ISSN 2307-8960 (online)

World Journal of *Clinical Cases*

World J Clin Cases 2023 August 16; 11(23): 5416-5627

Published by Baishideng Publishing Group Inc

World Journal of Clinical Cases

Contents

Thrice Monthly Volume 11 Number 23 August 16, 2023

REVIEW

ORIGINAL ARTICLE

Retrospective Cohort Study

Retrospective Study

Observational Study

Prospective Study

SYSTEMATIC REVIEWS

World Journal of Clinical Cases

Thrice Monthly Volume 11 Number 23 August 16, 2023

Contents

World Journal of Clinical Cases

Thrice Monthly Volume 11 Number 23 August 16, 2023

Contents

World Journal of Clinical Cases

Thrice Monthly Volume 11 Number 23 August 16, 2023

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Clinical Cases*, Ellis J Neufeld, MD, PhD, Chief Physician, Executive Vice President, Professor, Department of Hematology, St. Jude Children's Research Hospital, Memphis, TN 38105, United States. ellis.neufeld@stjude.org

AIMS AND SCOPE

The primary aim of *World Journal of Clinical Cases* (*WJCC*, *World J Clin Cases*) is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

INDEXING/ABSTRACTING

The *WJCC* is now abstracted and indexed in Science Citation Index Expanded (SCIE, also known as SciSearch®), Journal Citation Reports/Science Edition, Current Contents®/Clinical Medicine, PubMed, PubMed Central, Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 Edition of Journal Citation Reports® cites the 2022 impact factor (IF) for *WJCC* as 1.1; IF without journal self cites: 1.1; 5-year IF: 1.3; Journal Citation Indicator: 0.26; Ranking: 133 among 167 journals in medicine, general and internal; and Quartile category: Q4.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Clinical Cases

ISSN
ISSN 2307-8960 (online)

LAUNCH DATE
April 16, 2013

FREQUENCY
Thrice Monthly

PUBLICATION DATE
August 16, 2023

World Journal of Clinical Cases

Submit a Manuscript: https://www.f6publishing.com

World J Clin Cases 2023 August 16; 11(23): 5416-5429

DOI: 10.12998/wjcc.v11.i23.5416

ISSN 2307-8960 (online)

REVIEW

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

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Arumugam VA, India; Jeong KY, South Korea

Received: May 18, 2023
Peer-review started: May 18, 2023
First decision: July 3, 2023
Revised: July 14, 2023
Accepted: August 3, 2023
Article in press: August 3, 2023
Published online: August 16, 2023

Jiang Wang, Lan-Zhu Luo, Zhi-Hong Huang, Children Medical Center, Hunan Provincial People's Hospital, The First Affiliated Hospital of Hunan Normal University, Changsha 410013, Hunan Province, China

Dao-Miao Liang, Chao Guo, Department of Hepatobiliary Surgery, Hunan Provincial People's Hospital, The First Affiliated Hospital of Hunan Normal University, Changsha 410013, Hunan Province, China

Xiao-Hong Jian, Department of Anatomy, Hunan Normal University School of Medicine, Changsha 410013, Hunan Province, China

Jie Wen, Department of Pediatric Orthopedics, Hunan Provincial People's Hospital, The First Affiliated Hospital of Hunan Normal University, Changsha 410013, Hunan Province, China

Corresponding author: Jie Wen, PhD, Associate Professor, Department of Pediatric Orthopedics, Hunan Provincial People's Hospital, The First Affiliated Hospital of Hunan Normal University, No. 61 West Jiefang Road, Changsha 410013, Hunan Province, China. cashwj@qq.com

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-

cular target holds great promise for the diagnosis and treatment of HCC.

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

Core Tip: The progression and metastasis of hepatocellular carcinoma (HCC) are intricately associated with alterations in mitochondrial metabolism. Mitokines, as critical cellular factors during mitochondrial stress, play an indispensable role in maintaining dynamic equilibrium within cells, intercellularly, and intertissue during mitochondrial stress. Through quantifying mitokine levels, we can assess the severity of HCC and predict the efficacy of treatment in HCC patients. The pursuit of highly specific and sensitive drugs targeting mitokines for HCC treatment represents a promising avenue for future research endeavors.

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

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”.

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 TME of HCC plays a pivotal role in both the onset and progression of this disease. Besides tumor cells, this micro-environment comprises stromal cells (which include immune cells, fibroblasts, endothelial cells, *etc.*), as well as structural components (such as extracellular matrix, *etc.*), and signaling components (including chemokines, cytokines, and growth factors). By modulating tumor immune escape, they can impact both the response rate of patients to immunotherapy and their prognosis[12]. The TME of HCC exhibits certain specificities as compared to other tumors. On the one hand, the liver harbors a vast number of antigen-presenting cells and immune cells, along with chronic antigen activation of intestinal origin. Therefore, the liver can maintain a certain level of immune tolerance to avoid severe inflammation caused by non-pathogenic antigens. On the other hand, the liver needs to maintain a rapid and intense response to infections and tumors[13]. In addition, most Chinese patients with HCC have concurrent HBV infection. The interaction of HBV infection with other components of the TME is mediated by highly complex and intertwined signaling pathways, culminating in the formation of the specific TME of HCC[14].

Tumor-infiltrating lymphocytes can influence tumor progression through immune micro-environment interactions [15]. Interferon-7 produced by CD8+ T cells in TME is a key factor in anti-tumor immunity. This factor increases antigen presentation, produces pro-inflammatory cytokines, and directly kills tumor cells. Regulatory T cells (Treg), a sub-population of CD4+ T cells, are highly immunosuppressive. Regulatory T cells can suppress immune responses by inhibiting CD8+ T cell effector functions (*e.g.*, degranulation, perforin, and granzyme production). Additionally, they can directly promote tumor escape through a variety of contact-dependent and non-contact mechanisms. Therefore, such lymphocytes are associated with a poorer prognosis of patients with HCC[16]. Mucosa-associated invariant T cell accounts for 50% of all T cells in normal liver tissue. Mucosa-associated invariant T cell experiences a decrease in number and dysfunction in chronic liver diseases such as chronic HBV infection but is significantly enriched in the immune micro-environment of HCC. B cells can directly present tumor-associated antigens to CD4+ T cells and CD8+ T cells. In addition, B cells can promote the uptake of tumor antigens by tumor-associated macrophages and dendritic cells (DCs) through antibody production. Moreover, B cells can secrete relevant cytokines to promote anti-tumor immunity or produce direct killing of tumor-killing cells[17]. Natural killer cells account for 25%-40% of hepatic lymphocytes and play an important function in preventing fibrosis as well as fighting against cancer and viruses through their powerful cytotoxic effects[18].

HCC cells establish a dynamic communication network with other cells in the TME[19]. Hence, enabling them to adopt a range of different immune escape strategies through intercellular communication. HCC inhibits the maturation of DCs by secreting interleukin-10, vascular endothelial growth factor, transforming growth factor beta (TGF-β), or downregulating tumor antigens. Antigen presentation by immature DCs is accompanied by destabilization of the associated DC-T cell interactions. As a result, CD8+ T cells cannot be cross-activated, leading to T cell incompetence and tumor tolerance [20,21]. Tumor cells in the TME often experience a lack of glucose and oxygen supply, oxidative stress, and loss of Ca2+ homeostasis. These conditions lead to endoplasmic reticulum (ER) dysfunction, resulting in "ER stress." Moreover, HCC cells can impact other micro-environmental components through the induction of ER stress, which in turn plays 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[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[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)[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[35]. Mitochondria are one of the primary sources of mitochondrial DAMPs[36]. Deoxyribose on the inner membrane of mitochondria called mtDNA is the genetic material of mitochondria[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[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-κB, mtDNA-NLRP3-caspase-1, and mtDNA-GAS-STING-IRF3 signaling pathways, inducing diverse innate immune responses[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[40]. PRRs are categorized into four main families: Toll-like receptors, NOD-like receptors, c-type lectin receptors, and RIG receptors[41]. Ligand binding activates PRRs and downstream signals such as inflammatory complexes, interferon regulatory factors, nuclear transcription factor-κB (NF-κB), 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[42].

