REVIEW
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Changes of mitochondrial dynamics during the progression of non-alcoholic fatty liver disease: a review

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Ling Yang and Huan-Tian Cui provided the ideas; Man-Na Li, Ying Zhang and Hai-Di Wang edited the original draft; Man-Na Li wrote the initial draft; Jia-Bao Liao, Ning Wang and Jing Miao revised the manuscript.

Competing interests

The authors declare no conflicts of interest.

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Abbreviations

NAFLD, non-alcoholic fatty liver disease; ATP, adenosine triphosphate; TCM, traditional Chinese medicine; OMM, outer mitochondrial membrane; IMM, inner mitochondrial membrane; mtDNA, mitochondrial DNA; ER, endoplasmic reticulum; DRP1, mitochondrial dynamin 1; FIS1, mitochondrial fission protein; MFN1/2, mitochondrial fusion protein 1/2; CL, cardiolipin; OPA1, optic atrophy protein.

Citation

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is a chronic liver disease closely related to metabolic disorders that pose a serious threat to human health. Currently, no specific drugs are available for treating the aetiology of NAFLD in clinical practice. Mitochondria have various biological functions inside the cell. Studies have found that mitochondrial fission and fusion are closely related to NAFLD. Therefore, identifying therapeutic targets for NAFLD through mitochondrial fission and fusion is crucial. Particularly in the field of traditional Chinese medicine, good therapeutic effects have been achieved in the treatment of NAFLD by protecting mitochondrial fusion and fission. Therefore, this article reviews the relationship between mitochondrial dynamics and NAFLD as well as the treatment of NAFLD through the regulation of mitochondrial fission and fusion with traditional Chinese medicine to provide a reference for the clinical application of traditional Chinese medicine in regulating mitochondrial fission and fusion functions to treat NAFLD.

Keywords: mitochondrial dynamics; NAFLD; traditional Chinese medicine

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Background

Mitochondria are considered the “power stations” of cells, generating adenosine triphosphate (ATP), the energy required for cellular metabolism, through oxidative phosphorylation. Mitochondria within cells undergo constant fission and fusion, and this balance is crucial for maintaining normal cellular activity. Studies have found that abnormalities in mitochondrial fission and fusion are closely related to metabolic diseases such as NAFLD. NAFLD is caused by excessive fat accumulation in the liver and can progress from simple steatosis (simple NAFLD) to non-alcoholic steatohepatitis, cirrhosis, and hepatocellular carcinoma [1]. In recent years, the incidence of NAFLD, which seriously affects human health, has increased annually, with a global incidence of 32.4%, seriously affecting human health [2]. Therefore, it is of great significance to delve into the core factors of NAFLD development and search for related therapeutic drugs. Studies have shown that abnormalities in the mitochondrial structure and function are core factors in the progression of NAFLD, and mitochondria have been identified as potential therapeutic targets for NAFLD [1]. Given the close relationship between NAFLD and abnormalities in mitochondrial fission and fusion, preventing and treating NAFLD can be achieved by regulating mitochondrial fission and fusion. Currently, the efficacy of Western medicine in treating NAFLD is limited, whereas traditional Chinese medicine (TCM) has unique effects in preventing and treating NAFLD by regulating mitochondrial fission and fusion, providing an important alternative method for the treatment of NAFLD. Therefore, this article explores the relationship between mitochondrial fission and fusion and NAFLD, as well as the treatment of TCM, to provide references for further research on treatment strategies for NAFLD.

Mitochondrial fission and fusion

Mitochondria are organelles found in most cells, enclosed by two membranes and structurally divided into four functional zones: the mitochondrial matrix, containing enzymes, circular DNA, RNA, etc.; the outer mitochondrial membrane (OMM), facing the cytoplasm; the inner mitochondrial membrane (IMM), protruding into the mitochondrial matrix containing mitochondrial DNA (mtDNA); and the space separated by the IMM and OMM is called the intermembrane space (IMS) [3]. In addition, the OMM forms interfaces with other subcellular compartments, including the endoplasmic reticulum (ER), lysosomes, peroxisomes, endosomes, melanosomes, lipid droplets, and plasma membrane, to establish membrane contact sites [4]. Mitochondria have multiple biological functions that are achieved through mitochondrial fission and fusion. In animal cells, the mitochondria are organised into an interconnected tubular network that extends along the cytoskeleton throughout the cell. Mitochondrial fission and fusion, as well as their distribution along the cytoskeleton, are coordinated and balanced to maintain mitochondrial function. The process by which mitochondria regulate their morphology, structure, size, and distribution through fission and fusion to maintain normal cellular activities is called mitochondrial dynamics. The balance of mitochondrial dynamics controls the shape, number, and size of mitochondria. Mitochondrial fission allows for more efficient transport of smaller mitochondria in axons, mitochondrial fusion promotes the maintenance of a homogeneous mitochondrial population that can withstand higher levels of mitochondrial DNA mutations, and mitochondrial fission during mitosis facilitates the equitable inheritance of mitochondria by daughter cells [5]. Therefore, the inhibition of any of these processes in cells can lead to severe mitochondrial dysfunction, highlighting the critical importance of mitochondrial fission and fusion in cellular activities.

