УДК 616.74–007.17–053.1–06:616.127
https://doi.org/10.30702/card:sp.2018.09.033/07

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Brief abstract. Duchene Muscular Dystrophy (DMD) is a lethal, X-linked muscle wasting disease with serious cardiac complications. This review article summarizes recent findings on the cellular pathophysiology of dystrophic cardiomyopathy, identifies novel potential therapeutic targets and describes several novel pharmacological agents and genetic approaches that aim to slow down the progression of the disease.

Keywords: dystrophic cardiomyopathy; Ca^{2+} and redox signaling; mitochondria; pharmacological targets; gene therapy.

Introduction

Duchenne Muscular Dystrophy (DMD) is an inherited lethal muscular disease that affects 1 in 3500–6000 live male births. DMD was named after the French

physiologist Guillaume-Benjamin Duchenne who presented several cases of infants with dystrophy in the mid 19th century. DMD occurs as a result of an inherited or spontaneous out-of-frame mutation (manly deletions) in dystrophin gene. Mutations lead to the absence of or a defect in the protein dystrophin [1].

Most patients are diagnosed at approximately 5 years of age, when they start to show signs of physical disabilities including walking problems. Later they manifest progressive systemic muscle weakness and become wheelchair dependent before their teens. For a long time DMD was considered to be predominantly a skeletal muscle illness clinically associated with skeletal deformities and breathing disorders. However, myocardial involvement is inevitable in DMD patients as dystrophin serves similar functions in both skeletal and cardiac muscles. The reduction of respiratory disease-related deaths, due to nocturnal ventilation and spinal stabilization, has contributed to the relative increase of DMD cardiomyopathy. Cardiac dysfunction is therefore an increasingly more common cause of death for individuals with DMD [2].

The incidence of cardiomyopathy in DMD increases with age. Whereas about 25 % of boys have cardiac abnormalities at 6 years of age, more than 90 % of young men over 18 years of age exhibit cardiac dysfunction [3]. Pathological changes of the myocardium in DMD patients are quite heterogeneous and probably result from combination of cardiac atrophy and myocardial remodeling. Abnormalities in the electrocardiogram and sinus tachycardia are found in many DMD patients at early age. Later, echocardiography reveals motion abnormalities of the ventricular walls in areas of fibrosis. Progressive and aggressive spreading of fibrosis mediates a gradual enlargement of the ventricle, thinning of the ventricular wall and consequently a loss of contractility and heart failure. More than 40 % of DMD patients also develop arrhythmias that may lead to a sudden death [4–6].

Further extension of survival and amelioration in the quality of life for DMD patients depends not only on improving skeletal muscle performance but also on the development of therapies that enhance cardiac function. This requires a mechanistic understanding of the nature ofthe cardiac defects. In this reviewarticle

we discuss the current view of cellular and molecular pathomechanisms of the dystrophic cardiomyopathy that finally determine the clinical phenotype.

Genetic and molecular underpinning of DMD

The human dystrophin gene (DMD) is located on the Xp21 chromosome locus, spanning 2.2 megabases. It is one of the longest human genes known [7]. Skeletal and cardiac muscle of DMD patients either completely lacks or express a truncated form of dystrophin, which in muscle is a ~427 kDa protein. Dystrophin links the muscle cytoskeletal actin to a complex of transmembrane proteins (referred to as dystrophin-glycoprotein complex, DGC), which interacts with the extracellular matrix [1, 8]. In striated muscle, the dystrophin network covers almost the entire cytoplasmic surface of the plasma membrane. It is also present in T-tubular membranes in cardiac myocytes [9]. Dystrophin plays a crucial role in maintenance of membrane stability as well as in the transduction of mechanical force to the extracellular matrix. It is widely accepted that the predominant functional consequence of defective dystrophin is an increased cellular vulnerability to mechanical stress during muscle contraction. Levels of serum creatine kinase are elevated in DMD patients as creatine kinase leaks through the plasmalemmal membrane of mechanically damaged muscle cells. Optical methods also detect accumulation of large molecular weight indicators inside dystrophic muscle cells as these indicators can reach the cytosol through microruptures in cellular membrane [10–12]. However, the precise molecular underpinnings of the membrane vulnerability resulting from the lack of dystrophin are still poorly understood at present. In principle, the mechanism could be direct and mechanical, or indirect via Ca^{2+} overload or oxidative stress.