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

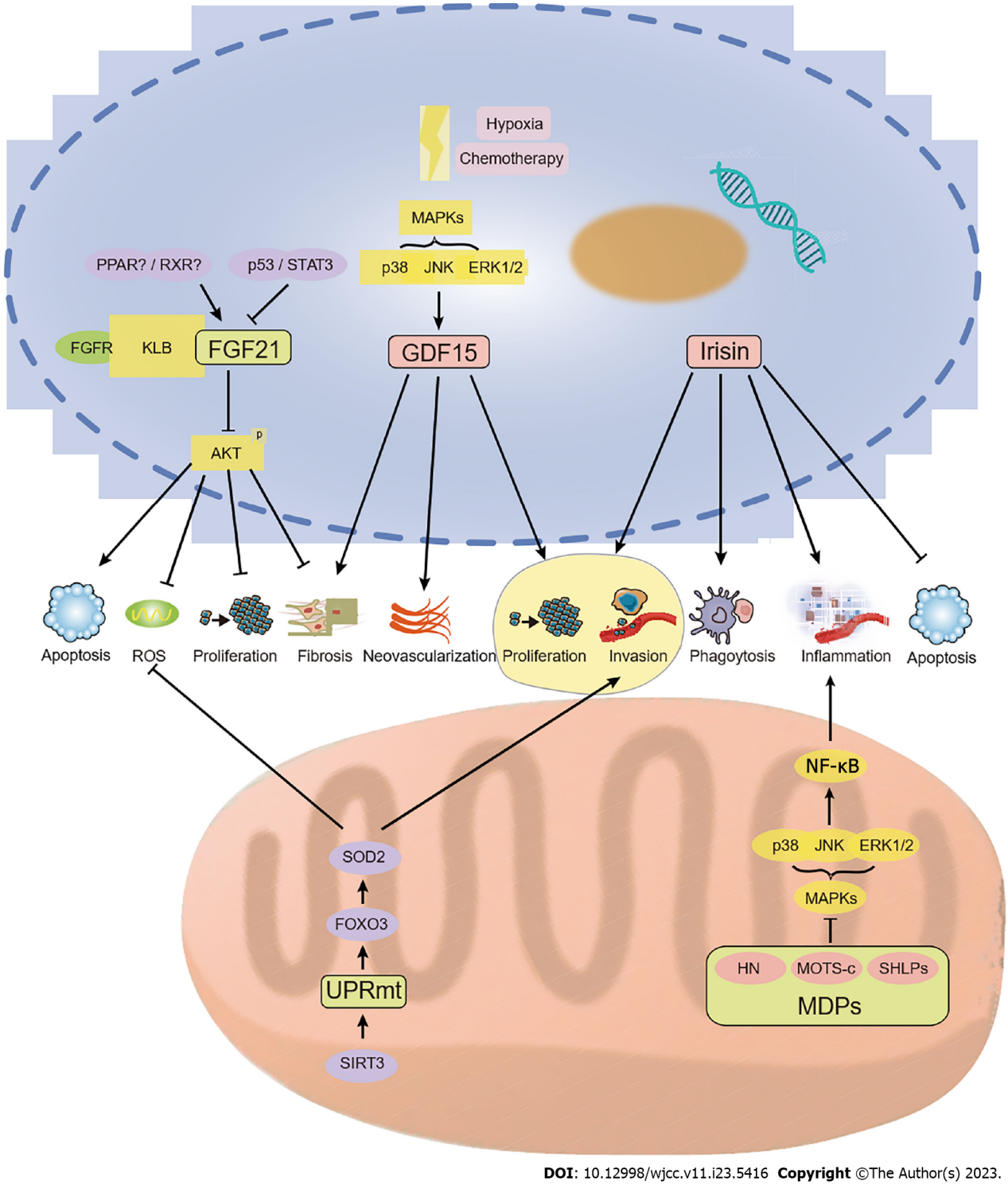
Mitokines are a class of peptides, cytokines, or signaling pathways generated, secreted, or triggered in response to mitochondrial stress. They have the potential to serve as new targets for clinical disease diagnosis and treatment research [43].

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[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[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[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 glucolipid metabolism, modulate inflammatory responses, inhibit oxidative stress, and ameliorate liver injury[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[47,48]. Fasting and starvation can increase FGF21 expression in the liver *via* peroxisome proliferator-activated receptor α/retinoid X receptor α signaling, thereby altering fatty acid levels[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[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[57,58].



DOI: 10.12998/wjcc.v11.i23.5416

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

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].

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 TEl3 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 astumor necrosis factor-alpha and interleukin 6, *etc.*, which further leads to liver tissue damage. Adropin treatment modulates the expression of inducible nitric carbon 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-κB-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[11]. 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 dismutase 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.

Table 1 Role of mitokines in the prognosis of patients with hepatocellular carcinoma

Mitokines	Role in the prognosis of patients with HCC
FGF21	Negative correlation[142]
GDF15	Negative correlation[143]
Irisin	Presumed positive correlation[144]
Adropin	Not mentioned
MDPs	Not mentioned
UPRmt	Presumed negative correlation[145]

HCC: Hepatocellular carcinoma; FGF21: Fibroblast growth factor 21; GDF15: Growth differentiation factor 15; MDPs: Mitochondria-derived peptides; UPRmt: Mitochondrial unfolded protein response.

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.

Country/Territory of origin: China

ORCID number: Jiang Wang 0000-0002-2036-1263; Jie Wen 0000-0002-5734-4678.

S-Editor: Yan JP
L-Editor: A
P-Editor: Yu HG

REFERENCES

1 **Forner A**, Reig M, Bruix J. Hepatocellular carcinoma. *Lancet* 2018; **391**: 1301-1314 [PMID: 29307467 DOI: 10.1016/S0140-6736(18)30010-2]

2 **Jiří T**, Igor K, Mba. Hepatocellular carcinoma future treatment options. *Klin Onkol* 2020; **33**: 26-29 [PMID: 33213162 DOI: 10.14735/amko20203S26]

3 **Siegel RL**, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin* 2022; **72**: 7-33 [PMID: 35020204 DOI: 10.3322/caac.21708]

4 **Rui L**. Energy metabolism in the liver. *Compr Physiol* 2014; **4**: 177-197 [PMID: 24692138 DOI: 10.1002/cphy.c130024]

5 **Auger C**, Alhasawi A, Contavadoo M, Appanna VD. Dysfunctional mitochondrial bioenergetics and the pathogenesis of hepatic disorders. *Front Cell Dev Biol* 2015; **3**: 40 [PMID: 26161384 DOI: 10.3389/fcell.2015.00040]

6 **Wallace DC**, Fan W, Procaccio V. Mitochondrial energetics and therapeutics. *Annu Rev Pathol* 2010; **5**: 297-348 [PMID: 20078222 DOI: 10.1146/annurev.pathol.4.110807.092314]

7 **Porporato PE**, Filigheddu N, Pedro JMB, Kroemer G, Galluzzi L. Mitochondrial metabolism and cancer. *Cell Res* 2018; **28**: 265-280 [PMID: 29219147 DOI: 10.1038/cr.2017.155]

8 **Kwon SM**, Lee YK, Min S, Woo HG, Wang HJ, Yoon G. Mitoribosome Defect in Hepatocellular Carcinoma Promotes an Aggressive Phenotype with Suppressed Immune Reaction. *iScience* 2020; **23**: 101247 [PMID: 32629612 DOI: 10.1016/j.isci.2020.101247]

9 **Kenny TC**, Craig AJ, Villanueva A, Germain D. Mitohormesis Primes Tumor Invasion and Metastasis. *Cell Rep* 2019; **27**: 2292-2303.e6 [PMID: 31116976 DOI: 10.1016/j.celrep.2019.04.095]

10 **Mills EL**, Kelly B, O'Neill LAJ. Mitochondria are the powerhouses of immunity. *Nat Immunol* 2017; **18**: 488-498 [PMID: 28418387 DOI: 10.1038/ni.3704]

11 **Münch C**, Harper JW. Mitochondrial unfolded protein response controls matrix pre-RNA processing and translation. *Nature* 2016; **534**: 710-713 [PMID: 27350246 DOI: 10.1038/nature18302]

