

New Strategies for the Treatment of Dilated Cardiomyopathy

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Conflict-of-interest statement: The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

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Received: April 20, 2022

Revised: May 28, 2022

Accepted: May 1, 2022

Published online: June 13, 2022

ABSTRACT

Dilated cardiomyopathy (DCM) is a type of cardiomyopathy that is characterized by an enlarged left ventricle or double ventricle accompanied by systolic dysfunction. It is a heterogeneous cardiomyopathy. It has an insidious onset and complicated aetiology, and its pathogenesis is unclear. The traditional treatment methods for

this condition include drugs and surgery. These methods can only help relieve the symptoms, as the condition cannot be permanently cured. Therefore, there is an urgent need to develop specific targeted therapies to treat dilated cardiomyopathy. This review aimed to introduce the aetiology and clinical manifestations of dilated cardiomyopathy, discuss the advantages and disadvantages of its traditional treatment methods and focus on gene- and cell-based targeted therapy strategies.

Key words: Dilated cardiomyopathy; Pathogenesis; Traditional treatment; Gene treatment

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Qin B, Wan YQ, Zhu P, Zhuang J, Wu XS. New Strategies for the Treatment of Dilated Cardiomyopathy. *Journal of Cardiology and Therapy* 2022; **9(1)**: 995-1003 Available from: URL: <http://www.ghrnet.org/index.php/jct/article/view/3308>

INTRODUCTION

Cardiomyopathy is a group of heterogeneous myocardial diseases. They are abnormalities of cardiac mechanical and electrical activity caused by different aetiologies, usually manifested as inappropriate ventricular hypertrophy or dilation^[1]. According to cardiac insufficiency and pathological morphology, the World Health Organization and the International Association of Cardiology divide cardiomyopathy into two types: (1) cardiomyopathy with cardiac insufficiency, such as dilated, hypertrophic, restrictive and cardiac rhythm, and abnormal and undefined types and (2) specific cardiomyopathy, such as perinatal, hypertensive and metabolic cardiomyopathy.

Dilated cardiomyopathy (DCM) refers to the presence of left ventricular or biventricular dilatation and systolic dysfunction without abnormal load conditions and severe coronary artery disease^[2,3]. It is the third leading cause of heart failure after coronary heart disease and hypertension and is also the most common cause of heart transplantation. This disease occurs in all age groups, including newborns^[4]; however, foetal presentation is uncommon^[5]. It is estimated that the prevalence of dilated cardiomyopathy is about 1:250-400 and the annual incidence rate is 5-7 cases per

100,000 people^[6]. The clinical incidence of the disease is about 2.5:1 between men and women, and there are ethnic differences^[7]. Given that dilated cardiomyopathy is a progressive disease with complex aetiology, there remains no specific treatment for dilated cardiomyopathy. Traditional treatment methods include drug therapy and surgical treatment, and cutting-edge treatment methods are mainly based on gene and cell therapy. This review reports the causes and clinical manifestations of dilatation, discusses the advantages and disadvantages of traditional treatment methods and focuses on new strategies based on gene- and cell-based targeted therapy.

AETIOLOGY

Dilated cardiomyopathy (DCM) is the final result of myocardial damage caused by many factors. Table 1 summarizes the causes of DCM. The aetiology of dilated cardiomyopathy can be divided into two groups, hereditary and non-hereditary, although there is a partial overlap between the two^[6]. According to reports, approximately 60% of DCM cases have genetic causes. The most common mode of inheritance is autosomal dominant inheritance. Autosomal recessive, X-linked and mitochondrial inheritance modes have also been described, although they are not common^[8]. With the development of diagnostic technology, more than 400 pathogenic variants have been identified in more than 60 genes, which are involved in encoding cytoskeleton, sarcomere or nuclear membrane, ion channels, mitochondrial proteins, etc. Among them, TTN and LMNA are the main pathogenic genes of familial DCM. Non-hereditary causes include infectious agents, inflammation, toxins and endocrine or metabolic disorders^[1,9]. With such a complicated aetiology, a multidisciplinary approach (such as genetic testing, echocardiography, cardiac MRI, endocardial and myocardial biopsy, etc.) is required to obtain accurate diagnostic results. However, overlapping phenotypes often make the differential diagnosis unclear, a major challenge in the field of cardiovascular disease.

