HSPI The Open Access Publisher

JCCM JOURNAL OF CARDIOLOGY AND CARDIOVASCULAR MEDICINE
ISSN 2575-0143

Research Article

OPA1 Regulates the Effects of Mitochondrial Dynamics Progress of Research on Different Cells of the Heart against Cardiomyopathy

Dongyang Li[1], Xinyve Zhang[1], Wang Qin[1]* and Yanwei Du[2]*

[1]Clinical School of Medicine, Changchun University of Traditional Chinese Medicine, Changchun 130117, P.R. China

[2]Department of Rehabilitation, School of Nursing, Jilin University, Changchun 130021, P.R. China

Abstract

Cardiomyopathies are critical clinical conditions. Their onset is associated with genetic factors, environmental impacts, and cellular dysfunctions. As a heterogeneous group of complex heart diseases, cardiomyopathies have been a central focus of medical research for a long time. With the advancement of science and technology and the deepening of research, an increasing number of genes and molecules have been demonstrated to be closely linked to the development and progression of cardiomyopathies. OPA1, a protein involved in the fusion of the inner mitochondrial membrane, plays a pivotal role in maintaining the normal function and morphology of mitochondria. In recent years, the significance of mitochondrial dynamics in cardiac health and disease has drawn considerable attention. Mitochondrial dysfunction is a major factor contributing to cardiac impairment. When the mitochondrial dynamics within cardiomyocytes are disrupted, it results in abnormal function and morphology of these cells. Overexpression of OPA1 significantly boosts the mitochondrial fusion activity in cardiomyocytes, enhances mitochondrial function, and alleviates oxidative stress-induced damage, thereby exerting a protective effect in the context of cardiomyopathy. Conversely, a deficiency of OPA1 leads to mitochondrial fragmentation and impaired energy metabolism, further deteriorating the function of cardiomyocytes. This article aims to delve into the mechanisms and effects by which OPA1 regulates mitochondrial dynamics to improve cardiomyopathy. It also summarizes the role of targeting OPA1 to regulate mitochondrial dynamics for the prevention and treatment of cardiomyopathy, with the intention of offering novel perspectives for the diagnosis and treatment of this condition.

More Information

***Address for correspondence:** Wang Qin, Clinical School of Medicine, Changchun University of Traditional Chinese Medicine, Changchun 130117, P.R. China, Email: wangqin0506@163.com

Yanwei Du, Department of Rehabilitation, School of Nursing, Jilin University, Changchun 130021, P.R. China, Email: dywu@jlu.edu.cn

Submitted: April 06, 2025
Approved: April 21, 2025
Published: April 23, 2025

How to cite this article: Li D, Zhang X, Qin W, Du Y. OPA1 Regulates the Effects of Mitochondrial Dynamics Progress of Research on Different Cells of the Heart against Cardiomyopathy. J Cardiol Cardiovasc Med. 2025; 10(2): 049-056. Available from: https://dx.doi.org/10.29328/journal.jccm.1001209

Keywords: Mitochondrial dynamics; Cardiomyocytes; Cardiomyopathy; Sepsis; Optic atrophy protein 1

Introduction

Cardiomyopathy is commonly observed as a complication of sepsis [1,2]. Individuals with a family history of cardiomyopathy, a record of viral myocarditis, a history of long-term excessive alcohol intake, or exposure to cardiotoxic drugs are more susceptible to developing cardiomyopathy [3]. Among the most common complications of sepsis, minimizing cardiac damage and restoring cardiac function in sepsis patients can effectively reduce the mortality rate and improve their prognosis [4,5]. Pathologically, it is firmly established that cardiomyopathy is closely linked to the derangement of cardiac mitochondrial dynamics and mitochondrial dysfunction [6]. In exploring prevention and treatment strategies for cardiomyopathy, research on mitochondrial dynamics has emerged as a focal point for researchers.

The stabilization of mitochondrial dynamics holds a crucial position in organs and tissues with high energy demands, such as the cardiovascular system [7]. Imbalances in mitochondrial dynamics can disrupt the organization and function of cardiomyocytes, giving rise to a range of cardiovascular diseases. Mitochondrial dynamics governs cell fate by regulating energy supply, the generation of intracellular reactive oxygen species, and calcium homeostasis [8]. Currently, there is a dearth of comprehensive studies that

explore the role of Optic Atrophy 1 (OPA1) in modulating mitochondrial dynamics to improve the status of different cell types in the context of cardiomyopathy. Therefore, this paper offers a thorough review and synthesis of the existing research on how OPA1 regulates mitochondrial dynamics and impacts various cardiac cells to prevent cardiomyopathy, from the perspectives mentioned above. This endeavor is of significant scientific and clinical importance for the alleviation of cardiomyopathy.

Correlation of OPA1 with mitochondrial dynamics

Research on mitochondrial dynamics can be traced back to 1914, when Lewis, et al. [9] indicated that mitochondrial dynamics refers to the dynamic process in which mitochondria within a cell continuously undergo division and fusion, thereby maintaining the stability of their morphology and network structure. Mitochondrial dynamics comprises two fundamental processes: mitochondrial fusion and fission, which are coordinated to sustain mitochondrial homeostasis.