12 **Wang M**, Zhao J, Zhang L, Wei F, Lian Y, Wu Y, Gong Z, Zhang S, Zhou J, Cao K, Li X, Xiong W, Li G, Zeng Z, Guo C. Role of tumor microenvironment in tumorigenesis. *J Cancer* 2017; **8**: 761-773 [PMID: 28382138 DOI: 10.7150/jca.17648]

13 **Nishida N**, Kudo M. Oncogenic Signal and Tumor Microenvironment in Hepatocellular Carcinoma. *Oncology* 2017; **93** Suppl 1: 160-164 [PMID: 29258072 DOI: 10.1159/000481246]

14 **Chen Y**, Tian Z. HBV-Induced Immune Imbalance in the Development of HCC. *Front Immunol* 2019; **10**: 2048 [PMID: 31507621 DOI: 10.3389/fimmu.2019.02048]

15 **Peng H**, Wisse E, Tian Z. Liver natural killer cells: subsets and roles in liver immunity. *Cell Mol Immunol* 2016; **13**: 328-336 [PMID: 26639736 DOI: 10.1038/cmi.2015.96]

16 **Pahl J**, Cerwenka A. Tricking the balance: NK cells in anti-cancer immunity. *Immunobiology* 2017; **222**: 11-20 [PMID: 26264743 DOI: 10.1016/j.imbio.2015.07.012]

17 **Ringelhan M**, Pfister D, O'Connor T, Pikarsky E, Heikenwalder M. The immunology of hepatocellular carcinoma. *Nat Immunol* 2018; **19**: 222-232 [PMID: 29379119 DOI: 10.1038/s41590-018-0044-z]

18 **Atanasov G**, Dino K, Schierle K, Dietel C, Aust G, Pratschke J, Seehofer D, Schmelzle M, Hau HM. Immunologic cellular characteristics of the tumour microenvironment of hepatocellular carcinoma drive patient outcomes. *World J Surg Oncol* 2019; **17**: 97 [PMID: 31170995 DOI: 10.1186/s12957-019-1635-3]

19 **Noy R**, Pollard JW. Tumor-associated macrophages: from mechanisms to therapy. *Immunity* 2014; **41**: 49-61 [PMID: 25035953 DOI: 10.1016/j.immuni.2014.06.010]

20 **Shaul ME**, Fridlender ZG. Neutrophils as active regulators of the immune system in the tumor microenvironment. *J Leukoc Biol* 2017; **102**: 343-349 [PMID: 28264904 DOI: 10.1189/jlb.5MR1216-508R]

21 **Dougan M**. Checkpoint Blockade Toxicity and Immune Homeostasis in the Gastrointestinal Tract. *Front Immunol* 2017; **8**: 1547 [PMID: 29230210 DOI: 10.3389/fimmu.2017.01547]

22 **Zhang J**, Bu X, Wang H, Zhu Y, Geng Y, Nihira NT, Tan Y, Ci Y, Wu F, Dai X, Guo J, Huang YH, Fan C, Ren S, Sun Y, Freeman GJ, Sicinski P, Wei W. Cyclin D-CDK4 kinase destabilizes PD-L1 *via* cullin 3-SPOP to control cancer immune surveillance. *Nature* 2018; **553**: 91-95 [PMID: 29160310 DOI: 10.1038/nature25015]

23 **Degli Esposti D**, Hamelin J, Bosselut N, Saffroy R, Sebagh M, Pommier A, Martel C, Lemoine A. Mitochondrial roles and cytoprotection in chronic liver injury. *Biochem Res Int* 2012; **2012**: 387626 [PMID: 22745910 DOI: 10.1155/2012/387626]

24 **Lemire J**, Mailloux R, Puiseux-Dao S, Appanna VD. Aluminum-induced defective mitochondrial metabolism perturbs cytoskeletal dynamics in human astrocytoma cells. *J Neurosci Res* 2009; **87**: 1474-1483 [PMID: 19084901 DOI: 10.1002/jnr.21965]

25 **Lartigue L**, Kushnareva Y, Seong Y, Lin H, Faustin B, Newmeyer DD. Caspase-independent mitochondrial cell death results from loss of respiration, not cytotoxic protein release. *Mol Biol Cell* 2009; **20**: 4871-4884 [PMID: 19793916 DOI: 10.1091/mbc.e09-07-0649]

26 **Kuznetsov AV**, Javadov S, Saks V, Margreiter R, Grimm M. Synchronism in mitochondrial ROS flashes, membrane depolarization and calcium sparks in human carcinoma cells. *Biochim Biophys Acta Bioenerg* 2017; **1858**: 418-431 [PMID: 28279675 DOI: 10.1016/j.bbabio.2017.03.001]

27 **Wang W**, Zhu M, Xu Z, Li W, Dong X, Chen Y, Lin B, Li M. Ropivacaine promotes apoptosis of hepatocellular carcinoma cells through damaging mitochondria and activating caspase-3 activity. *Biol Res* 2019; **52**: 36 [PMID: 31300048 DOI: 10.1186/s40659-019-0242-7]

28 **Zhang Z**, Li TE, Chen M, Xu D, Zhu Y, Hu BY, Lin ZF, Pan JJ, Wang X, Wu C, Zheng Y, Lu L, Jia HL, Gao S, Dong QZ, Qin LX. MFN1-dependent alteration of mitochondrial dynamics drives hepatocellular carcinoma metastasis by glucose metabolic reprogramming. *Br J Cancer* 2020; **122**: 209-220 [PMID: 31819189 DOI: 10.1038/s41416-019-0658-4]

29 **Han YS**, Yi EY, Jegal ME, Kim YJ. Cancer Stem-Like Phenotype of Mitochondria Dysfunctional Hep3B Hepatocellular Carcinoma Cell Line. *Cells* 2021; **10** [PMID: 34198967 DOI: 10.3390/cells10071608]

30 **Salimi A**, Saboji M, Seydi E. Synergistic Effects of Ellagic Acid and Sorafenib on Hepatocytes and Mitochondria Isolated from a Hepatocellular Carcinoma Rat Model. *Nutr Cancer* 2021; **73**: 2460-2468 [PMID: 33030061 DOI: 10.1080/01635581.2020.1829653]

31 **Yuan P**, Fu C, Yang Y, Adila A, Zhou F, Wei X, Wang W, Lv J, Li Y, Xia L, Li J. Cistanche tubulosa Phenylethanoid Glycosides Induce Apoptosis of Hepatocellular Carcinoma Cells by Mitochondria-Dependent and MAPK Pathways and Enhance Antitumor Effect through Combination with Cisplatin. *Integr Cancer Ther* 2021; **20**: 15347354211013085 [PMID: 33949239 DOI: 10.1177/15347354211013085]

32 **Lee HY**, Nga HT, Tian J, Yi HS. Mitochondrial Metabolic Signatures in Hepatocellular Carcinoma. *Cells* 2021; **10** [PMID: 34440674 DOI:

10.3390/cells10081901]
33 **Ko CY**, Shih PC, Huang PW, Lee YH, Chen YF, Tai MH, Liu CH, Wen ZH, Kuo HM. Sinularin, an Anti-Cancer Agent Causing Mitochondria-Modulated Apoptosis and Cytoskeleton Disruption in Human Hepatocellular Carcinoma. *Int J Mol Sci* 2021; **22** [PMID: 33920454 DOI: 10.3390/ijms22083946]
34 **McInerney J**, Pisani D, O'Connell MJ. The ring of life hypothesis for eukaryote origins is supported by multiple kinds of data. *Philos Trans R Soc Lond B Biol Sci* 2015; **370**: 20140323 [PMID: 26323755 DOI: 10.1098/rstb.2014.0323]
35 **Chan DC**. Mitochondrial Dynamics and Its Involvement in Disease. *Annu Rev Pathol* 2020; **15**: 235-259 [PMID: 31585519 DOI: 10.1146/annurev-pathmechdis-012419-032711]
36 **Shadel GS**, Horvath TL. Mitochondrial ROS signaling in organismal homeostasis. *Cell* 2015; **163**: 560-569 [PMID: 26496603 DOI: 10.1016/j.cell.2015.10.001]
37 **Chan DC**. Mitochondria: dynamic organelles in disease, aging, and development. *Cell* 2006; **125**: 1241-1252 [PMID: 16814712 DOI: 10.1016/j.cell.2006.06.010]
38 **Larsson NG**. Somatic mitochondrial DNA mutations in mammalian aging. *Annu Rev Biochem* 2010; **79**: 683-706 [PMID: 20350166 DOI: 10.1146/annurev-biochem-060408-093701]
39 **Liu S**, Zhang Y, Ren J, Li J. Microbial DNA recognition by cGAS-STING and other sensors in dendritic cells in inflammatory bowel diseases. *Inflamm Bowel Dis* 2015; **21**: 901-911 [PMID: 25581829 DOI: 10.1097/MIB.0000000000000299]
40 **West AP**, Shadel GS, Ghosh S. Mitochondria in innate immune responses. *Nat Rev Immunol* 2011; **11**: 389-402 [PMID: 21597473 DOI: 10.1038/nri2975]
41 **McCormack WJ**, Parker AE, O'Neill LA. Toll-like receptors and NOD-like receptors in rheumatic diseases. *Arthritis Res Ther* 2009; **11**: 243 [PMID: 19835640 DOI: 10.1186/ar2729]
42 **Marakalala MJ**, Ndlovu H. Signaling C-type lectin receptors in antimycobacterial immunity. *PLoS Pathog* 2017; **13**: e1006333 [PMID: 28640912 DOI: 10.1371/journal.ppat.1006333]
43 **Conte M**, Martucci M, Chiariello A, Franceschi C, Salvioli S. Mitochondria, immunosenescence and inflammaging: a role for mitokines? *Semin Immunopathol* 2020; **42**: 607-617 [PMID: 32757036 DOI: 10.1007/s00281-020-00813-0]
44 **Durieux J**, Wolff S, Dillin A. The cell-non-autonomous nature of electron transport chain-mediated longevity. *Cell* 2011; **144**: 79-91 [PMID: 21215371 DOI: 10.1016/j.cell.2010.12.016]
45 **Kim KH**, Lee MS. Autophagy as a crosstalk mediator of metabolic organs in regulation of energy metabolism. *Rev Endocr Metab Disord* 2014; **15**: 11-20 [PMID: 24085381 DOI: 10.1007/s11154-013-9272-6]
46 **Yu Y**, Bai F, Liu Y, Yang Y, Yuan Q, Zou D, Qu S, Tian G, Song L, Zhang T, Li S, Wang W, Ren G, Li D. Fibroblast growth factor (FGF21) protects mouse liver against D-galactose-induced oxidative stress and apoptosis *via* activating Nrf2 and PI3K/Akt pathways. *Mol Cell Biochem* 2015; **403**: 287-299 [PMID: 25701356 DOI: 10.1007/s11010-015-2358-6]
47 **Al-Aqil FA**, Monte MJ, Peleteiro-Vigil A, Briz O, Rosales R, González R, Aranda CJ, Ocón B, Uriarte I, de Medina FS, Martinez-Augustín O, Avila MA, Marín JJG, Romero MR. Interaction of glucocorticoids with FXR/FGF19/FGF21-mediated ileum-liver crosstalk. *Biochim Biophys Acta Mol Basis Dis* 2018; **1864**: 2927-2937 [PMID: 29883717 DOI: 10.1016/j.bbadis.2018.06.003]
48 **Nishimura T**, Nakatake Y, Konishi M, Itoh N. Identification of a novel FGF, FGF-21, preferentially expressed in the liver. *Biochim Biophys Acta* 2000; **1492**: 203-206 [PMID: 10858549 DOI: 10.1016/s0167-4781(00)00067-1]
49 **Inagaki T**, Dutchak P, Zhao G, Ding X, Gautron L, Parameswara V, Li Y, Goetz R, Mohammadi M, Esser V, Elmquist JK, Gerard RD, Burgess SC, Hammer RE, Mangelsdorf DJ, Kliewer SA. Endocrine regulation of the fasting response by PPARalpha-mediated induction of fibroblast growth factor 21. *Cell Metab* 2007; **5**: 415-425 [PMID: 17550777 DOI: 10.1016/j.cmet.2007.05.003]
50 **Badman MK**, Pissios P, Kennedy AR, Koukos G, Flier JS, Maratos-Flier E. Hepatic fibroblast growth factor 21 is regulated by PPARalpha and is a key mediator of hepatic lipid metabolism in ketotic states. *Cell Metab* 2007; **5**: 426-437 [PMID: 17550778 DOI: 10.1016/j.cmet.2007.05.002]
51 **Gälman C**, Lundåsen T, Kharitonenkov A, Bina HA, Eriksson M, Hafström I, Dahlin M, Amark P, Angelin B, Rudling M. The circulating metabolic regulator FGF21 is induced by prolonged fasting and PPARalpha activation in man. *Cell Metab* 2008; **8**: 169-174 [PMID: 18680716 DOI: 10.1016/j.cmet.2008.06.014]
52 **Kang SG**, Yi HS, Choi MJ, Ryu MJ, Jung S, Chung HK, Chang JY, Kim YK, Lee SE, Kim HW, Choi H, Kim DS, Lee JH, Kim KS, Kim HJ, Lee CH, Oike Y, Shong M. ANGPTL6 expression is coupled with mitochondrial OXPHOS function to regulate adipose FGF21. *J Endocrinol* 2017; **233**: 105-118 [PMID: 28184000 DOI: 10.1530/JOE-16-0549]
53 **Estall JL**, Ruas JL, Choi CS, Laznik D, Badman M, Maratos-Flier E, Shulman GI, Spiegelman BM. PGC-1alpha negatively regulates hepatic FGF21 expression by modulating the heme/Rev-Erb(alpha) axis. *Proc Natl Acad Sci U S A* 2009; **106**: 22510-22515 [PMID: 20018698 DOI: 10.1073/pnas.0912533106]
54 **Cyphert HA**, Ge X, Kohan AB, Salati LM, Zhang Y, Hillgartner FB. Activation of the farnesoid X receptor induces hepatic expression and secretion of fibroblast growth factor 21. *J Biol Chem* 2012; **287**: 25123-25138 [PMID: 22661717 DOI: 10.1074/jbc.M112.375907]
55 **Uebanso T**, Taketani Y, Yamamoto H, Amo K, Ominami H, Arai H, Takei Y, Masuda M, Tanimura A, Harada N, Yamanaka-Okumura H, Takeda E. Paradoxical regulation of human FGF21 by both fasting and feeding signals: is FGF21 a nutritional adaptation factor? *PLoS One* 2011; **6**: e22976 [PMID: 21829679 DOI: 10.1371/journal.pone.0022976]
56 **Uebanso T**, Taketani Y, Yamamoto H, Amo K, Tanaka S, Arai H, Takei Y, Masuda M, Yamanaka-Okumura H, Takeda E. Liver X receptor negatively regulates fibroblast growth factor 21 in the fatty liver induced by cholesterol-enriched diet. *J Nutr Biochem* 2012; **23**: 785-790 [PMID: 21889884 DOI: 10.1016/j.jnutbio.2011.03.023]
57 **Zhang F**, Yu L, Lin X, Cheng P, He L, Li X, Lu X, Tan Y, Yang H, Cai L, Zhang C. Minireview: Roles of Fibroblast Growth Factors 19 and 21 in Metabolic Regulation and Chronic Diseases. *Mol Endocrinol* 2015; **29**: 1400-1413 [PMID: 26308386 DOI: 10.1210/me.2015-1155]
58 **Yang C**, Lu W, Lin T, You P, Ye M, Huang Y, Jiang X, Wang C, Wang F, Lee MH, Yeung SC, Johnson RL, Wei C, Tsai RY, Frazier ML, McKeehan WL, Luo Y. Activation of Liver FGF21 in hepatocarcinogenesis and during hepatic stress. *BMC Gastroenterol* 2013; **13**: 67 [PMID: 23590285 DOI: 10.1186/1471-230X-13-67]
59 **Zhang D**, Wang S, Ospina E, Shabandri O, Lank D, Akakpo JY, Zhao Z, Yang M, Wu J, Jaeschke H, Saha P, Tong X, Yin L. Fructose Protects Against Acetaminophen-Induced Hepatotoxicity Mainly by Activating the Carbohydrate-Response Element-Binding Protein α-Fibroblast Growth Factor 21 Axis in Mice. *Hepatol Commun* 2021; **5**: 992-1008 [PMID: 34141985 DOI: 10.1002/hep4.1683]
60 **Schaap FG**, Kremer AE, Lamers WH, Jansen PL, Gaemers IC. Fibroblast growth factor 21 is induced by endoplasmic reticulum stress. *Biochimie* 2013; **95**: 692-699 [PMID: 23123503 DOI: 10.1016/j.biochi.2012.10.019]