CLINICAL MANIFESTATIONS

Most cases of dilated cardiomyopathy have a slow and insidious onset and may be asymptomatic in the early stages. Different patients with dilated cardiomyopathy have different clinical manifestations, which are mainly caused by a wide range of genetic and non-genetic factors. According to reports, patients with dilated cardiomyopathy usually have symptoms of heart failure and arrhythmia. These symptoms include palpitation, excessive sweating, ankle swelling, progressive dyspnoea and fatigue after mild exercise. In addition to the above symptoms, abdominal distension, loss of appetite, oedema, pleural effusion and ascites may also occur in the late stage of the disease. In addition, thromboembolic events and sudden death may occur at various stages of the onset of disease^[10]. Physical

examination can find signs of accelerated heart rate, apical beats shifted to the lower left, third or fourth heart sounds and mitral regurgitation murmurs^[11].

TRADITIONAL THERAPY

The treatment goal of dilated cardiomyopathy is to prevent the underlying cause of myocardial damage, effectively control heart failure and arrhythmia, prevent sudden death and embolism and improve the quality of life and survival rate of patients. The clinical treatment of dilated cardiomyopathy is mainly divided into two types: drug and non-drug therapy.

1. Medication

At present, there is no consensus among clinicians on the best medication regimen for DCM. Due to the complex condition of dilated cardiomyopathy, clinically, the symptoms and complications of the disease are usually treated with appropriate drugs. In the process of drug treatment, it is necessary to determine the timing of treatment, control the dosage of the drug and minimize the side effects of the drug.

For the symptoms of heart failure, the combination of angiotensin-converting enzyme inhibitors (ACE-I) and β -blockers is now considered to be the most basic treatment for chronic heart failure^[10]. If the patient is intolerant to angiotensin-converting enzyme inhibitors (ACE-I), consider using angiotensin receptor blockers (ARB), which have a similar biological functional effects to ACE-I, with fewer side effects^[12,13]. However, neonates should be careful to use drugs that block the renin-angiotensin system^[14]. When ACE-I/ARB and beta-blockers are used in combination, the addition of mineralocorticoid receptor antagonists and channel inhibitor ivabradine has been shown to increase the survival rate of patients and reduce the hospitalization rate^[15,16]. If the patient still has symptoms, it is recommended to use sacubitril/valsartan to replace ACE-I/ARB, which can significantly reduce the risk of hospitalization and death in patients with heart failure with reduced ejection fraction^[17]. In addition, positive inotropic agents (such as dobutamine and dopamine)^[18] and diuretics (such as furosemide)^[19] can be used for treating acute heart failure.

For arrhythmia symptoms, anti-arrhythmic drugs should be used rationally. According to reports, amiodarone is safe and effective in the prevention and treatment of arrhythmia, but it increases the risk of toxicity in the lungs and thyroid^[20]. Since most anti-arrhythmic drugs have negative inotropic effects that can aggravate heart failure, that class of drugs should be used on the premise of strengthening heart failure treatment.

For patients with dilated cardiomyopathy with atrial fibrillation or a history of embolism, when there is no contraindication to anticoagulation, oral anticoagulation therapy may be considered^[21]. It aims to prevent thrombosis and embolism. Common drugs include

Table 1 Causes of dilated cardiomyopathy.

Mutated genes	TTN, LMNA, MYH7, MYH6, TNNT2, ACTC1, MYBPC3, TPM1, DMD, SCN5A, etc.
Infection (myocarditis)	Coxsackie virus B, parvovirus (B19), adenovirus, influenza virus, human immunodeficiency virus (HIV), etc. Some bacteria, fungi, rickettsiae and parasites, etc.
Autoimmune	Giant cell myocarditis, sarcoidosis, dermatitis, systemic vasculitis, systemic lupus erythematosus, etc.
Toxins	Alcohol, cocaine, amphetamines, anthracyclines, heavy metals (cobalt, lead and mercury), etc.
Endocrine or metabolic disorders	Hypothyroidism, hyperthyroidism, pheochromocytoma, diabetes mellitus, etc.
Neuromuscular diseases	Duchenne muscular dystrophy (DMD), Becker muscular dystrophy (BMD)
Pregnancy and perinatal cardiomyopathy	

warfarin and dabigatran.