The fusion process facilitates the sharing of mitochondrial resources and the repair of damaged mitochondria. By forming a larger mitochondrial network, it enhances the efficiency of energy production. In contrast, the fission process ensures the even distribution of mitochondria and the transmission of genetic information. This guarantees that each daughter cell acquires an adequate number of mitochondria during cell division. OPA1, a mitochondrial fusion protein, plays a pivotal role in maintaining the morphology of mitochondrial cristae and is involved in mitochondria-mediated apoptosis, among other processes. It is indispensable for maintaining mitochondrial homeostasis and is crucial for preserving the stability of mitochondrial dynamics. The mitochondrial fusion process is primarily regulated by two proteins: Mitochondrial fusion proteins (Mfn) 1 and 2, and Optic Atrophy Protein 1 (OPA1). OPA1 participates in the entire process of the fusion of the inner mitochondrial membrane and plays a vital role in maintaining the structure and function of the inner mitochondrial membrane and supporting its morphological integrity [11]. Research findings have demonstrated that when the mechanisms of mitochondrial fusion and fission are disrupted in the hearts of mice, it gives rise to an imbalance in mitochondrial dynamics, which severely impairs cardiac function [12]. Mitochondrial function is a crucial pathophysiological factor in septic cardiomyopathy (SCM) [13]. Studies have indicated that sustaining the dynamic equilibrium of mitochondrial dynamics is essential for the normal function of cardiomyocytes. An imbalance between mitochondrial fission and fusion results in the accumulation of fragmented mitochondria, which triggers myocardial injury and eventually leads to cardiac diseases [14]. In summary, OPA1 is closely associated with mitochondrial dynamics, and this relationship can be manifested in its contribution to maintaining the normal structure and function of mitochondria as well as cellular homeostasis.

The mitochondrial swelling-contraction cycle is a fundamental process in mitochondrial dynamics, playing a pivotal role in maintaining energy metabolism, redox homeostasis, and cellular survival, with significant implications for cardiac health. This cycle regulates mitochondrial membrane permeability, ion balance, and ATP synthesis efficiency, and its dysregulation is strongly linked to the pathogenesis of various cardiovascular diseases.

Mitochondrial membrane potential serves as a critical functional indicator of mitochondrial integrity [15]. Under physiological conditions, mitochondria sustain an optimal by modulating inner membrane permeability, thereby ensuring efficient oxidative phosphorylation and a stable ATP supply for cardiomyocytes. However, during ischemia/reperfusion (I/R) injury, pathological mitochondrial swelling occurs, driven by aberrant opening of the mitochondrial Permeability Transition Pore (mPTP). This results in catastrophic Ca^{2}, overload, excessive ROS production, and severe ATP depletion, culminating in cardiomyocyte apoptosis or necrosis. Studies demonstrate that reperfusion-induced mitochondrial swelling coincides with cristae disruption, which impairs electron transport chain activity and exacerbates myocardial damage. Furthermore, in heart failure, chronic overactivation of β-adrenergic receptors disrupts mitochondrial homeostasis, leading to dysregulation of the swelling-contraction cycle and progressive deterioration of cardiac function. In recent years, therapeutic interventions targeting mitochondrial dynamics have emerged as a key research focus. For instance, inhibition of the mitochondrial fission protein DRP1 has been shown to attenuate pathological swelling and improve myocardial energy metabolism. Conversely, enhancement of mitophagy facilitates the clearance of damaged, swollen mitochondria, thereby preserving cardiomyocyte viability. Notably, antioxidant agents such as reduced coenzyme Q10 (ubiquinol) demonstrate protective effects by mitigating oxidative stress, which helps stabilize mitochondrial membrane integrity and maintain normal swelling-contraction cycles. In pulmonary hypertension, modulation of MCJ protein expression has been found to improve mitochondrial adaptability and preserve right ventricular function. These findings collectively suggest that targeted regulation of mitochondrial dynamics may represent a promising novel approach for future cardiovascular therapies.

OPA1 and cardiomyopathy

Currently, Cardiomyopathies are generally classified into five types, namely hypertrophic cardiomyopathy, dilated cardiomyopathy, non-dilated left ventricular cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, and restrictive cardiomyopathy. Below is a concise description of the mechanism by which OPA1 exerts its effects in the context of cardiomyopathy.

OPA1 and hypertrophic cardiomyopathy: Hypertrophic Cardiomyopathy (HCM) often has a genetic basis. It is

characterized by asymmetric hypertrophy of the ventricular wall, typically involving the encroachment of the ventricular septum. This encroachment reduces the volume of the ventricular chambers and hinders the filling of blood [16]. As a myocardial disease, HCM can eventually lead to heart failure when the heart endures prolonged loading or chronic stress. Studies have revealed that myocardial hypertrophy and remodeling are closely associated with mitochondrial fusion. In a mouse model of heart failure, the expressions of OPA1 and MFN2 are downregulated in hypertrophied cardiomyocytes [17,18]. Compared with the control group, mice with OPA1 gene knockout exhibited more severe myocardial hypertrophy following 6 weeks of aortic constriction-induced pressure overload [19]. Research has demonstrated that upregulating the expression of OPA1 can enhance mitochondrial function and has a beneficial effect on pressure overload-induced cardiomyopathy and heart failure [20]. Evidently, maintaining the homeostasis of mitochondrial dynamics is crucial for preserving normal myocardial function.