61 **Degirolamo C**, Sabbà C, Moschetta A. Therapeutic potential of the endocrine fibroblast growth factors FGF19, FGF21 and FGF23. *Nat Rev Drug Discov* 2016; **15**: 51-69 [PMID: 26567701 DOI: 10.1038/nrd.2015.9]

62 **Luo Y**, Yang C, Lu W, Xie R, Jin C, Huang P, Wang F, McKeehan WL. Metabolic regulator betaKlotho interacts with fibroblast growth factor receptor 4 (FGFR4) to induce apoptosis and inhibit tumor cell proliferation. *J Biol Chem* 2010; **285**: 30069-30078 [PMID: 20657013 DOI: 10.1074/jbc.M110.148288]

63 **Wang D**, Liu F, Zhu L, Lin P, Han F, Wang X, Tan X, Lin L, Xiong Y. FGF21 alleviates neuroinflammation following ischemic stroke by modulating the temporal and spatial dynamics of microglia/macrophages. *J Neuroinflammation* 2020; **17**: 257 [PMID: 32867781 DOI: 10.1186/s12974-020-01921-2]

64 **Lu W**, Li X, Luo Y. FGF21 in obesity and cancer: New insights. *Cancer Lett* 2021; **499**: 5-13 [PMID: 33264641 DOI: 10.1016/j.canlet.2020.11.026]

65 **Wang Z**, He L, Li W, Xu C, Zhang J, Wang D, Dou K, Zhuang R, Jin B, Zhang W, Hao Q, Zhang K, Wang S, Gao Y, Gu J, Shang L, Tan Z, Su H, Zhang Y, Zhang C, Li M. GDF15 induces immunosuppression *via* CD48 on regulatory T cells in hepatocellular carcinoma. *J Immunother Cancer* 2021; **9** [PMID: 34489334 DOI: 10.1136/jitc-2021-002787]

66 **Myojin Y**, Hikita H, Sugiyama M, Sasaki Y, Fukumoto K, Sakane S, Makino Y, Takemura N, Yamada R, Shigekawa M, Kodama T, Sakamori R, Kobayashi S, Tatsumi T, Suemizu H, Eguchi H, Kokudo N, Mizokami M, Takehara T. Hepatic Stellate Cells in Hepatocellular Carcinoma Promote Tumor Growth Via Growth Differentiation Factor 15 Production. *Gastroenterology* 2021; **160**: 1741-1754.e16 [PMID: 33346004 DOI: 10.1053/j.gastro.2020.12.015]

67 **Breit SN**, Johnen H, Cook AD, Tsai VW, Mohammad MG, Kuffner T, Zhang HP, Marquis CP, Jiang L, Lockwood G, Lee-Ng M, Husaini Y, Wu L, Hamilton JA, Brown DA. The TGF-β superfamily cytokine, MIC-1/GDF15: a pleotrophic cytokine with roles in inflammation, cancer and metabolism. *Growth Factors* 2011; **29**: 187-195 [PMID: 21831009 DOI: 10.3109/08977194.2011.607137]

68 **Choi MJ**, Jung SB, Lee SE, Kang SG, Lee JH, Ryu MJ, Chung HK, Chang JY, Kim YK, Hong HJ, Kim H, Kim HJ, Lee CH, Mardinoglu A, Yi HS, Shong M. An adipocyte-specific defect in oxidative phosphorylation increases systemic energy expenditure and protects against diet-induced obesity in mouse models. *Diabetologia* 2020; **63**: 837-852 [PMID: 31925461 DOI: 10.1007/s00125-019-05082-7]

69 **Emmerson PJ**, Wang F, Du Y, Liu Q, Pickard RT, Gonciarz MD, Coskun T, Hamang MJ, Sindelar DK, Ballman KK, Foltz LA, Muppidi A, Alsina-Fernandez J, Barnard GC, Tang JX, Liu X, Mao X, Siegel R, Sloan JH, Mitchell PJ, Zhang BB, Gimeno RE, Shan B, Wu X. The metabolic effects of GDF15 are mediated by the orphan receptor GFRAL. *Nat Med* 2017; **23**: 1215-1219 [PMID: 28846098 DOI: 10.1038/nm.4393]

70 **Chung HK**, Ryu D, Kim KS, Chang JY, Kim YK, Yi HS, Kang SG, Choi MJ, Lee SE, Jung SB, Ryu MJ, Kim SJ, Kweon GR, Kim H, Hwang JH, Lee CH, Lee SJ, Wall CE, Downes M, Evans RM, Auwerx J, Shong M. Growth differentiation factor 15 is a myomitokine governing systemic energy homeostasis. *J Cell Biol* 2017; **216**: 149-165 [PMID: 27986797 DOI: 10.1083/jcb.201607110]

71 **Lee SE**, Kang SG, Choi MJ, Jung SB, Ryu MJ, Chung HK, Chang JY, Kim YK, Lee JH, Kim KS, Kim HJ, Lee HK, Yi HS, Shong M. Growth Differentiation Factor 15 Mediates Systemic Glucose Regulatory Action of T-Helper Type 2 Cytokines. *Diabetes* 2017; **66**: 2774-2788 [PMID: 28874416 DOI: 10.2337/db17-0333]

72 **Fujita Y**, Ito M, Ohsawa I. Mitochondrial stress and GDF15 in the pathophysiology of sepsis. *Arch Biochem Biophys* 2020; **696**: 108668 [PMID: 33188737 DOI: 10.1016/j.abb.2020.108668]

73 **Wallin U**, Glimelius B, Jirström K, Darmanis S, Nong RY, Pontén F, Johansson C, Påhlman L, Birgisson H. Growth differentiation factor 15: a prognostic marker for recurrence in colorectal cancer. *Br J Cancer* 2011; **104**: 1619-1627 [PMID: 21468045 DOI: 10.1038/bjc.2011.112]

74 **Lee DH**, Yang Y, Lee SJ, Kim KY, Koo TH, Shin SM, Song KS, Lee YH, Kim YJ, Lee JJ, Choi I, Lee JH. Macrophage inhibitory cytokine-1 induces the invasiveness of gastric cancer cells by up-regulating the urokinase-type plasminogen activator system. *Cancer Res* 2003; **63**: 4648-4655 [PMID: 12907645]

75 **Albertoni M**, Shaw PH, Nozaki M, Godard S, Tenan M, Hamou MF, Fairlie DW, Breit SN, Paralkar VM, de Tribolet N, Van Meir EG, Hegi ME. Anoxia induces macrophage inhibitory cytokine-1 (MIC-1) in glioblastoma cells independently of p53 and HIF-1. *Oncogene* 2002; **21**: 4212-4219 [PMID: 12082608 DOI: 10.1038/sj.onc.1205610]

76 **Baek SJ**, Kim KS, Nixon JB, Wilson LC, Eling TE. Cyclooxygenase inhibitors regulate the expression of a TGF-beta superfamily member that has proapoptotic and antitumorigenic activities. *Mol Pharmacol* 2001; **59**: 901-908 [PMID: 11259636]

77 **Zhang L**, Yang X, Pan HY, Zhou XJ, Li J, Chen WT, Zhong LP, Zhang ZY. Expression of growth differentiation factor 15 is positively correlated with histopathological malignant grade and in vitro cell proliferation in oral squamous cell carcinoma. *Oral Oncol* 2009; **45**: 627-632 [PMID: 18805046 DOI: 10.1016/j.oraloncology.2008.07.017]