In recent years, with the extensive development of clinical trials, Chinese medicine has also been vigorously promoted in the clinical treatment of cardiovascular diseases. A recent study^[22] systematically evaluated the effectiveness and safety of traditional Chinese medicine in the treatment of DCM. However, the mechanism of traditional Chinese medicine in the treatment of DCM remains unclear.

2. Non-drug treatment

Non-drug treatments include electrical device therapies and heart transplantation. If the patient's left ventricular ejection fraction is still $\leq 35\%$ under the maximum dose of heart failure drugs, consider using an implantable cardioverter-defibrillator (ICD)^[6]. However, a study showed that the implantation of ICD as a method of primary prevention did not significantly reduce the overall mortality, although the rate of sudden deaths was reduced^[23]. In addition, patients with NT-proBNP > 1000 pg/mL cannot benefit from ICD. Cardiac resynchronization therapy (CRT) for heart failure is suitable for patients with sinus rhythm and QRS ≥ 150 ms with left bundle branch block, persistent symptoms after drug treatment and left ventricular ejection fraction $\leq 35\%$ ^[13,24,25]. CRT helps synchronize the contraction of the left and right ventricles, reduce functional mitral regurgitation (FMR) and reduce the morbidity and mortality of patients^[26,27]. However, a study pointed out that 30-35% of patients received CRT without response, no symptom improvement or left ventricular remodelling, and some even experienced clinical deterioration after implanting the device. More importantly, although both ICD and CRT studies have been conducted in large randomized trials, these two devices are still underutilized in many countries^[28,29]. Other auxiliary devices include the intra-aortic balloon pump^[30], extracorporeal membrane oxygenator^[31] and ventricular mechanical assist device^[32], which are suitable for end-stage dilated cardiomyopathy, hemodynamic instability, cardiogenic shock and other conditions and are prepared for the transition before heart transplantation.

Heart transplantation (HT) is the gold standard for the treatment of patients with end-stage heart failure and is an effective way to improve the quality of life and survival rate of patients. Indications for heart transplantation include failure of medical therapy, severe failure to thrive, intractable arrhythmias and severe limitations to activity^[4,33-35]. However, the shortage of heart donors limits the realization of heart transplantation, and heart transplantation rejection is still the Achilles heel of transplantation^[36].

NEW TREATMENT STRATEGIES

Since most cases of DCM have genetic causes, currently, drugs and surgical treatments for the symptoms of dilated cardiomyopathy have certain shortcomings. They are only nonspecific treatments to improve symptoms. There is an urgent clinical need for specific targets for genetic causes. In recent years, more and more studies for treatment have shown that gene- and cell-based therapies have shown certain advantages. It provides an innovative method of normalizing the structure and function of the heart, thereby reducing the need for heart transplantation. Dilated cardiomyopathy is a heterogeneous cardiomyopathy. The prerequisite for seeking specific targeted therapy is to understand the gene regulation that causes DCM to occur as deeply as possible. Therefore, before introducing gene- and cell-based targeted therapy, we first introduce the relationship between gene regulation and disease occurrence.

GENE REGULATION AND DISEASE OCCURRENCE

1. Sarcomere genes and DCM

The frequency of the main mutated genes in familial dilated cardiomyopathy is different. Among them, the most frequently mutated genes are the sarcomere genes, which includes *TTN*, *MYH7*, *MYH6*, *TNNT2*, *ACTC1*, *MYBPC3*, *TPM1*, etc.^[37-43]. According to reports, up to 25% of DCM cases are associated with mutations in the *TTN* gene^[6]. *TTN* encodes the TITIN protein, the largest protein in the human body and an important part of sarcomere. The TITIN protein originates from the M line of the sarcomere and stretches along the myosin fibres, passes through the A zone of the sarcomere and finally reaches the Z disk. As a biological spring, the TITIN protein has scaffold and signalling functions. *TTN* truncation mutations (truncation mutations) are the most common genetic causes of DCM, mainly missense mutations, followed by deletions and nonsense mutations. In recent years, many studies have shown that *TTN* truncation mutations are mainly concentrated in the A-band region^[44,45]. However, interestingly, *TTN* truncation mutations were also found in about 1% of asymptomatic people^[46,47]. It is speculated that *TTN* truncation mutations can cause haploinsufficiency and loss of function or produce a 'toxic peptide' effect, which can damage cardiomyocytes and sarcomere^[37]. However, the exact mechanism by which *TTN* mutations cause DCM has not yet been clearly confirmed.