OPA1 and dilated cardiomyopathy: Dilated Cardiomyopathy (DCM) is characterized by the dilation of the left ventricle and the presence of either global or localized systolic dysfunction. It is commonly triggered by factors such as hypertension, valvular heart disease, and coronary artery disease [16]. Studies have demonstrated that in a mouse model of DCM, the mitochondrial structure shows signs of disorganization, with swelling and the formation of vacuoles. There is an abnormal increase in the content of Reactive Oxygen Species (ROS). The expressions of mitochondrial fission proteins DRP1 and FIS1 are upregulated, while the expressions of mitochondrial fusion proteins OPA1 and MFN2 are downregulated. This impairment of mitochondrial morphology and the disruption of mitochondrial homeostasis ultimately lead to myocardial injury [21].

Other research findings have indicated that when the function of OPA1 is compromised, it gives rise to both morphological and functional abnormalities in mitochondria. These abnormalities, in turn, have a significant impact on the structure and function of the heart and are closely associated with the onset and progression of cardiomyopathy [22]. OPA1 is considered to be a key molecular regulator in the development of dilated cardiomyopathy, participating in the regulation of mitochondrial dynamics and the changes in the structure of mitochondrial cristae. Therefore, abnormal mitochondrial dynamics is likely to be a crucial contributing factor to the development of dilated cardiomyopathy.

OPA1 and non-dilated left ventricular cardiomyopathy: Non-dilated left ventricular cardiomyopathy (ND-LVCM) is a condition where the left ventricular myocardium is replaced by non-ischemic scar or adipose tissue, or shows isolated hypokinesia without the presence of scarring [23]. The normal mitochondrial fusion process plays a crucial role in regulating mitochondrial morphology, facilitating content exchange within mitochondria, and maintaining mitochondrial genetic stability. In doing so, it helps to sustain mitochondrial homeostasis, which is vital for various aspects of cardiomyocyte function, including cell cycle progression and the regulation of apoptosis [24]. Abnormalities in OPA1 can potentially lead to an imbalance in mitochondrial dynamics. This imbalance, in turn, can disrupt the energy metabolism of cardiomyocytes and affect their survival. Although a direct and specific association between OPA1 and non-dilated left ventricular cardiomyopathy has not been established, when considering the known role of OPA1 in cardiomyocytes and the findings from its study in other types of cardiomyopathies, it is clear that mutations or abnormal expressions of the OPA1 gene can impair the normal function of mitochondria. Such impairments can trigger a cascade of pathological changes in cardiomyocytes, including metabolic disorders, heightened oxidative stress, and an increased rate of apoptosis. These changes may ultimately contribute to the development of non-dilated left ventricular cardiomyopathy.

OPA1 and restrictive cardiomyopathy: Restrictive Cardiomyopathy (RCM) is characterized by a pathophysiological state where, in the restrictive left and/or right ventricle, the diastolic volume is either normal or decreased (in one or both ventricles), while the systolic volume and the thickness of the ventricular wall remain normal [16]. There is a significant association between the OPA1 gene and restrictive cardiomyopathy. When mutations occur in the OPA1 gene, they can lead to abnormal function of the OPA1 protein. This, in turn, impairs normal mitochondrial function, manifested as changes in mitochondrial morphology, disruptions in energy metabolism, and an increase in apoptosis. These consequences may ultimately cause damage and death of cardiomyocytes, thereby facilitating the progression of restrictive cardiomyopathy. Studies have demonstrated that the fusion of OPA1 to the inner mitochondrial membrane enhances oxidative phosphorylation. For this reason, OPA1 is often considered as a therapeutic target for the treatment of cardiomyopathy and heart failure [11]. Evidently, the OPA1 gene, serving as a crucial regulator of mitochondrial dynamics, is closely intertwined with the development of restrictive cardiomyopathy.

OPA1 and arrhythmogenic right ventricular cardiomyopathy: Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is a type of cardiomyopathy characterized by a predominantly dilated and/or dysfunctional right ventricle, accompanied by histological changes and/or electrocardiographic abnormalities [25].Considering the crucial role of OPA1 in maintaining mitochondrial function and promoting cellular health, as well as the potential association between mitochondrial dysfunction and cardiac diseases, it is plausible that OPA1 may play a role in the pathogenesis of ARVC to some degree. While current studies have not directly linked OPA1 to ARVC. Given the significant function of OPA1 in cardiac cells, future research may uncover its potential involvement in the development and progression of ARVC.

OPA1 and cardiac cells

The heart is a sophisticated multicellular organ comprising cardiomyocytes, myocardial fibroblasts, endothelial cells, inflammatory cells, and stem cells. These cell types are subject to regulation and engage in interactions to maintain normal myocardial function and govern cardiac repair processes [26]. The proper functioning of OPA1 is of utmost importance for safeguarding the health of cardiomyocytes and exerts a significant influence on the alleviation of cardiomyopathy. By conducting in-depth investigations into the specific mechanisms through which OPA1 acts within different cell types, there is an expectation that novel therapeutic strategies can be formulated. These strategies are anticipated to confer substantial benefits to the vast majority of patients suffering from cardiomyopathy.

OPA1 and cardiomyocytes: Cardiomyocytes are the primary constituents of the heart and are tasked with performing the heart's contractile and diastolic functions. They make up approximately 30% of all cells within the heart. The initiation and progression of cardiomyopathy are intricately linked to the level of apoptosis in cardiomyocytes. Studies have demonstrated that the degree of cardiomyocyte apoptosis is heightened in cardiovascular diseases. As the rate of cardiomyocyte apoptosis increases, cardiac function deteriorates, ultimately leading to myocardial fibrosis or heart failure. Conversely, inhibiting cardiomyocyte apoptosis has been shown to alleviate cardiomyopathy [27].