78 **Wang L**, Liu Y, Li W, Song Z. Growth differentiation factor 15 promotes cell viability, invasion, migration, and angiogenesis in human liver carcinoma cell line HepG2. *Clin Res Hepatol Gastroenterol* 2017; **41**: 408-414 [PMID: 28161428 DOI: 10.1016/j.clinre.2016.12.009]

79 **de Zegher F**, Díaz M, Villarroya J, Cairó M, López-Bermejo A, Villarroya F, Ibáñez L. The relative deficit of GDF15 in adolescent girls with PCOS can be changed into an abundance that reduces liver fat. *Sci Rep* 2021; **11**: 7018 [PMID: 33782413 DOI: 10.1038/s41598-021-86317-9]

80 **Zhang IW**, Curto A, López-Vicario C, Casulleras M, Duran-Güell M, Flores-Costa R, Colsch B, Aguilar F, Aransay AM, Lozano JJ, Hernández-Tejero M, Toapanta D, Fernández J, Arroyo V, Clària J. Mitochondrial dysfunction governs immunometabolism in leukocytes of patients with acute-on-chronic liver failure. *J Hepatol* 2022; **76**: 93-106 [PMID: 34450236 DOI: 10.1016/j.jhep.2021.08.009]

81 **Zhou Y**, Yin X, Ying J, Zhang B. Golgi protein 73 versus alpha-fetoprotein as a biomarker for hepatocellular carcinoma: a diagnostic meta-analysis. *BMC Cancer* 2012; **12**: 17 [PMID: 22244200 DOI: 10.1186/1471-2407-12-17]

82 **Qi P**, Ma MZ, Kuai JH. Identification of growth differentiation factor 15 as a pro-fibrotic factor in mouse liver fibrosis progression. *Int J Exp Pathol* 2021; **102**: 148-156 [PMID: 33983642 DOI: 10.1111/iep.12398]

83 **Li L**, Zhang R, Yang H, Zhang D, Liu J, Li J, Guo B. GDF15 knockdown suppresses cervical cancer cell migration in vitro through the TGF-β/Smad2/3/Snail1 pathway. *FEBS Open Bio* 2020; **10**: 2750-2760 [PMID: 33098235 DOI: 10.1002/2211-5463.13013]

84 **Adolph TE**, Grabherr F, Mayr L, Grander C, Enrich B, Moschen AR, Tilg H. Weight Loss Induced by Bariatric Surgery Restricts Hepatic GDF15 Expression. *J Obes* 2018; **2018**: 7108075 [PMID: 30533221 DOI: 10.1155/2018/7108075]

85 **Chen J**, Tang D, Xu C, Niu Z, Li H, Li Y, Zhang P. Evaluation of Serum GDF15, AFP, and PIVKA-II as Diagnostic Markers for HBV-Associated Hepatocellular Carcinoma. *Lab Med* 2021; **52**: 381-389 [PMID: 33159511 DOI: 10.1093/labmed/lmaa089]

86 **Li Q**, Tan Y, Chen S, Xiao X, Zhang M, Wu Q, Dong M. Irisin alleviates LPS-induced liver injury and inflammation through inhibition of NLRP3 inflammasome and NF-κB signaling. *J Recept Signal Transduct Res* 2021; **41**: 294-303 [PMID: 32814473 DOI: 10.1080/10799893.2020.1808675]

87 **Kukla M**, Skladany L, Menżyk T, Derra A, Stygar D, Skonieczna M, Hudy D, Nabrdalik K, Gumprecht J, Marlicz W, Koulaouzidis A, Koller

T. Irisin in Liver Cirrhosis. *J Clin Med* 2020; **9** [PMID: 33003490 DOI: 10.3390/jcm9103158]

88 **Shi G**, Tang N, Qiu J, Zhang D, Huang F, Cheng Y, Ding K, Li W, Zhang P, Tan X. Irisin stimulates cell proliferation and invasion by targeting the PI3K/AKT pathway in human hepatocellular carcinoma. *Biochem Biophys Res Commun* 2017; **493**: 585-591 [PMID: 28867187 DOI: 10.1016/j.bbrc.2017.08.148]

89 **Gaggini M**, Cabiati M, Del Turco S, Navarra T, De Simone P, Filipponi F, Del Ry S, Gastaldelli A, Basta G. Increased FNDC5/Irisin expression in human hepatocellular carcinoma. *Peptides* 2017; **88**: 62-66 [PMID: 28012856 DOI: 10.1016/j.peptides.2016.12.014]

90 **Myint PK**, Ito A, Appiah MG, Obeng G, Darkwah S, Kawamoto E, Gaowa A, Park EJ, Shimaoka M. Irisin supports integrin-mediated cell adhesion of lymphocytes. *Biochem Biophys Rep* 2021; **26**: 100977 [PMID: 33732908 DOI: 10.1016/j.bbrep.2021.100977]

91 **Pinkowska A**, Podhorska-Okołów M, Dzięgiel P, Nowińska K. The Role of Irisin in Cancer Disease. *Cells* 2021; **10** [PMID: 34204674 DOI: 10.3390/cells10061479]

92 **Gannon NP**, Vaughan RA, Garcia-Smith R, Bisoffi M, Trujillo KA. Effects of the exercise-inducible myokine irisin on malignant and non-malignant breast epithelial cell behavior in vitro. *Int J Cancer* 2015; **136**: E197-E202 [PMID: 25124080 DOI: 10.1002/ijc.29142]

93 **Shao L**, Li H, Chen J, Song H, Zhang Y, Wu F, Wang W, Zhang W, Wang F, Tang D. Irisin suppresses the migration, proliferation, and invasion of lung cancer cells *via* inhibition of epithelial-to-mesenchymal transition. *Biochem Biophys Res Commun* 2017; **485**: 598-605 [PMID: 27986567 DOI: 10.1016/j.bbrc.2016.12.084]

94 **Tekin S**, Erden Y, Sandal S, Yılmaz B. Is Irisin an Anticarcinogenic Peptide. *Med Sci* 2015; **4**: 2172

95 **Kong G**, Jiang Y, Sun X, Cao Z, Zhang G, Zhao Z, Zhao Y, Yu Q, Cheng G. Irisin reverses the IL-6 induced epithelial-mesenchymal transition in osteosarcoma cell migration and invasion through the STAT3/Snail signaling pathway. *Oncol Rep* 2017; **38**: 2647-2656 [PMID: 29048621 DOI: 10.3892/or.2017.5973]

96 **Moon HS**, Mantzoros CS. Regulation of cell proliferation and malignant potential by irisin in endometrial, colon, thyroid and esophageal cancer cell lines. *Metabolism* 2014; **63**: 188-193 [PMID: 24268368 DOI: 10.1016/j.metabol.2013.10.005]

97 **Provatopoulou X**, Georgiou GP, Kalogera E, Kalles V, Matiatou MA, Papapanagiotou I, Sagkriotis A, Zografos GC, Gounaris A. Serum irisin levels are lower in patients with breast cancer: association with disease diagnosis and tumor characteristics. *BMC Cancer* 2015; **15**: 898 [PMID: 26560078 DOI: 10.1186/s12885-015-1898-1]

98 **Zhao J**, Qiao L, Dong J, Wu R. Antioxidant Effects of Irisin in Liver Diseases: Mechanistic Insights. *Oxid Med Cell Longev* 2022; **2022**: 3563518 [PMID: 35035659 DOI: 10.1155/2022/3563518]

99 **Aydin S**, Kuloglu T, Ozercan MR, Albayrak S, Aydin S, Bakal U, Yilmaz M, Kalayci M, Yardim M, Sarac M, Kazez A, Kocdor H, Kanat B, Ozercan İH, Gonen M, Bilgen M, Balgetir F. Irisin immunohistochemistry in gastrointestinal system cancers. *Biotech Histochem* 2016; **91**: 242-250 [PMID: 26963139 DOI: 10.3109/10520295.2015.1136988]

100 **Kuloglu T**, Celik O, Aydin S, Hanifi Ozercan I, Acet M, Aydin Y, Artas G, Turk A, Yardim M, Ozan G, Hanifi Yalcin M, Kocaman N. Irisin immunostaining characteristics of breast and ovarian cancer cells. *Cell Mol Biol (Noisy-le-grand)* 2016; **62**: 40-44 [PMID: 27545213]