Mutations in other sarcomere genes (such as *MYH7*, *MYH6*, *TNNT2*, *ACTC1*, *MYBPC3*, *TPM1*) are also associated with DCM and mainly encode thick and thin filament proteins. These proteins participate in the contraction and regulation of cardiomyocytes and play a structural role. Mutations in the genes encoding these proteins can interfere with their normal interactions and cause dilated cardiomyopathy. The incidence of pathogenic variants of these sarcomere genes in DCM cases is less than 5%^[48].

2 Cytoskeleton genes and DCM

Mutations in cardiac cytoskeleton protein genes are also highly correlated with DCM. The *DMD* gene encodes the DYSTROPHIN protein, which connects the extracellular matrix with the cytoskeleton and stabilizes the muscle membrane^[49]. If this gene is mutated, it can lead to muscular dystrophy diseases, such as Duchenne muscular dystrophy (DMD), Becker muscular dystrophy (BMD) and sex-linked DCM. In DMD, the lack of anti-muscular atrophy protein causes the fragile muscle membrane to be easily damaged by stress, increases the instability and permeability of the muscle membrane and increases calcium influx leading to calcium overload and oxidative stress. Over time, excessive calcium and reactive oxygen species (ROS) will activate cell death pathways, fibrosis and expansion^[50].

3. Nuclear envelope genes and DCM

The *LMNA* gene is one of the most common mutant genes in dilated cardiomyopathy (DCM), accounting for about 10% of DCM cases. *LMNA* encodes LMNA A and C and has the characteristics of a head-rod-tail domain. These two protein isoforms are derived from the alternative splicing of a single transcript. The LMNA A and C proteins are intermediate-filament nuclear envelope proteins, which are involved in DNA replication, cell cycle regulation, maintenance of differentiation, nuclear stability, gene expression and signal transduction^[51]. Mutations in *LMNA* can not only cause dilated

cardiomyopathy (its disease characteristics are characterized by large heart chambers and thin ventricular walls) but can also cause progressive conduction diseases (including atrioventricular block, atrial standstill and ventricular arrhythmia). These two diseases can exist independently or overlap^[52,53]. According to the study by Fatkin D *et al.*^[54], missense mutations in the rod domain of LMNA A/C protein are the genetic cause of dilated cardiomyopathy and can cause changes in the assembly of LMNA polymers. This indicates a major negative mechanism. However, the molecular mechanism of LMNA mutations causing DCM remains unclear^[55].

4. Mitochondrial dysfunction and DCM

Mitochondrial diseases dominate among the syndromes of DCM. Mutations in mitochondrial DNA or nuclear genes encoding mitochondrial components are also associated with DCM. Tafazzin, located in the lobules of mitochondria, is a phospholipid transylase, which is encoded by the *TAZ* gene. Mutations in the *TAZ* gene may change mitochondrial function, may cause multiple organ dysfunctions and may also cause the DCM phenotype of left ventricular insufficiency (LVNC)^[56].

5. Ion channel genes and DCM

SCN5A encodes the alpha subunit of the main myocardial sodium channel NaV1.5, and its role is to maintain the normal function of inward sodium current (I_{Na}). I_{Na} is the main component of the rapid depolarization of cardiomyocytes, and periodic depolarization is the basis for the synchronized and rhythmic contraction of the heart chambers^[57]. *SCN5A* mutations have been found to be associated with cardiac systolic dysfunction, dilated cardiomyopathy and heart failure. On the one hand, *SCN5A* mutations cause the destruction of ion channels, and ion channel disorders cause cytoskeletal protein binding partners to dysfunction and lead to DCM phenotypes; on the other hand, electrical dysfunction caused by mutations leads to mechanical instability and eventually myocardial expansion^[58].

In addition to the above mentioned genes, the *DES* gene encoding desmosomal proteins, the *RBM20* gene of RNA binding protein 20, the *PLN* gene of phospholamban and the *FLNC* gene of filamin C, these gene mutations are all related to arrhythmia-causing DCM, accounting for about 1%-5% of all DCM cases^[59]. In addition to the mutated genes that have been found to be associated with DCM, there must be other mutated genes that have not yet been discovered, which require researchers to persistently explore.