Mitochondrial fission

Mitochondrial fission is the process by which mitochondria gradually divide into smaller, ring-shaped structures within cells. Molecules involved in mitochondrial fission include mitochondrial dynamin 1 (DRP1), mitochondrial dynamin 2, mitochondrial fission factor, mitochondrial dynamins (MID49 and MID51), and mitochondrial fission protein (FIS1). Mitochondrial fission is a multi-step process. During mitochondrial fission, the first step is mtDNA replication and ER-labeled recruitment sites; DRP1 accumulates in the form of oligomers to the pre-contractile sites labelled by ER; at the mitochondrial-ER contact sites, the interaction of inverted formin 2 on the ER with mitochondrial Spire1C induces actin nucleation and polymerization; Myosin II A at these sites provides mechanical force to drive mitochondrial pre-contraction; mitochondrial fission factor and MIDs recruit DRP1, resulting in oligomerization into ring structures; GTP hydrolysis enhances membrane contraction; mitochondrial dynamin 2 is recruited to the contractile site for assembly and membrane rupture, forming two daughter mitochondria [3].

Mitochondrial fusion

Mitochondrial fusion is the process by which two or more mitochondria merge into larger mitochondria within a cell. This process requires the activation of GTPases associated with actin, such as mitochondrial fusion protein 1/2 (MFN1/2) on the OMM and optic atrophy protein (OPA1) on the IMM, for the stepwise fusion of the OMM, IMM, and inner mitochondrial components [4]. During outer mitochondrial membrane fusion, MFN1 and MFN2 on adjacent mitochondrial outer membranes are connected to initiate OMM fusion [3, 5]. After OMM fusion, OPA1 and cardiolipin (CL) mediate IMM fusion. GTP hydrolysis results in the interaction of OPA1 and CL on both sides of the membrane, binding the two IMMs together and completing IMM fusion (Figure 1).

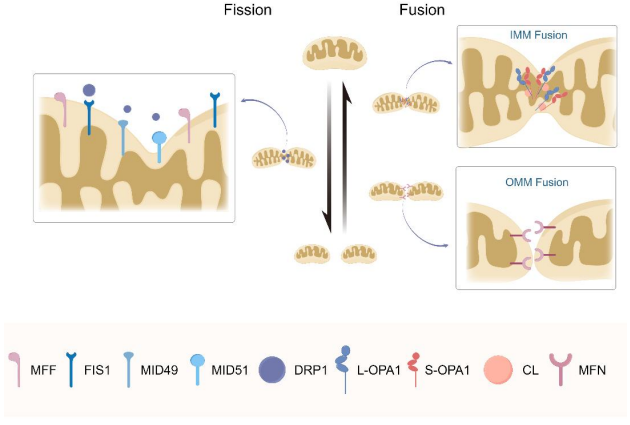

Figure 1 Mitochondrial fission and fusion. Source of figure: author using Figdraw, ID: IROUP44250.