The stability of mitochondrial morphology plays a decisive role in determining cell fate and influencing disease development. The dynamic function of mitochondria enables the formation of new mitochondria through the fusion of adjacent damaged mitochondria. This process enhances the mitochondrial mass, thereby maintaining the physiological functions of cardiomyocytes. Research has indicated that mitochondrial fission and cristae defects are present in the subepicardial left ventricular tissues of heart failure patients. These abnormalities significantly impair energy metabolism and the apoptosis of cardiomyocytes. Notably, OPA1 serves as a crucial regulator of mitochondrial fusion and the structure of mitochondrial cristae [28]. It has been discovered that an imbalance between mitochondrial fusion and fission, along with the accumulation of abnormal mitochondria, contributes to mitochondrial dysfunction and myocardial injury. Moreover, a reduction in OPA1 levels accelerates the apoptosis and progressive loss of cardiomyocytes, which may further exacerbate the advancement of heart failure [29]. These studies imply a strong correlation between the alteration of mitochondrial fusion proteins and the development of cardiomyopathy. The disruption of the mitochondrial fusion mechanism intensifies mitochondrial fission, which may ultimately result in the apoptosis of cardiomyocytes [30]. Cardiomyocytes are densely populated with mitochondria. Any disarray in mitochondrial dynamics can have a detrimental impact on mitochondrial function. Among these, the expression level of OPA1 plays a critical role in regulating mitochondrial fusion [31]. As one of the cell types in the body with the highest energy demands, cardiomyocytes rely heavily on the efficient operation of mitochondrial dynamics to carry out their normal functions. In conclusion, by increasing the expression of OPA1 or suppressing its shearing process, it is possible to effectively inhibit excessive mitochondrial fission and promote mitochondrial fusion. This, in turn, enhances the energy supply and the anti-oxidative stress capacity of cardiomyocytes. Such a regulatory mechanism contributes to mitigating cardiomyocyte injury and slowing down the progression of heart failure. The imbalance of mitochondrial dynamics is especially evident in pathological conditions like cardiomyopathy. OPA1 is indispensable for maintaining mitochondrial homeostasis and proper energy metabolism within cardiomyocytes.

OPA1 and fibroblasts: In addition to cardiomyocytes, cardiac fibroblasts also play a crucial role in the development of cardiomyopathy. Fibroblasts originate from mesenchymal cells. When the myocardium is damaged and an inflammatory response ensues, the abnormal proliferation of cardiac fibroblasts and the excessive deposition of the extracellular matrix may be significant contributing factors to the onset of cardiomyopathy.

Studies have demonstrated that OPA1-mediated mitochondrial fusion promotes the proliferation of fibroblasts [32]. Mitochondrial dynamics serve as a key mechanism for regulating mitochondrial stability and safeguarding fibroblasts [33]. In fibroblasts, mutations or dysfunctions of OPA1 can trigger alterations in a variety of cellular mechanisms. Research has shown that knocking down OPA1 within embryonic fibroblasts can induce apoptosis [34]. Researchers have found that patients with OPA1 gene–associated inherited optic atrophy (OPA1-OA) exhibit a significantly higher proportion of fragmented mitochondria in their cells compared to normal control subjects. Additionally, the cell proliferation ability of OPA1 mutant fibroblasts is reduced when there is increased cell density or nutrient deficiencies [35]. These findings suggest that OPA1 is essential for maintaining the normal growth and metabolism of fibroblasts. The mechanisms by which mitochondria and fibroblasts act in the alleviation of cardiomyopathy are interrelated. On one hand, a decline in mitochondrial function may lead to an inadequate energy supply, thereby impairing the normal repair function of fibroblasts. On the other hand, the abnormal activation of fibroblasts may further exacerbate the disruption of mitochondrial homeostasis [36]. In conclusion, when the heart is damaged, cardiac fibroblasts proliferate and secrete collagen fibers, leading to myocardial fibrosis. This, in turn, further impairs cardiac function. In a nutshell, enhancing the function of OPA1 can stimulate the activation of fibroblasts while suppressing the excessive deposition of collagen fibers. As a result, it can reduce the extent of myocardial fibrosis and

enhance the overall function of the heart. The function of OPA1 in fibroblasts is primarily manifested in its ability to maintain mitochondrial homeostasis and functionality. Abnormalities in OPA1 may lead to mitochondrial dysfunction, which subsequently disrupts the normal physiological functions of cells. Therefore, by improving mitochondrial dynamics through OPA1, the regulation of fibroblasts can influence their activation status, potentially contributing to an improved prognosis for patients with cardiomyopathy.

OPA1 and vascular endothelial cells: Vascular endothelial cells, which form a single layer of cells within the vascular lumen, are a vital component of the cardiac vasculature. Functional abnormalities of these cells are closely intertwined with a diverse range of cardiovascular diseases. Under pathological conditions, vascular endothelial cells are capable of secreting a substantial amount of inflammatory factors. This secretion contributes to an elevation in microvascular permeability and can trigger the development of various cardiovascular diseases, including cardiomyopathy [37]. The vascular intima is lined with endothelial cells, which create an impermeable yet somewhat leaky barrier between the circulating blood and the outer substrate of the blood vessel [38].

Studies have revealed a strong correlation between abnormal endothelial barrier function and mitochondrial dysfunction [39]. When mitochondrial function is abnormal, it increases the permeability of the vascular endothelial cell membrane and further worsens the impairment of the endothelial barrier function [40]. Research has demonstrated that in the coronary artery endothelial cells of a mouse model of cardiomyopathy, mitochondria exhibit significant disruptions, which are associated with a decrease in OPA1 expression. By promoting the expression of OPA1, the levels of mitochondrial fusion and oxidative phosphorylation can be enhanced [41].