Current treatment of DMD

Currently there is no cure for DMD. However, there are several widely accepted approaches that aim to increase muscle strength, reduce problems with joints and spine, and improve cardiac function in order to prolong the mobility of the patients and their life. They include several medications, physical therapy, various mobility aids, ventilation assistance and some surgical procedures to correct severe changes in spine curvature. The most common pharmacological interventions target symptoms associated with the degeneration/regeneration cycles. Usually these are corticosteroids, which have been shown to significantly reduce muscle inflammation and improve muscle function, strength and patient's pulmonary function. Prednisone or deflazacort, which has fewer side effects compared to prednisone, are the most frequently used ones. Unfortunately, the response to this treatment varies significantly between patients and ~2 % of patients do not respond at all to steroids. Moreover, prolonged use of corticosteroids can cause weight gain and weaken bones, increasing fracture risk. Therefore the development of novel hormonal therapies with less pronounced side effects is currently on the way. In particular, VBP15 (Vamorolone), a new drug developed by Dr. Hoffmann's group at Children's National Medical Center in Washington DC, USA [13, 14], is currently in clinical trials by ReveraGen Biopharma.

Regarding cardiac pathology, the use of angiotensin-converting enzyme inhibitors is considered to be a first-line therapy. β-blockers and diuretics are also used and published guidelines are followed for the management of heart failure. Patients taking glucocorticoids require additional monitoring of cardiovascular parameters, particularly for hypertension. If developed, systemic arterial hypertension should be treated and the glucocorticoid dose has to be adjusted. Because morbidity and mortality due to development of dystrophic cardiomyopathy are currently on the rise, additional research is definitely needed to identify specific treatments for

dystrophin deficient myocardium. Mechanistic studies are on the way to identify specific pharmacological interventions that target early symptoms of cardiac disease and delay its development. Some of these studies are summarized below.

Search for novel pharmacological targets: cellular manifestations of cardiac dystrophy

Overview

Ventricular cardiomyocytes isolated from hearts of a mouse model of DMD (mdx mice) exhibit a number of distinct characteristics compared to cells from hearts of wild type (control group) animals: 1) their plasmalemmal membrane is more fragile [10, 11]; 2) ionic fluxes across the membrane are increased [11, 15]; 3) resting cytosolic Ca^{2+} and Na^{+} levels are elevated [11, 15, 16]; 4) intracellular Ca^{2+} transients evoked by mechanical challenges are enhanced [10, 17, 18]; 5) excitation-contraction coupling (EC-coupling) is hypersensitive [19, 20]; 6) the cytosolic compartment is severely oxidized due to enhanced activity of sarcolemmal NAD(P)H oxidase type II (NOX2) [16, 21]; 7) mitochondrial redox state is shifted towards a more oxidative state [22]; and 8) mitochondria undergo irreversible depolarizations during increased workload due to enhanced opening of mitochondrial permeability transitions pore [16, 22, 23]. Moreover, damaged mitochondria are not efficiently removed from the hearts due to deficiency in the PINK1/PARKIN mitophagy pathway [24], eventually leading to the deficit in ATP supply. In addition, there were several reports of remodeling of Cx43 gap junctions and Cx43 hemichannels, that may contribute to the defects in cardiac conductivity [25].

The findings listed above have to be critically evaluated and combined in order to understand the cellular pathomechanisms driving progression of cardiac dystrophy downstream of these initial injuries. Overall, currently three major mechanisms are proposed to explain the progressive muscle damage. The first mechanism is related to the mechanical forces acting on the sarcolemmal membrane. Absence of DGC in DMD weakens the strong link between extracellular matrix and cytoskeleton during muscle contraction, causing membrane tears and miroruptures. The direct consequence of the microruptures is the increased intracellular Na+ and Ca^{2+} levels and ionic misbalance. The second mechanism is directly related to the misregulation of intracellular Ca $^{2+}$ homeostasis and activation of several Ca $^{2+}$ -dependent pathological pathways. The third major mechanism is associated with enhanced production of reactive oxygen and nitrogen species and subsequent oxidative / nitrosative stress. All three mechanisms are likely to work synergistically, ultimately leading to loss of functional myocardium and the development of dystrophic cardiomyopathy. New pharmacological tools that target these pathophysiological mechanisms (individually or in combination) are currently under development.

Mechanical damage of the sarcolemma and activation of Ca^{2+} entry pathways in DMD

As we mentioned above, the absence of dystrophin in DMD muscle leads to the formation of microruptures in the sarcolemma that allow influx/efflux of various ions (including Ca^{2+} and Na^{+}) and small molecules (including CK and ATP) into/out of muscle cell. The membrane sealer Poloxamer-188 (a.k.a. Carmeseal-MDTM, Phrixus Pharmaceutical) has been shown to improve function of dystrophic muscle and is currently available for patients in Europe, Argentina and New Zeeland as an unlicensed (“special”) medical product. Clinical trials are

currently underway in the U.S.A.