Mitochondrial dynamics disruption and NAFLD

Manifestations of mitochondrial dynamics imbalance

The expression of proteins related to mitochondrial fission and fusion affects the mitochondrial dynamic balance. The expression of proteins related to mitochondrial fission and fusion affects the mitochondrial dynamic balance. When the expression of mitochondrial fusion-related proteins is decreased, or the expression of fission-related proteins is increased, mitochondrial fission dominates, and mitochondrial fusion is impaired; otherwise, the expression of mitochondrial fusion-related proteins is increased, or the expression of fission-related proteins is decreased, mitochondrial fusion dominates, and mitochondrial division is impaired. Abnormalities in mitochondrial fission and fusion are closely associated with NAFLD [6, 7]. In NAFLD, the mitochondrial dynamics are unbalanced, resulting in impaired mitochondrial fusion and enhanced mitochondrial fission [8, 9]. An imbalance in mitochondrial dynamics leads to changes in the normal morphological structure of mitochondria, destruction of the mitochondrial tubular network structure, fragmentation, swelling, short rod and round spherical shape, reduction in mitochondrial membrane potential, destruction of cristome structure and loss of cristome, which inhibits cell metabolism, affects mitochondrial function, and accelerates cell death [10, 11]. When the expression of mitochondrial fusion-related proteins is decreased, or the expression of fission-related proteins is increased, mitochondrial fission dominates, and mitochondrial fusion is impaired; otherwise, the expression of mitochondrial fusion-related proteins is increased, or the expression of fission-related proteins is decreased, mitochondrial fusion dominates, and mitochondrial division is impaired. Abnormalities in mitochondrial fission and fusion are closely associated with NAFL [6, 7]. In NAFLD, the mitochondrial dynamics are unbalanced, resulting in impaired mitochondrial fusion and enhanced mitochondrial fission [8, 9]. An imbalance in mitochondrial dynamics leads to changes in the normal morphological structure of mitochondria, destruction of the mitochondrial tubular network structure, fragmentation, swelling, short rod and round spherical shape, reduction in mitochondrial membrane potential, destruction of cristome structure and loss of cristome, which inhibits cell metabolism, affects mitochondrial function, and accelerates cell death [10, 11].

Mechanisms of mitochondrial dynamics imbalance in NAFLD

In NAFLD, mitochondrial dynamics are imbalanced owing to various factors. Compared with normal hepatocytes, the expression levels of MFN2 and OPA1 proteins were reduced, and the expression levels of FIS1 and DRP1 proteins were enhanced in the hepatocytes of NAFLD patients. Studies have found that the mitochondrial structure of patients has undergone significant changes, and MFN2 is reduced [12]. Xin et al. detected the expression of mitochondrial fusion- and fission-related proteins in the liver of mice fed a high-fat diet [13]. The results showed that the expression of mitochondrial fission proteins (FIS1 and DRP1) increased, whereas that of mitochondrial fusion proteins (MFN2 and OPA1) decreased. Therefore, in NAFLD, the expression of mitochondrial fusion-related proteins is reduced, and the expression of mitochondrial fission-related proteins is enhanced, leading to mitochondrial fusion weakening, mitochondrial fission enhancement, and an imbalance in mitochondrial dynamics. In contrast, increased OXPHOS activity stimulates mitochondrial fusion, and OXPHOS defects lead to defects in mitochondrial inner membrane fusion [14]. In NAFLD, OXPHOS gene mutations lead to OXPHOS defects, which in turn lead to mitochondrial inner membrane fusion defects, mitochondrial fusion obstacles, and an imbalance in mitochondrial dynamics [15]. Additionally, OXPHOS defects or inhibition can cause oxidative stress development, increase reactive oxygen species (ROS) production, and further damage the respiratory chain so that free fatty acids cannot be completely oxidised, affecting β-oxidation. Therefore, mitochondrial fission and fusion can affect fatty acid oxidation under certain conditions. Additionally, studies have reported that mitochondrial autophagy is impaired in NAFLD, leading to damaged mitochondria that cannot be cleared in a timely manner, affecting the stability of the mitochondrial network and further affecting the stability of mitochondrial dynamics [16].