Conversely, the overexpression of mitochondrial fission mediated by Drp1 in mitochondrial dynamics can stimulate the production of mitochondrial reactive oxygen species (ROS). Excessive ROS can increase the phosphorylation of Drp1 by activating the C-Jun amino-terminal protein kinase signaling pathway. This excessive division creates a feedback loop of mitochondrial damage that may ultimately result in the death of endothelial cells [42]. Evidently, the dysfunction of endothelial cells is closely linked to the imbalance of mitochondrial dynamics.

In conclusion, OPA1 has the ability to impact the proliferation, migration, and apoptosis of vascular endothelial cells by modulating their mitochondrial dynamics. During vascular injury or an inflammatory response, an increased expression of OPA1 can facilitate the repair and regeneration of vascular endothelial cells. It can also mitigate the inflammatory response and oxidative stress-induced damage within the vessel wall. As a result, it plays a crucial role in safeguarding the health of the cardiovascular system.

OPA1 and inflammatory cells: A significant pathological manifestation of septic cardiomyopathy is the inflammatory response [43,44]. Moreover, the inflammatory response in cardiomyocytes often serves as an early indicator of myocardial injury. Cardiomyopathy may be initiated when the levels of inflammatory cytokines in the body rise. If these cytokines are not completely cleared or if the inflammatory response persists even after clearance, inflammatory cardiomyopathy will ensue [45]. Studies have demonstrated that OPA1 can regulate the metabolism and function of macrophages via the P65 signaling pathway. Macrophages play a crucial role in the host's response to pathogens, in the modulation of inflammation, and tissue regeneration. The activity of OPA1 may affect the polarization state of macrophages, determining whether they tend to promote or suppress inflammation [46]. Evidence has shown that OPA1 helps maintain mitochondrial homeostasis by promoting mitochondrial fusion and reducing the stress response of inflammatory cells. Imbalances in mitochondrial dynamics, such as decreased mitochondrial fusion, can lead to mitochondrial dysfunction, which further intensifies the inflammatory response [47]. Zhou, et al. reported that engeletin improved cardiac function by activating the AMPK pathway. This activation promoted the expression of mitochondrial fusion proteins OPA1 and Mfn1, inhibited the expression of mitochondrial fission proteins Drp1 and Fis1, and alleviated the degree of mitochondrial functional impairment [48].

In conclusion, OPA1 may mitigate the inflammatory response by regulating mitochondrial dynamics and contributing to the preservation of mitochondrial integrity and function. In doing so, it helps to improve the pathological condition of cardiomyopathy.

OPA1 and stem cells: The restoration of functional myocardium using stem cells has emerged as a viable therapeutic strategy. Cardiomyocytes differentiated from stem cells can replicate the successive stages of embryonic heart development. After implantation, they secrete a diverse array of biologically active substances. These substances influence the damaged myocardium via paracrine signaling, accelerating angiogenesis, repairing injured cardiomyocytes, enhancing cardiac function, and promoting myocardial remodeling [49]. Research has indicated that a high level of OPA1 expression can influence the survival and paracrine function of stem cells. As a result, it helps maintain the normal morphology and function of mitochondria under hypoxic conditions. Another study demonstrated that by examining the upstream factors of OPA1, GDF11 was found to enhance the anti-apoptotic capacity of Mesenchymal Stem cells (MSCs) under hypoxic stress. This is achieved by activating the TGFβ-Smad2/3-YME1L-OPA1 signaling pathway, providing a solid foundation for the clinical application of stem cell therapy

in the treatment of cardiomyopathy [50]. In conclusion, OPA1 may contribute to maintaining the metabolic health of stem cells and facilitating their therapeutic efficacy. Normal cardiomyocyte development depends on effective mitochondrial fusion, and the expression level of OPA1 has the ability to regulate the state and function of stem cells.

Summary and outlook

Our group's preliminary results demonstrated that in mice with Lipopolysaccharide (LPS)-induced septic cardiomyopathy, the expression of the mitochondrial fusion protein OPA1 was significantly diminished, while the expression of the fission protein Drp1 was upregulated [51]. Even though OPA1 is not the most pivotal fusion protein within cellular mitochondria, we propose from an alternative viewpoint that targeting OPA1 to regulate mitochondrial dynamics could potentially serve as a therapeutic target for combating cardiomyopathy. Moreover, promoting the fusion mediated by mitochondrial OPA1 represents a promising strategy to enhance cardiac function without disregarding the roles of related fission proteins such as Mfn1, Mfn2, and Drp1. In essence, by modulating mitochondrial dynamics through OPA1, which in turn improves mitochondrial function, there is an involvement in the regulation of cardiac structure and function. This mechanism plays a crucial and multifaceted role in both the diagnostic and therapeutic aspects of cardiomyopathy.