NEW TREATMENT STRATEGIES

1. Gene therapy

Gene therapy refers to the introduction of foreign genes into target cells to correct or compensate diseases caused by defects and abnormal genes to achieve the purpose of treatment. With the in-depth study of the genetics of DCM and the discovery of related pathogenic genes, targeted gene therapy has become a new field in the treatment of DCM. According to different target genes, gene therapy of DCM can be divided into two different mechanisms: (1) to treat the mutant gene itself and (2) to correct the pathophysiological changes caused by the gene mutation.

Daniel R Stroik *et al.*^[60] used pluripotent stem cell-derived cardiomyocytes (hiPSC-CMS) derived from healthy individuals. In this cell line, the authors used adeno-associated virus 2 (RAAV2) to overexpress a loss-of-inhibition mutant (*PLB_M*), *PLB_M* and the inhibitory wild-type *PLB* (*PLB_{WT}*) compete with *SERCA2a* (SR Ca-ATPase) (the cardiac Ca²⁺ pump), and *PLB_M* relieves the inhibition of

SERCA2a and enhances the Ca²⁺ transport activity, thereby restoring the contractile ability of cardiomyocytes. Felix Woitek *et al.*^[61] used adeno-associated virus serotype 9 viral vectors to carry *VEGF-B167* (vascular endothelial growth factor-B167) gene (*VEGF-B167* activates cells through VEGF receptors). Protective/anti-apoptotic mechanism), oral treatment was given to dogs with compensatory heart failure. Results showed that compared with the control group, *VEGF-B167* significantly retained diastolic and systolic function, reduced ventricular remodelling and prevented compensatory heart failure (the progression from failure to decompensated heart failure). In another study, the authors demonstrated the tolerability and feasibility of the adeno-associated virus vector carrying *VEGF-B167* in the coronary arteries of canine DCM patients^[62].

In recent years, with the rapid development of clinical discovery and basic scientific research, next-generation sequencing and bioinformatics analysis, researchers have continuously discovered new genes associated with dilated cardiomyopathy, which provides new treatments for genome editing the target also provides information for the realization of precision medicine^[63-65]. On the other hand, the development of non-viral vector gene delivery systems for genome editing is also underway, such as lipid nanoparticles^[66], DNA nanoparticles^[67] and inorganic nanoparticles^[68]. These non-viral vector gene delivery methods have the advantages of low immunogenicity, safety and reliability and the ability to carry gene fragments of different sizes^[69]. In a study, the authors used a catheter delivery to target the new therapeutic gene *VEGF-DANAC* to the ischemic myocardium; this technique has produced promising results^[70].

Although the current DCM gene therapy has some practical problems to be solved, such as the optimization of vector selection, the improvement of transfection efficiency, the long-term stable expression of genes, etc., recent studies have confirmed the effect and feasibility of gene therapy. In future experimental studies, gene therapy should be combined with existing treatments to improve the quality of life and longevity of patients, which is expected to be successful in the near future^[71,72].

2. Stem cell transplantation treatment

Stem cell transplantation as a new method for the management of end-stage cardiovascular disease has become a research focus in recent years. One of the unique characteristics of stem cells is that they can differentiate into cardiomyocytes, smooth muscle cells and endothelial cells, thereby contributing to the regeneration process. Stem cells used for the treatment of cardiovascular diseases are mainly divided into two types: embryonic and adult stem cells. The latter can be derived from bone marrow, adipose tissue, umbilical cord, skeletal muscle and induced pluripotent stem cells^[73].

The differentiation and regeneration ability of stem cells gives them an advantage in the treatment of heart disease. At present, stem cell transplantation therapy has been successfully used in small studies of dilated cardiomyopathy. Ricardo João Westphal *et al.*^[74] injected bone marrow adult stem cells into 24 patients with dilated idiopathic cardiomyopathy through the coronary arteries. The improved functional class was observed during follow-up for 3, 6 and 12 months. The improvement in left ventricular ejection fraction was also monitored. In another study, Bryon A Tompkins *et al.*^[75] proved that intramyocardial injection of bone marrow mesenchymal stem cells is beneficial to DCM patients since it improves the heart function and quality of life of DCM patients. Rong *et al.*^[76] evaluated the effectiveness and safety of stem cells in the treatment of dilated cardiomyopathy through a systematic appraisal and meta-analysis

and confirmed that stem cell therapy can improve left ventricular evacuation in patients with dilated cardiomyopathy. Blood fraction reduces left ventricular end-systolic volume and left ventricular end-diastolic volume.

