-correspondent author; all authors reviewed the results and approved the final version of the manuscript.

**Supported by** Scientific Research Project of Hunan Education Department, No. 21A0054.

**Conflict-of-interest statement:** The authors declare that they have no competing interests.

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**S-Editor:** Yan JP

**L-Editor:** A

**P-Editor:** Yu HG
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