Mitochondrial fusion disorder and NAFLD

Annually, the incidence of NAFLD is increasing, and specific drugs for this disease are lacking. The mitochondria play an important role in lipid metabolism in the liver. The dysfunction of mitochondrial fusion in NAFLD can lead to multiple abnormalities. First, mitochondrial fusion disorder leads to ATP reduction because it affects mitochondrial function, hinders the electron transport chain, interferes with the fatty acid oxidation process, and may lead to apoptosis and damage, all of which reduce ATP production [10]. Mitochondrial fusion disorders can affect the electron transport chain and oxidative phosphorylation process in the mitochondria, resulting in electron leakage and reactions with oxygen to form ROS, resulting in the accumulation of ROS products [9]. In addition, fusion disorders may affect the mitochondrial antioxidant defence system. Disordered mitophagy reduces the ability of cells to remove ROS and increases ROS accumulation. Excessive ROS production can cause oxidative stress damage to cells, trigger a cellular inflammatory response, affect the normal function and survival of cells, and aggravate liver damage [17]. Excessive ROS production can damage the respiratory chain. With the damage to the respiratory chain, mitochondria cannot completely oxidiate the excess free fatty acids, and these free fatty acids are oxidised outside the mitochondria, producing peroxidation products and more ROS and damaging the vicious cycle [18–21]. mtDNA can also be damaged in the fatty liver, and mitochondrial dysfunction affects mtDNA replication and transcription, whereas oxidative stress damage causes ROS to attack mtDNA, causing strand breaks, point mutations, and oxidative damage, and also affects the repair mechanism of mtDNA, thereby reducing mtDNA content [22]. The decrease in the ATP production rate caused by mitochondrial fusion disorders, accumulation of ROS products, mtDNA damage, and lipid oxidation disorders can cause abnormal intracellular lipid metabolism, liver lipid accumulation, liver cell damage, and aggravate disease deterioration. In the early course of NAFLD, increased uncoupling of oxidative phosphorylation leads to increased mitochondrial respiration and decreased ATP synthesis, accompanied by increased ROS production [23]. Thus, NAFLD is closely associated with mitochondrial fusion and division. Dysfunction of hepatocyte-mitochondrial fusion is also an important factor influencing NAFLD, and maintaining mitochondrial dynamic balance is also of great significance in improving NAFLD. Correction of the mitochondrial dynamic imbalance is an important target in the treatment of NAFLD.

TCM regulation of mitochondrial dynamics for the treatment of NAFLD

TCM has the advantages of multiple components and targets and has advantages in regulating mitochondrial dynamics balance and treating NAFLD. Many studies have shown that TCMs (including monomers and compounds) have a positive effect on the regulation of mitochondrial dynamics to treat NAFLD.

TCM monomer

Quercetin. Quercetin, a widely distributed flavonoid compound in vegetable foods, often exists in the form of glycosides such as rutin, quercitrin, and hyperoside. This can be achieved via acid hydrolysis [24]. Studies have found that quercetin has strong antioxidant and anti-inflammatory effects, improves the expression of lipid metabolism-related genes, regulates mitochondrial function and biosynthesis, protects mitochondrial integrity, and maintains mitochondrial dynamics stability [25–27]. Liu et al. showed that quercetin improved mitochondrial morphological damage and dysfunction in the liver of hyperlipidaemia-induced mice, promoted mitochondrial biosynthesis and mitochondrial fusion and division, enhanced the level of mitochondrial autophagy mediated by

PINK1-Parkin, improved mitochondrial stability, and inhibited liver steatosis [28].

Ginsenosides. Ginsenoside, an active substance extracted from the root of ginseng, has a variety of pharmacological effects, and studies have shown that ginsenosides can improve NAFLD by regulating mitochondrial dynamics [29]. Li et al. used ginsenoside IVa to treat a high-fat diet combined with CCl-4 induced non-alcoholic steatohepatitis [30]. After the intervention, the mRNA and protein expression of MFN2 in mice increased, the expression of lipid metabolism-related genes decreased, and steatosis decreased. Ginsenoside Rg5 can significantly increase the mitochondrial mass of mice and activate the Sirt1/PGC-1α/MFN2 mitochondrial biosynthesis pathway to improve liver dysfunction [31].

Salvianolic acid B. Salvianolic acid B, an organic compound extracted from the root and rhizome of Salvia miltiorrhiza, has strong antioxidant and anti-fibrosis effects and has good efficacy in the treatment of liver diseases [32]. Studies have shown that salvianolic acid B can regulate the overexpression of mortalin, thereby reducing the expression of FIS1, increasing the expression of MFN1, reducing mitochondrial fission, improving the structure of the mitochondrial network, and maintaining the balance of mitochondrial dynamics [33]. Wang et al. showed that salvianolic acid B could treat NAFLD by upregulating the expression of MFN2, promoting mitochondrial fusion, protecting the morphological characteristics and function of liver mitochondria, regulating lipid metabolism, controlling oxidative stress and lipid peroxidation, and inhibiting apoptosis [34].

Dihydromyricetin. Dihydromyricetin is a flavonoid compound with various effects such as anti-oxidation, inhibition of lipogenesis, prevention of alcoholic liver disease, fatty liver disease, inhibition of hepatocyte deterioration, and reduction in the incidence of liver cancer [35–37]. Dihydromyricetin can reduce fat content by enhancing the expression of mitochondrial dynamic-related proteins [38]. Xin et al. showed that dihydromyricetin improved liver fat accumulation in high-fat diet-fed mice by regulating the balance of fission and fusion of liver mitochondria [13].