Regarding the diagnosis of cardiomyopathy, the detection of the OPA1 gene offers a novel and precise approach. Conventionally, the diagnosis of cardiomyopathy has predominantly relied on imaging examinations such as electrocardiograms and echocardiograms. However, these methods often suffer from a lack of specificity, rendering it challenging to accurately differentiate between various types of cardiomyopathy. In contrast, the OPA1 gene test can directly identify the presence by analyzing patient DNA samples in the patient's blood sample. This provides medical professionals with a more accurate and dependable basis for making a diagnosis. When it comes to treatment, the OPA1 gene and the protein it encodes have the potential to become a new therapeutic target for cardiomyopathy. For cardiomyopathies caused by mutations in the OPA1 gene, scientists are actively exploring innovative treatment modalities, including gene therapy and drug therapy. For instance, single-cell sequencing technology or gene editing techniques (such as CRISPR-Cas9) can be employed to repair the mutated OPA1 gene. By doing so, the mitochondrial fusion function can be restored, thereby enhancing cardiac function. Additionally, cellular mapping enables improved understanding of developmental and pathological processes of different cardiac cell types, researchers are developing drugs that target the OPA1 protein to modulate its activity, with the ultimate goal of treating cardiomyopathy. Although these strategies are still under investigation, they have demonstrated significant promise and offer new hope to patients suffering from cardiomyopathy.

Funding

This work was supported by Natural Science Foundation General Program of Jilin Provincial Science and Technology Department (NO. YDZJ202301ZYTS107), National Natural Science Foundation of China (NO. 81600207).

References

1. Beesley SJ, Weber G, Sarge T, Nikravan S, Grissom CK, Lanspa MJ, et al. Septic Cardiomyopathy. Crit Care Med. 2018;46(4):625-634. Available from: https://doi.org/10.1097/ccm.0000000000002851
2. Qi Z, Liu R, Ju H, Huang M, Li Z, Li W, et al. microRNA-130b-3p Attenuates Septic Cardiomyopathy by Regulating the AMPK/mTOR Signaling Pathways and Directly Targeting ACSL4 against Ferroptosis. Int J Biol Sci. 2023;19(13):4223-4241. Available from: https://doi.org/10.7150/ijbs.82287
3. Espinola-Zavaleta N, Vega A, Basto DM, Alcantar-Fernández AC, Guarner Lans V, Soto ME. Survival and clinical behavior of hypertrophic cardiomyopathy in a Latin American cohort in contrast to cohorts from the developed world. J Cardiovasc Ultrasound. 2015;23(1):20-6. Available from: https://doi.org/10.4250/jcu.2015.23.1.20
4. Bréchot N, Hajage D, Kimmoun A, Demiselle J, Agerstrand C, Montero S, et al. Venoarterial extracorporeal membrane oxygenation to rescue sepsis-induced cardiogenic shock: a retrospective, multicentre, international cohort study. Lancet. 2020;396(10250):545-552. Available from: https://doi.org/10.1016/s0140-6736(20)30733-9
5. Lu SM, Yang B, Tan ZB, Wang HJ, Xie JD, Xie MT, et al. TaoHe ChengQi decoction ameliorates sepsis-induced cardiac dysfunction through anti-ferroptosis via the Nrf2 pathway. Phytomedicine. 2024;129:155597. Available from: https://doi.org/10.1016/j.phymed.2024.155597
6. Piamsiri C, Jinawong K, Maneechote C, Arunsak B, Chattipakorn SC, Chattipakorn N. Chronic mitochondrial fusion promotor as a novel pharmacological intervention to alleviate left ventricular dysfunction in rats with chronic myocardial infarction. Eur Heart J. 2022;43(Suppl_2):ehac544.960. Available from: http://dx.doi.org/10.1093/eurheartj/ehac544.960
7. Varuzhanyan G, Chan DC. Mitochondrial dynamics during spermatogenesis. J Cell Sci. 2020 Jul 15;133(14):jcs235937. Available from: https://doi.org/10.1242/jcs.235937
8. Ren L, Chen X, Chen X, Li J, Cheng B, Xia J. Mitochondrial Dynamics: Fission and Fusion in Fate Determination of Mesenchymal Stem Cells. Front Cell Dev Biol. 2020 Oct 15;8:580070. Available from: https://doi.org/10.3389/fcell.2020.580070
9. Lewis M, Lewis W. Mitochondria in tissue culture. Science. 1914;39(1000):330-333. Available from: https://doi.org/10.1126/science.39.1000.330
10. Zhang T, Liu Q, Gao W, Sehgal SA, Wu H. The multifaceted regulation of mitophagy by endogenous metabolites. Autophagy. 2022;18(6):1216-1239. Available from: https://doi.org/10.1080/15548627.2021.1975914
11. Noone J, O'Gorman DJ, Kenny HC. OPA1 regulation of mitochondrial dynamics in skeletal and cardiac muscle. Trends Endocrinol Metab. 2022;33(10):710-721. Available from: https://doi.org/10.1016/j.tem.2022.07.003
12. Wang C, Liu L, Wang Y, Xu D. Advances in the mechanism and treatment of mitochondrial quality control involved in myocardial infarction. J Cell Mol Med. 2021;25(15):7110-7121. Available from: https://doi.org/10.1111/jcmm.16744
13. Zhu XX, Wang X, Jiao SY, Liu Y, Shi L, Xu Q, et al. Cardiomyocyte peroxisome proliferator-activated receptor - prevents septic cardiomyopathy via improving mitochondrial function. Acta Pharmacol Sin. 2023;44(11):2184-2200. Available from: https://doi.org/10.1038/s41401-023-01107-5
14. Ma T, Huang X, Zheng H, Huang G, Li W, Liu X, et al. SFRP2 Improves Mitochondrial Dynamics and Mitochondrial Biogenesis, Oxidative