In addition to the differentiation effect of stem cells in the treatment of cardiovascular diseases, there is also a paracrine effect. Some researchers believe that the paracrine mechanism plays a major therapeutic role after stem cell transplantation. This is due to the observation that the survival rate of stem cells in the ischemic and hypoxic environment after transplantation is low, and a small amount of stem cells is not enough to play a therapeutic role. Stem cells can secrete a variety of cytokines, growth factors and exosomes and other biologically active substances^[77]. Stem cell-derived exosomes are macrovesicles released from the endosomal membrane to the outside of the cell. They contain molecules such as proteins, lipids, mRNA and miRNAs, which participate in the exchange of information between cells. Compared with the injection of stem cells, stem cell-derived exosomes have the advantages of non-teratogenicity and less vascular occlusion^[78]. Due to its strong clinical application prospects, more and more researchers have begun to conduct more in-depth research on exosomes. Sun *et al.*^[79] injected mesenchymal stem cell-derived exosomes into a DCM mouse model intravenously, and results showed that exosome treatment can significantly reduce ventricular dilatation and improve heart function. In addition, the authors also found that exosomes improve the protective effect of myocardial inflammation microenvironment by regulating the activity of macrophages. At present, it is generally believed that stem cell transplantation is a safe treatment method for dilated cardiomyopathy in the short term, but the long-term clinical effect remains uncertain and requires large-scale clinical observation and verification. In addition, the treatment mechanism of stem cells remains unclear, and more research has to be carried out on the mechanism.

3. Cardiac Reprogramming

Heart reprogramming by transforming cardiac fibroblasts into induced cardiomyocyte-like cells (iCMs) has become a promising strategy for heart regeneration. According to reports, the combination of cardiac transcription factors *Gata4*, *MEF2C* and *Tbx5* (GMT) can quickly and efficiently transform fibroblasts into iCMs^[80]. However, the transformation efficiency is very low. Mohamed *et al.*^[81] found that the combination of transforming growth factor (TGF)- β inhibitor SB431542 and WNT inhibitor XAV939 can increase the reprogramming efficiency of cardiomyocytes *in vitro* by eight times. Zhou *et al.*^[82] conducted single-cell transcription analysis of cell fate transitions in the process of human heart reprogramming and revealed the molecular characteristics of human heart reprogramming. In their research, they determined a 'decision' point at which cells are either reprogrammed or regress to their initial fate. In addition, they developed a 'cell fate index', which quantitatively evaluates the progress of reprogramming.

Cellular reprogramming technology has created new opportunities in understanding human disease, drug discovery and regenerative medicine. In the future, when its epigenetic and delivery barriers are overcome, this technology will have unlimited possibilities to completely cure intractable diseases (including DCM)^[83].

CONCLUSION

DCM, the most common cardiovascular disease and one of the most difficult-to-treat diseases, is a worldwide problem. The aetiology is complicated and the clinical manifestations are many. Traditional

treatment methods can only relieve the symptoms, and the overall prognosis is poor. Targeted therapy based on genes and cells is a promising new treatment strategy, and it will still be the direction of future research. Therefore, researchers should continue to use various animal models to conduct research in the molecular field of DCM, explore new pathogenesis of DCM and deeply understand the pathogenesis of DCM to discover new therapeutic targets. In the near future, through continuous efforts, gene- and cell-based targeted therapy can be safely and effectively applied to DCM patients to achieve the goal of eradicating the disease.

ACKNOWLEDGMENTS

This study was supported in part by grants from the National Natural Science Foundation of China (grant nos. 81670290, 81974019), the National Key Research and Development Program of China (2018YFA0108700 and 2017YFA0105602), NSFC Projects of International Cooperation and Exchanges (81720108004), the Research Team Project of Natural Science Foundation of Guangdong Province of China (2017A030312007), The Key Program of the Guangzhou Science Research Plan (201904020047), the Special Project of the Dengfeng Program of Guangdong Provincial People's Hospital (DFJH201812, KJ012019119, and KJ012019423).

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