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Therapeutic effect of recombinant lentiviral vector containing succinate dehydrogenase iron-sulfur protein on the treatment of experimental autoimmunity myocarditis

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ABSTRACT

Cardiac autoimmune reaction takes part in myocarditis, dilated cardiomyopathy and heart failure. Existing literature has confirmed that the occurrence of cardiomyopathy belongs to mitochondrial diseases and is related to the oxidative respiratory chain subunit. The special structure of iron-sulfur protein (ISP) is responsible for the oxidative stress in oxidative phosphorylation, which is also a target that is easily attacked by various damage factors. Using gene therapy technology to restore succinate dehydrogenase iron-sulfur protein (SDISP) function— and thus resume myocardial mitochondria function and myocardial function is hypothesized to alleviate the experimental autoimmunity myocarditis (EAM).

Introduction

Autoimmune reaction takes part in myocarditis, dilated cardiomyopathy and heart failure [1]. Existing literature has confirmed that the occurrence of cardiomyopathy belongs to mitochondrial diseases and is related to the oxidative respiratory chain subunit: flavoprotein, cytochrome (cyto), iron-sulfur protein (ISP), and coenzyme Q (CoQ) [2–5]. Additionally, there have been numerous previous reports about the relationship between flavoprotein or cyto and cardiomyopathy. Moreover, due to recent advancements in research methods, the structure of ISP was gradually deduced. It was found that its special structure is responsible for the oxidative stress in oxidative phosphorylation, which is also a target that is easily attacked by various damage factors [6]. Accordingly, determining how to use gene therapy technology to restore SDISP protein function— and thus resume myocardial mitochondria function and myocardial function— was bound to become a new research direction.

Hypotheses

The recombinant lentivirus vectors containing the succinate dehydrogenase iron-sulfur protein (SDISP) gene can be used to alleviate the experimental autoimmunity myocarditis (EAM) from the perspective of myocardial inflammation and remodeling, systemic inflammation and myocardial autoantibodies, and cardiac structure and function through the mechanism of myocyte apoptosis and mitochondrial function.

Basis for hypotheses

Domestic and foreign scholars have previously conducted research that has led to the characterization of mitochondrial energy metabolism in the normal myocardium and in the myocardium of EAM. The myocardial mitochondrial genes, which are from the mother, are like other tissues in that variation exists among the cells [7], and they can be divided into flake fiber in the myocardial fiber and tubular mitochondria each other between the myocardial fibers. Furthermore, this is the site where aerobic respiration takes place and where ATP— an energy material— and reactive oxygen species are produced. Additionally, this aerobic process is closely related to the positioning and strict order of the major constituents of the mitochondrial electron transport chain on the mitochondrial membrane. These major constituent of the mitochondrial electron transport chain are nicotinamide adenine dinucleotide

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(nicotinamide adenine dinucleotide phosphate), flavin adenine dinucleotide, ISP, coenzyme Q (CoQ), and cytochrome (cyto). Accordingly, current research hotspots in the field of myocardial mitochondrial disease are primarily centered on the four electron carriers: flavoprotein, cyto, ISP, and CoQ. Previously, there has been extensive verification of the relationship between cyto and cardiomyopathy. For example, it has been verified that the cyto C oxidase activity in the viral cardiomyopathy mouse heart that was assayed by spectrophotometer was found to be decreased in mitochondrial oxidative phosphorylation function. Additionally, the endomyocardial ratio of cytosolic/mitochondrial cyto C concentrations as determined by an ELISA assay was found to be significantly increased in Enterovirus than in non- Enterovirus -related myocarditis patients [8].

SDH, an important catalyzing enzyme of the tricarboxylic acid cycle, is the component of the mitochondrial complex II that connects the oxidative phosphorylation and the electron transport. ISP provides electrons as the electron carrier of SDH for the aerobic respiratory chain to be able to produce energy in eukaryotic and prokaryotic cells' mitochondria. Therefore, any changes that occur to SDISP are bound to affect the cellular aerobic process. SDISP is coded and translated together by the mitochondrial DNA and the nucleoprotein; the central component is an iron-sulfur center that contains iron and sulfur atoms. The iron can be reduced ferrous iron or oxidized ferric iron, and one electron is passed each time the reversible redox reaction has reacted. In the respiratory chain, the iron-sulfur protein mainly exists as a compound combined with flavoprotein or cyto b, and the redox state of Fe-S can be inferred by the isoelectric point in addition to the characteristics of the enzymatic activity of aconitase, etc [9].