Stress, and Apoptosis in Diabetic Cardiomyopathy. Oxid Med Cell Longev. 2021;2021:9265016. Available from: https://doi.org/10.1155/2021/9265016

15. Han L, Zhang Y, Li J, Xiao Y, Lu M, Li Y, et al. Phloretin attenuation of hepatic steatosis via an improvement of mitochondrial dysfunction by activating AMPK-dependent signaling pathways in C57BL/6J mice and HepG2 cells. Food Funct. 2021;12(24):12421-12433. Available from: https://doi.org/10.1039/d1fo02577e
16. Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P, et al. Classification of the cardiomyopathies: a position statement from the European Society Of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J. 2008;29(2):270-6. Available from: https://doi.org/10.1093/eurheartj/ehm342
17. Chen L, Gong Q, Stice JP, Knowlton AA. Mitochondrial OPA1, apoptosis, and heart failure. Cardiovasc Res. 2009;84(1):91-9. Available from: https://doi.org/10.1093/cvr/cvp181
18. Fang L, Moore XL, Gao XM, Dart AM, Lim YL, Du XJ. Down-regulation of mitofusin-2 expression in cardiac hypertrophy in vitro and in vivo. Life Sci. 2007;80(23):2154-2160. Available from: https://doi.org/10.1016/j.lfs.2007.04.003
19. Piquereau J, Caffin F, Novotova M, Prola A, Garnier A, Mateo P, et al. Down-regulation of OPA1 alters mouse mitochondrial morphology, PTP function, and cardiac adaptation to pressure overload. Cardiovasc Res. 2012;94(3):408-17. Available from: https://doi.org/10.1093/cvr/cvs117
20. Mohammed SA, Paramesha B, Meghwani H, Kumar Reddy MP, Arava SK, Banerjee SK. Allyl Methyl Sulfide Preserved Pressure Overload-Induced Heart Failure Via Modulation of Mitochondrial Function. Biomed Pharmacother. 2021;138:111316. Available from: https://doi.org/10.1016/j.biopha.2021.111316
21. Chang H, Wang Z, Wu H. Research on the Mechanism of Kangxian Yixin Formula in Regulating Mitochondrial Dynamics and Its Effect on Myocardial Cell Apoptosis in Mice with Dilated Cardiomyopathy. J Beijing Univ Chin Med. 2023;46(10):1391-1399.
22. Luo H, Sun L, Wang Y, et al. Research Progress on Mitochondrial Fusion Protein of Optic Nerve Atrophy Type 1 in Cardiovascular Diseases. Chin J Cardiovasc Dis Res. 2024;22(01):3-7.
23. Li Y, Xu Y, Chen Y. Understanding the Diagnosis and Treatment of Non-Expansive Left Ventricular Cardiomyopathy. J Clin Intern Med. 2024;41(06):374-378.
24. Green A, Hossain T, Eckmann DM. Mitochondrial dynamics involves molecular and mechanical events in motility, fusion and fission. Front Cell Dev Biol. 2022;10:1010232. Available from: https://doi.org/10.3389/fcell.2022.1010232
25. Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke DA, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the task force criteria. Circulation. 2010;121(13):1533-41. Available from: https://doi.org/10.1093/eurheartj/ehq025
26. Frangogiannis NG. Cardiac fibrosis: Cell biological mechanisms, molecular pathways and therapeutic opportunities. Mol Aspects Med. 2019;65:70-99. Available from: https://doi.org/10.1016/j.mam.2018.07.001
27. Cong L, Bai Y, Guo Z. The crosstalk among autophagy, apoptosis, and pyroptosis in cardiovascular disease. Front Cardiovasc Med. 2022;9:997469. Available from: https://doi.org/10.3389/fcvm.2022.997469
28. Chapa-Dubocq XR, Rodríguez-Graciani KM, García-Báez J, et al. The Role of Swelling in the Regulation of OPA1-Mediated Mitochondrial Function in the Heart In Vitro. Cells. 2023;12(16):2017. Available from: https://doi.org/10.3390/cells12162017
29. Diwan A. Preserving mitochondria to treat hypertrophic cardiomyopathy: From rare mitochondrial DNA mutation to heart failure therapy? J Clin Invest. 2023;133(14):e171965. Available from: https://doi.org/10.1172/jci171965
30. Yapa NMB, Lisnyak V, Reljic B, Ryan MT. Mitochondrial dynamics in health and disease. FEBS Lett. 2021 Apr;595(8):1184-1204. Available from: https://doi.org/10.1002/1873-3468.14077
31. Bhatti JS, Bhatti GK, Reddy PH. Mitochondrial dysfunction and oxidative stress in metabolic disorders—A step towards mitochondria based therapeutic strategies. Biochim Biophys Acta Mol Basis Dis. 2017;1863(5):1066-1077. Available from: https://doi.org/10.1016/j.bbadis.2016.12.013
32. Li M, Wang L, Wang Y, Zhang S, Zhou G, Lieshout R, et al. Mitochondrial Fusion Via OPA1 and MFN1 Supports Liver Tumor Cell Metabolism and Growth. Cells. 2020 Jan 4;9(1):121. Available from: https://doi.org/10.3390/cells9010121
33. Hu Y, Chen H, Zhang L, Lin X, Li X, Zhuang H, et al. The AMPK-MFN2 axis regulates MAM dynamics and autophagy induced by energy stresses. Autophagy. 2021;17(5):1142-1156. Available from: https://doi.org/10.1080/15548627.2020.1749490
34. Patten DA, Wong J, Khacho M, Soubannier V, Mailloux RJ, Pilon-Larose K, et al. OPA1-dependent cristae modulation is essential for cellular adaptation to metabolic demand. EMBO J. 2014;33(22):2676-91. Available from: https://doi.org/10.15252/embj.201488349
35. A clinical and molecular genetic study of hereditary optic nerve atrophy associated with the OPA1 gene and mechanism research based on patient-derived cell models. 2021.
36. Zhuang Q, Guo F, Fu L, Dong Y, Xie S, Ding X, et al. 1-Deoxynojirimycin promotes cardiac function and rescues mitochondrial cristae in mitochondrial hypertrophic cardiomyopathy. J Clin Invest. 2023;133(14):e164660. Available from: https://doi.org/10.1172/jci164660
37. Bloom SI, Islam MT, Lesniewski LA, Donato AJ. Mechanisms and consequences of endothelial cell senescence. Nat Rev Cardiol. 2023;20(1):38-51. Available from: https://doi.org/10.1038/s41569-022-00739-0
38. Komarova YA, Kruse K, Mehta D, Malik AB. Protein interactions at endothelial junctions and signaling mechanisms regulating endothelial permeability. Circ Res. 2017;120(1):179-206. Available from: https://doi.org/10.1161/circresaha.116.306534
39. Sharma A, Ahmad S, Ahmad T, Ali S, Syed MA. Mitochondrial dynamics and mitophagy in lung disorders. Life Sci. 2021 Nov 1;284:119876. Available from: https://doi.org/10.1016/j.lfs.2021.119876
40. Wang HH, Wu YJ, Tseng YM, Su CH, Hsieh CL, Yeh HI. Mitochondrial fission protein 1 up-regulation ameliorates senescence-related endothelial dysfunction of human endothelial progenitor cells. Angiogenesis. 2019 Nov;22(4):569-582. Available from: https://doi.org/10.1007/s10456-019-09680-2
41. Makino A, Suarez J, Gawlowski T, Han W, Wang H, Scott BT, et al. Regulation of mitochondrial morphology and function by O-GlcNAcylation in neonatal cardiac myocytes. Am J Physiol Regul Integr Comp Physiol. 2011;300(6):R1296-302. Available from: https://doi.org/10.1152/ajpregu.00437.2010
42. Chen Y, Liu C, Zhou P, Li J, Zhao X, Wang Y, et al. Coronary Endothelium No-Reflow Injury Is Associated with ROS-Modified Mitochondrial Fission through the JNK-Drp1 Signaling Pathway. Oxid Med Cell Longev. 2021 Jan 30;2021:6699516. Available from: https://doi.org/10.1155/2021/6699516
43. Chen ZS, Yu MM, Wang K, Meng XL, Liu YC, Shou ST, et al. Omega-3 polyunsaturated fatty acids inhibit cardiomyocyte apoptosis and attenuate sepsis-induced cardiomyopathy. Nutrition. 2023;106:111886. Available from: https://doi.org/10.1016/j.nut.2022.111886
44. Fu Y, Zhang HJ, Zhou W, Lai ZQ, Dong YF. The protective effects of sophocarpine on sepsis-induced cardiomyopathy. Eur J Pharmacol.; 950:175745. Available from: https://doi.org/10.1016/j.ejphar.2023.175745
45. Tschöpe C, Ammirati E, Bozkurt B, Caforio ALP, Cooper LT, Felix SB, et al. Myocarditis and inflammatory cardiomyopathy: current evidence and future directions. Nat Rev Cardiol. 2021 Mar;18(3):169-193. Available from: https://doi.org/10.1038/s41569-020-00435-x