101 **Kumar KG**, Trevaskis JL, Lam DD, Sutton GM, Koza RA, Chouljenko VN, Kousoulas KG, Rogers PM, Kesterson RA, Thearle M, Ferrante AW Jr, Mynatt RL, Burris TP, Dong JZ, Halem HA, Culler MD, Heisler LK, Stephens JM, Butler AA. Identification of adropin as a secreted factor linking dietary macronutrient intake with energy homeostasis and lipid metabolism. *Cell Metab* 2008; **8**: 468-481 [PMID: 19041763 DOI: 10.1016/j.cmet.2008.10.011]

102 **Zhang S**, Chen Q, Lin X, Chen M, Liu Q. A Review of Adropin as the Medium of Dialogue between Energy Regulation and Immune Regulation. *Oxid Med Cell Longev* 2020; **2020**: 3947806 [PMID: 32190172 DOI: 10.1155/2020/3947806]

103 **Chen S**, Zeng K, Liu QC, Guo Z, Zhang S, Chen XR, Lin JH, Wen JP, Zhao CF, Lin XH, Gao F. Adropin deficiency worsens HFD-induced metabolic defects. *Cell Death Dis* 2017; **8**: e3008 [PMID: 28837146 DOI: 10.1038/cddis.2017.362]

104 **Chao HC**, Tsai PF, Lee SC, Lin YS, Wu MC. Effects of Myricetin-Containing Ethanol Solution on High-Fat Diet Induced Obese Rats. *J Food Sci* 2017; **82**: 1947-1952 [PMID: 28675777 DOI: 10.1111/1750-3841.13755]

105 **Celik E**, Yilmaz E, Celik O, Ulas M, Turkcuoglu I, Karaer A, Simsek Y, Minareci Y, Aydin S. Maternal and fetal adropin levels in gestational diabetes mellitus. *J Perinat Med* 2013; **41**: 375-380 [PMID: 23314506 DOI: 10.1515/jpm-2012-0227]

106 **Lian W**, Gu X, Qin Y, Zheng X. Elevated plasma levels of adropin in heart failure patients. *Intern Med* 2011; **50**: 1523-1527 [PMID: 21804276 DOI: 10.2169/internalmedicine.50.5163]

107 **Yang C**, DeMars KM, Hawkins KE, Candelario-Jalil E. Adropin reduces paracellular permeability of rat brain endothelial cells exposed to ischemia-like conditions. *Peptides* 2016; **81**: 29-37 [PMID: 27020249 DOI: 10.1016/j.peptides.2016.03.009]

108 **Ganesh Kumar K**, Zhang J, Gao S, Rossi J, McGuinness OP, Halem HH, Culler MD, Mynatt RL, Butler AA. Adropin deficiency is associated with increased adiposity and insulin resistance. *Obesity (Silver Spring)* 2012; **20**: 1394-1402 [PMID: 22318315 DOI: 10.1038/oby.2012.31]

109 **Miyao M**, Kotani H, Ishida T, Kawai C, Manabe S, Abiru H, Tamaki K. Pivotal role of liver sinusoidal endothelial cells in NAFLD/NASH progression. *Lab Invest* 2015; **95**: 1130-1144 [PMID: 26214582 DOI: 10.1038/labinvest.2015.95]

110 **Niepolski L**, Grzegorzewska AE. Salusins and adropin: New peptides potentially involved in lipid metabolism and atherosclerosis. *Adv Med Sci* 2016; **61**: 282-287 [PMID: 27128818 DOI: 10.1016/j.advms.2016.03.007]

111 **Kim SJ**, Xiao J, Wan J, Cohen P, Yen K. Mitochondrially derived peptides as novel regulators of metabolism. *J Physiol* 2017; **595**: 6613-6621 [PMID: 28574175 DOI: 10.1113/JP274472]

112 **Zhu WW**, Wang SR, Liu ZH, Cao YJ, Wang F, Wang J, Liu CF, Xie Y, Zhang YL. Gly[14]-humanin inhibits ox-LDL uptake and stimulates cholesterol efflux in macrophage-derived foam cells. *Biochem Biophys Res Commun* 2017; **482**: 93-99 [PMID: 27815075 DOI: 10.1016/j.bbrc.2016.10.138]

113 **Hashimoto Y**, Niikura T, Tajima H, Yasukawa T, Sudo H, Ito Y, Kita Y, Kawasumi M, Kouyama K, Doyu M, Sobue G, Koide T, Tsuji S, Lang J, Kurokawa K, Nishimoto I. A rescue factor abolishing neuronal cell death by a wide spectrum of familial Alzheimer's disease genes and Abeta. *Proc Natl Acad Sci U S A* 2001; **98**: 6336-6341 [PMID: 11371646 DOI: 10.1073/pnas.101133498]

114 **Cobb LJ**, Lee C, Xiao J, Yen K, Wong RG, Nakamura HK, Mehta HH, Gao Q, Ashur C, Huffman DM, Wan J, Muzumdar R, Barzilai N, Cohen P. Naturally occurring mitochondrial-derived peptides are age-dependent regulators of apoptosis, insulin sensitivity, and inflammatory markers. *Aging (Albany NY)* 2016; **8**: 796-809 [PMID: 27070352 DOI: 10.18632/aging.100943]

115 **Kim KH**, Son JM, Benayoun BA, Lee C. The Mitochondrial-Encoded Peptide MOTS-c Translocates to the Nucleus to Regulate Nuclear Gene Expression in Response to Metabolic Stress. *Cell Metab* 2018; **28**: 516-524.e7 [PMID: 29983246 DOI: 10.1016/j.cmet.2018.06.008]

116 **Qin Q**, Delrio S, Wan J, Jay Widmer R, Cohen P, Lerman LO, Lerman A. Downregulation of circulating MOTS-c levels in patients with coronary endothelial dysfunction. *Int J Cardiol* 2018; **254**: 23-27 [PMID: 29242099 DOI: 10.1016/j.ijcard.2017.12.001]

117 **Maruhashi T**, Kihara Y, Higashi Y. Assessment of endothelium-independent vasodilation: from methodology to clinical perspectives. *J Hypertens* 2018; **36**: 1460-1467 [PMID: 29664811 DOI: 10.1097/HJH.0000000000001750]

118 **Hazafa A**, Batool A, Ahmad S, Amjad M, Chaudhry SN, Asad J, Ghuman HF, Khan HM, Naeem M, Ghani U. Humanin: A mitochondrial-derived peptide in the treatment of apoptosis-related diseases. *Life Sci* 2021; **264**: 118679 [PMID: 33130077 DOI: 10.1016/j.lfs.2020.118679]

119 **Mehta HH**, Xiao J, Ramirez R, Miller B, Kim SJ, Cohen P, Yen K. Metabolomic profile of diet-induced obesity mice in response to humanin and small humanin-like peptide 2 treatment. *Metabolomics* 2019; **15**: 88 [PMID: 31172328 DOI: 10.1007/s11306-019-1549-7]

120 **Chacinska A**, Koehler CM, Milenkovic D, Lithgow T, Pfanner N. Importing mitochondrial proteins: machineries and mechanisms. *Cell* 2009; **138**: 628-644 [PMID: 19703392 DOI: 10.1016/j.cell.2009.08.005]

121 **Zhao Q**, Wang J, Levichkin IV, Stasinopoulos S, Ryan MT, Hoogenraad NJ. A mitochondrial specific stress response in mammalian cells. *EMBO J* 2002; **21**: 4411-4419 [PMID: 12198143 DOI: 10.1093/emboj/cdf445]

122 **Mohrin M**, Shin J, Liu Y, Brown K, Luo H, Xi Y, Haynes CM, Chen D. Stem cell aging. A mitochondrial UPR-mediated metabolic checkpoint regulates hematopoietic stem cell aging. *Science* 2015; **347**: 1374-1377 [PMID: 25792330 DOI: 10.1126/science.aaa2361]

123 **Nargund AM**, Fiorese CJ, Pellegrino MW, Deng P, Haynes CM. Mitochondrial and nuclear accumulation of the transcription factor ATFS-1 promotes OXPHOS recovery during the UPR(mt). *Mol Cell* 2015; **58**: 123-133 [PMID: 25773600 DOI: 10.1016/j.molcel.2015.02.008]