In regards to the structure of the iron-sulfur center, in the 1980s scholars agreed that the iron combines with the inorganic sulfur atoms or the sulfur of cysteine residues of a protein. There are three common kinds of ISP combinations: (a) a single iron atom connected to four thiol sulfurs on cysteine residues; (b) two iron atoms combine with two inorganic sulfur atoms (2Fe-2S), and each iron atom also combines with two thiol sulfurs on cysteine residues; and (c) four iron atoms connect with four inorganic sulfur atoms (4Fe-4S), and the iron and the sulfur are alternately arranged in eight vertex of a regular hexahedron. In addition, each of the four iron atoms connects with one thiol sulfur on cysteine residues. Three kinds of ISP conformations can transform to each other when the environment or the chemical condition changes. Furthermore, Kennedy MC [10] separated the cis-aconitic acid containing an $[3Fe\text{-}4S]^{1+}$ center from a bovine heart under an aerobic environment. After the protein was incubated under alkaline conditions at a greater than 9.5 pH or treated with 4–8 M urea, the brown-colored protein became purple. Meanwhile, the iron changed into the stable and inactive state, and ISP was incompletely open, the EPR signal was at $g = 4.3$ ($S = 5/2$), the Fe/S ratio was 0.66–0.74, and the iron appeared to either be an $[Fe\text{-}S]^{2-}$ or [2Fe-2S] center which was high spiral. In the reductive condition of the iron, its structure changed to be $[4Fe\text{-}4S]^{2+}$ which was black and active; Moreover, the Fe/S ratio was 0.90–1.03. Lorusso [11] reported that the conformation of the Fe-S protein is affected by the modification of the hoxyformic anhydride of the core protein II serene residues (one of the elements of the cell surface proteoglycans).

In the electron transport chain, the iron-sulfur center is the site of oxidative stress, but it is also a target that is actively attacked by various disease damage factors. For instance, Glycyrrhetinic acid, when it is above the threshold concentration of 7.5 microM, induced oxidative stress. The mitochondrial permeability transition, in rat heart mitochondria by interacting with a Fe-S center of Complex I, thus produces ROS and also amplifies the opening of the transition pore that is induced by Ca^{2+} [12]. Puccio [13] reported that having a severely reduced level of Frataxin, a mitochondrial protein, resulted in Friedreich ataxia and Frataxin defects pathophysiologically caused the ISP deficiency and intramitochondrial iron accumulation. The neuron/cardiac muscle frataxin-deficient line showed cardiac hypertrophy, large sensory neuron dysfunction, and deficient activities of complexes I–III of the respiratory chain and of the aconitases. Furthermore, the time-dependent intramitochondrial iron accumulation occurs after the onset of the pathology as well as the inactivation of the Fe-S-dependent enzymes. In 2008, Elas M [14] reported that the transgenic Tgalphaq44 mice, mimic of the phenotypic characteristics of DCM in humans, displayed a wide array of adverse effects: pulmonary congestion, increased heart/body ratio, and impaired cardiac function at the age of 14 months. However, in the hearts of the 10-month old Tgalphaq44 mice, EPR signals of semiquinones as well as cyto c oxidase activity were decreased. Furthermore, the following characteristics were observed in the 14-month old Tgalphaq44 mice: loss of iron in Fe-S clusters, impaired citrate synthase activity, and altered mitochondrial ultrastructure.

The mammal iron-sulfur center strongly function towards antioxidation and anti-nitrosation stress. In the oxidation respiratory chain (including the Fe-S center), it was verified that the ability to resist oxidation/nitrosation stress from strong to weak was: compound II, compound I, and compound III. More specifically, less iron sulfur content was associated with a greater sensitivity to oxidation conditions and associated with a greater irreversible damage of both mitochondrial and cell function [15]. This relationship inspired researchers to investigate the ability to treat disease by using drugs to restore the ISP structure and to strengthen ISP function. For example, the Anticancer drug doxorubicin, used by Minotti G [16] et al. in 1998, was limited by severe cardiotoxicity; this cardiotoxicity was primarily due to doxorubicinol, a secondary alcohol metabolite of doxorubicin. It delocalized low molecular weight Fe(II) from the [4Fe-4S] cluster of cytoplasmic aconitase, which resulted in an elimination of aconitase activity as well as affected the reversible ability of the apoprotein to function as an ion regulatory protein or to reincorporate iron within new Fe-S motifs. They predicted that the recovery of ISP was the direction of drug treatment to alleviate adriamycin toxicity.

An autoimmune mechanism may be involved in the cardiac muscle disorder that is characterized by progressive myocyte inflammatory destruction, which ultimately leads to fibrosis pathogenesis of DCM and an idiopathic heart. Organ-specific cardiac antibodies, including cTnI— the marker of the cardiac mini injury, were more frequent in patients with dilated cardiomyopathy then in those with other cardiac diseases or in normal subjects [17]. The EAM animal model mimics the impaired cardiac function and the pathological change of cardiac infiltration of inflammatory cells, cardiac fibrosis, systemic inflammation, and serum anti-autoantibody in human myocarditis, DCM, and heart failure induced by autoimmunity [18]. Additionally, the antibody complex and complement generated in immune responses can promote the phagocytes to produce superoxide anion free radicals, which may then lead to an intr-acellular ROS increase and subsequently irreversible myocardial damage or even apoptosis. Additionally, there is growing evidence that ROS may cause cell death via the mediation of mitogen-activated protein kinases [19]. In addition, ROS, produced by myocytes, downregulates the Kv4.2 transient outward potassium current and reduces myocardial action potential duration; this, in turn, leads to damaged mitochondrial electron transportation and ATP formation, ultimately resulting in mitochondrial injury, myocardial cell death, proinflammatory cytokines up-regulation, myocardial reconstruction, and myocarditis [20]. Moreover, MTP regulates mitochondria inner membrane