Gynostemma. Gynostemma is a climbing plant in the Cucurbitaceae family that functions as an antioxidant, reduces blood lipids, and protects the liver [39]. It is used in the treatment of liver diseases because of its pharmacological effects on the regulation of mitochondria and antioxidation [40]. Müller C et al. showed that in the treatment of primary cultured hepatocytes with high-concentration glucose, Gynostemma extract can regulate mitochondrial CL molecular structure, regulate mitochondrial fusion, improve mitochondrial function, and reduce lipid accumulation [41].

Nuciferine. Nuciferine is an aporphine alkaloid found in lotus leaves , which is the main lipid-lowering active ingredient in lotus leaves and can regulate the expression of lipid metabolism-related genes to reduce liver injury [42, 43]. Studies have shown that Nuciferine improves steatosis in NAFLD mice by regulating lipid metabolism [44]. Studies have reported that Nuciferine reduces ROS overproduction, removes damaged mitochondria, and reduces steatosis in NAFLD mice [45].

The use of TCM monomers to regulate mitochondrial dynamics in the treatment of NAFLD has attracted increasing attention and provides a new approach to the clinical treatment of NAFLD.

TCM compound

Many TCM compounds also effectively treat NAFLD by regulating mitochondrial dynamics. A self-made “Zhi Gan prescription” can reduce the expression of the mitochondrial fission-related protein FIS, increase the expression of the fusion-related proteins MFN1 and OPA1, promote mitochondrial fusion, and improve the degradation of mitochondrial debris to improve NAFLD [43, 46, 47]. Zhongqin et al. found that Huoxue Huatan Fang (Shiwei Ganzhikang capsule) can repair the cristae and membranes of damaged mitochondria, protect the normal morphological structure of mitochondria, and have obvious curative effects on NAFLD [48]. Qingzhi Hugan Fang reduced mitochondrial swelling, improved mitochondrial morphology in mice with NAFLD, and effectively improved liver lipid metabolis [48].

These results suggest that TCM has unique advantages in correcting the imbalance of mitochondrial dynamics and, thus, in treating NAFLD, which can be targeted for further exploration in future research.

Conclusions and prospects

Mitochondria play a central role in lipid metabolism in the liver, and mitochondrial dynamics play an important role in NAFLD. Maintaining the balance of mitochondrial dynamics by regulating the expression of mitochondrial fusion- and fission-related proteins can improve NAFLD. TCM has unique advantages in correcting and regulating imbalances in mitochondrial dynamics, and it is of great clinical significance to explore TCM treatment plans for NAFLD.

Mechanism of action of TCM in regulating mitochondrial dynamic balance to improve NAFLD (Table 1).

Table 1 Mechanism of action of TCM in regulating mitochondrial dynamic balance to improve NAFLD

Types of traditional Chinese medicine	Traditional Chinese medicine names	Targets of action	References
Traditional Chinese medicine monomer	Quercetin	It promotes impaired mitochondrial biosynthesis, mitochondrial fusion and fission, and maintains mitochondrial dynamic homeostasis.	[25–28]
	Ginsenosides	Upregulation of MFN2 expression significantly increased mitochondrial mass.	[30, 31]
	Salvianolic acid B	Downregulation of FIS1 expression and up-regulation of MFN1/MFN2 expression reduced mitochondrial fission and promoted mitochondrial fusion.	[33, 34]
	Dihydromyricetin	It regulates the balance between fission and fusion of mitochondria.	[13, 38]
	Gynostemma	Mitochondrial fusion is regulated by modulating CL molecular structure.	[41]
	nuciferine	Remove damaged mitochondria.	[44, 45]
Traditional Chinese medicine compound	Self-made “Zhi Gan prescription”	Downregulation of FIS1 expression and up-regulation of MFN1 and OPA1 expression promoted mitochondrial fusion.	[46, 47]
	Huoxue Huatan Fang (Shiwei Ganzhikang Capsule)	Repair the cristae and membrane of damaged mitochondria and protect the normal morphological structure of mitochondria.	[49]
	Qingzhi Hugan Prescription	Reduced swelling and improved mitochondrial morphology.	[48]

MFN1/2, mitochondrial fusion protein 1/2; CL, cardiolipin; FIS1, mitochondrial fission protein; OPA1, optic atrophy protein.

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