124 **Smyrnias I**, Gray SP, Okonko DO, Sawyer G, Zoccarato A, Catibog N, López B, González A, Ravassa S, Díez J, Shah AM. Cardioprotective Effect of the Mitochondrial Unfolded Protein Response During Chronic Pressure Overload. *J Am Coll Cardiol* 2019; **73**: 1795-1806 [PMID: 30975297 DOI: 10.1016/j.jacc.2018.12.087]

125 **Xu M**, Xue RQ, Lu Y, Yong SY, Wu Q, Cui YL, Zuo XT, Yu XJ, Zhao M, Zang WJ. Choline ameliorates cardiac hypertrophy by regulating metabolic remodelling and UPRmt through SIRT3-AMPK pathway. *Cardiovasc Res* 2019; **115**: 530-545 [PMID: 30165480 DOI: 10.1093/cvr/cvy217]

126 **Martinez BA**, Petersen DA, Gaeta AL, Stanley SP, Caldwell GA, Caldwell KA. Dysregulation of the Mitochondrial Unfolded Protein Response Induces Non-Apoptotic Dopaminergic Neurodegeneration in C. elegans Models of Parkinson's Disease. *J Neurosci* 2017; **37**: 11085-11100 [PMID: 29030433 DOI: 10.1523/JNEUROSCI.1294-17.2017]

127 **Shpilka T**, Haynes CM. The mitochondrial UPR: mechanisms, physiological functions and implications in ageing. *Nat Rev Mol Cell Biol* 2018; **19**: 109-120 [PMID: 29165426 DOI: 10.1038/nrm.2017.110]

128 **Sorrentino V**, Romani M, Mouchiroud L, Beck JS, Zhang H, D'Amico D, Moullan N, Potenza F, Schmid AW, Rietsch S, Counts SE, Auwerx J. Enhancing mitochondrial proteostasis reduces amyloid-β proteotoxicity. *Nature* 2017; **552**: 187-193 [PMID: 29211722 DOI: 10.1038/nature25143]

129 **Kenny TC**, Germain D. mtDNA, Metastasis, and the Mitochondrial Unfolded Protein Response (UPR(mt)). *Front Cell Dev Biol* 2017; **5**: 37 [PMID: 28470001 DOI: 10.3389/fcell.2017.00037]

130 **Yi HS**. Implications of Mitochondrial Unfolded Protein Response and Mitokines: A Perspective on Fatty Liver Diseases. *Endocrinol Metab (Seoul)* 2019; **34**: 39-46 [PMID: 30912337 DOI: 10.3803/EnM.2019.34.1.39]

131 **Yi HS**, Chang JY, Shong M. The mitochondrial unfolded protein response and mitohormesis: a perspective on metabolic diseases. *J Mol Endocrinol* 2018; **61**: R91-R105 [PMID: 30307158 DOI: 10.1530/JME-18-0005]

132 **Fiorese CJ**, Schulz AM, Lin YF, Rosin N, Pellegrino MW, Haynes CM. The Transcription Factor ATF5 Mediates a Mammalian Mitochondrial UPR. *Curr Biol* 2016; **26**: 2037-2043 [PMID: 27426517 DOI: 10.1016/j.cub.2016.06.002]

133 **Teske BF**, Fusakio ME, Zhou D, Shan J, McClintick JN, Kilberg MS, Wek RC. CHOP induces activating transcription factor 5 (ATF5) to trigger apoptosis in response to perturbations in protein homeostasis. *Mol Biol Cell* 2013; **24**: 2477-2490 [PMID: 23761072 DOI: 10.1091/mbc.E13-01-0067]

134 **Guo X**, Aviles G, Liu Y, Tian R, Unger BA, Lin YT, Wiita AP, Xu K, Correia MA, Kampmann M. Mitochondrial stress is relayed to the cytosol by an OMA1-DELE1-HRI pathway. *Nature* 2020; **579**: 427-432 [PMID: 32132707 DOI: 10.1038/s41586-020-2078-2]

135 **Kenny TC**, Manfredi G, Germain D. The Mitochondrial Unfolded Protein Response as a Non-Oncogene Addiction to Support Adaptation to Stress during Transformation in Cancer and Beyond. *Front Oncol* 2017; **7**: 159 [PMID: 28798902 DOI: 10.3389/fonc.2017.00159]

136 **Smyrnias I**. The mitochondrial unfolded protein response and its diverse roles in cellular stress. *Int J Biochem Cell Biol* 2021; **133**: 105934 [PMID: 33529716 DOI: 10.1016/j.biocel.2021.105934]

137 **Kenny TC**, Hart P, Ragazzi M, Sersinghe M, Chipuk J, Sagar MAK, Eliceiri KW, LaFramboise T, Grandhi S, Santos J, Riar AK, Papa L, D'Aurello M, Manfredi G, Bonini MG, Germain D. Selected mitochondrial DNA landscapes activate the SIRT3 axis of the UPR(mt) to promote metastasis. *Oncogene* 2017; **36**: 4393-4404 [PMID: 28368421 DOI: 10.1038/onc.2017.52]

138 **Davis RL**, Liang C, Edema-Hildebrand F, Riley C, Needham M, Sue CM. Fibroblast growth factor 21 is a sensitive biomarker of mitochondrial disease. *Neurology* 2013; **81**: 1819-1826 [PMID: 24142477 DOI: 10.1212/01.wnl.0000436068.43384.ef]

139 **Fujita Y**, Taniguchi Y, Shinkai S, Tanaka M, Ito M. Secreted growth differentiation factor 15 as a potential biomarker for mitochondrial dysfunctions in aging and age-related disorders. *Geriatr Gerontol Int* 2016; **16** Suppl 1: 17-29 [PMID: 27018280 DOI: 10.1111/ggi.12724]

140 **Xu X**, Krumm C, So JS, Bare CJ, Holman C, Gromada J, Cohen DE, Lee AH. Preemptive Activation of the Integrated Stress Response Protects Mice From Diet-Induced Obesity and Insulin Resistance by Fibroblast Growth Factor 21 Induction. *Hepatology* 2018; **68**: 2167-2181 [PMID: 29698569 DOI: 10.1002/hep.30060]

141 **Patel V**, Adya R, Chen J, Ramanjaneya M, Bari MF, Bhudia SK, Hillhouse EW, Tan BK, Randeva HS. Novel insights into the cardio-protective effects of FGF21 in lean and obese rat hearts. *PLoS One* 2014; **9**: e87102 [PMID: 24498293 DOI: 10.1371/journal.pone.0087102]

142 **Liu ZY**, Luo Y, Fang AP, Wusiman M, He TT, Liu XZ, Yishake D, Chen S, Lu XT, Zhang YJ, Zhu HL. High serum fibroblast growth factor 21 is associated with inferior hepatocellular carcinoma survival: A prospective cohort study. *Liver Int* 2022; **42**: 663-673 [PMID: 34812573 DOI: 10.1111/liv.15100]

143 **Marquard S**, Thomann S, Weiler SME, Sticht C, Gretz N, Schirmacher P, Breuhahn K. [Nonautonomous effects of oncogenic YAP in hepatocarcinogenesis]. *Pathologe* 2017; **38**: 175-179 [PMID: 29018944 DOI: 10.1007/s00292-017-0361-2]

144 **Pazgan-Simon M**, Zuwala-Jagiello J, Menzyk T, Bator M, Derra A, Lekstan A, Grzebyk E, Simon K, Kukla M. Serum betatrophin and irisin levels in hepatocellular carcinoma. *J Physiol Pharmacol* 2020; **71** [PMID: 32554846 DOI: 10.26402/jpp.2020.1.11]

145 **Chattopadhyay M**, Jenkins EC, Lechuga-Vieco AV, Nie K, Fiel MI, Rialdi A, Guccione E, Enriquez JA, Sia D, Lujambio A, Germain D. The portrait of liver cancer is shaped by mitochondrial genetics. *Cell Rep* 2022; **38**: 110254 [PMID: 35045282 DOI: 10.1016/j.celrep.2021.110254]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com