46. Sánchez-Rodríguez R, Tezze C, Agnellini AHR, Angioni R, Venegas FC, Cioccarelli C, et al. OPA1 drives macrophage metabolism and functional commitment via p65 signaling. Cell Death Differ. 2023 Mar;30(3):742-752. Available from: https://doi.org/10.1038/s41418-022-01076-y

47. Yu J, Li R, Xia T, Wang J, Jin J, Yuan M, et al. PDCD4 knockdown ameliorates lipopolysaccharide-induced endothelial cell damage by improving mitochondrial dynamics. Nan Fang Yi Ke Da Xue Xue Bao. 2024;44(1):25-35.

48. Zhou H, Wang S, Zhu P, Hu S, Chen Y, Ren J. Empagliflozin rescues diabetic myocardial microvascular injury via AMPK-mediated inhibition of mitochondrial fission. Redox Biol. 2018;15:335-346. Available from: https://doi.org/10.1016/j.redox.2017.12.019

49. Li H, Wu F, Huang G, Wu D, Wang T, Wang X, et al. Cardiomyocytes induced from hiPSCs by well-defined compounds have therapeutic potential in heart failure by secreting PDGF-BB. Signal Transduct Target Ther. 2022;7(1):253. Available from: https://doi.org/10.1038/s41392-022-01045-4

50. Zhao Y, Zhu J, Zhang N, Liu Q, Wang Y, Hu X, et al. GDF11 enhances therapeutic efficacy of mesenchymal stem cells for myocardial infarction via YME1L-mediated OPA1 processing. Stem Cells Transl Med. 2020;9(10):1257-1271. Available from: https://doi.org/10.1002/sctm.20-0005

51. Yang Z, Gao Y, Li D. Panaxadiol Saponin alleviates LPS-induced cardiomyopathy similar to dexamethasone via improving mitochondrial quality control. Shock; 2023: 10.1097.