The disruption of sarcolemmal integrity also leads to the activation of several other Ca^{2+} (and other ions) entry pathways. They include (but are probably not limited to) mechanosensitive stretched activated channels (SAC), store operated Ca^{2+} entry pathway (SOCE) activated upon depletion of Ca^{2+} from the sarcoplasmic reticulum (SR) and Na^{+}/Ca^{2+} exchanger operating in the reverse mode (see [26–28] for review).

SACs are opened following mechanical stretch during muscle contraction and allow non-selective influx of cations. Their activity is increased in muscle of mdx mice, as well as in humans with DMD. Inhibitors of SACs, such as Gd3+ and streptomycin, have been shown to normalize intracellular Ca^{2+} homeostasis in mdx cardiomyocytes. The more specific SAC inhibitor GsMTx-4 (a.k.a. AT-300 Akashi Theraputics, Inc.) has shown some promise in pre-clinical trials and has been granted Orphan drug designation status by the U.S. Food and Drug Administration. The molecular composition of SACs is still not clear, but some mechanosensitive transient receptor potential cation channels, such as TRPC1, TRPC3, TRPC6 and TRPV2 seem to be potential candidates. In addition, the more recently discovered mechano-sensitive Piezo channels also have to be considered.

Also the SOCE pathway has been shown to be upregulated in dystrophic muscle [29]. The proteins Orai and STIM, as well as some members of the TRP channels family have been implicated in composing the SOCE Ca^{2+} influx pathway. Orai (named after mythological characters that served as gate keepers) is a highly selective Ca^{2+} channel located in sarcolemmal membrane. STIM1 (stromal interaction molecule 1) is a

transmembrane protein located in the sarcoplasmic reticulum (SR). It has a luminal EF-hand Ca
2+
-binding domain that senses SR Ca
2+
concentration. Upon Ca
2+
depletion in the SR, Ca
2+
sensing STIM1 proteins translocate to close proximity of the plasma membrane, where they aggregate into multiple puncta, associate with Orai molecules and activate Ca
2+
influx. Orai1 and STIM1 are three-fold upregulated in mdx skeletal mice compared to wild type, and this increase is associated with enhanced SOCE in mdx mice, suggesting an increased Ca
2+
influx triggered by store depletion. TRPC channels were also proposed to be components of the SOCE pathways. There is a possibility for SOCE to include a complex formation between TRPC and STIM or a triad between TRPC, Orai and STIM.

Overall, there is some convincing evidence that members of the TRP channel family together with STIM1 and Orai1 contribute to enhanced Ca^{2+} permeability of the sarcolemma in dystrophic muscle. Thus, these proteins may be appealing to new candidates for therapeutic interventions.

A secondary Ca^{2+} influx pathway, the Na^{+}-Ca^{2+} exchanger is also held responsible for enhanced Ca
2+
influx in mdx cardiomyocytes. It contributes to Ca
2+
entry in exchange for Na
+
that had previously entered the cell via primary contraction-induced pathways (microruptures and SACs) or via voltage-dependent Na

+

channels.

In summary, stretch-induced Ca^{2+} influx through several transmembrane pathways is undoubtedly enhanced in dystrophic cardiomyocytes. However, the magnitude of the total Ca^{2+} influx appears to be relatively small and not sufficient to entirely explain cellular and mitochondrial Ca^{2+} overload and other significant changes in intracellular Ca^{2+} homeostasis and point to abnormally sensitive Ca^{2+}-induced Ca^{2+} release (CICR) from the SR viaCa2+ release channels (a.k.a. ryanodine receptors, RyRs).

Nitro-oxidative stress in DMD

Reactive oxygen (ROS) and reactive nitrogen (RNS) species are produced by various cellular processes in all eukaryotes and are either beneficial or harmful for cellular functions. Oxidative or nitrosative stress occurs when generation of ROS/RNS outweighs the action of endogenous cellular defense mechanisms, involving various antioxidants. Overproduction of ROS/RNS may have deleterious consequences for cells. Among the detrimental effects of ROS/RNS are DNA and RNA damage; lipid peroxidation; oxidation, nitrosation, glutathionylation of various amino acids and proteins etc.

Oxidative stress is a prominent feature of various muscular and cardiovascular diseases. DMD is not an exception. Initially this pathophysiological state has been described for skeletal muscle. Improved muscle pathology has been reported in many preclinical studies where dystrophic mdx mice was treated with various antioxidant compounds and interventions, such as green tea extract, resveratrol, coenzyme 10, catalase and N-acetylcysteine (NAC) (reviewed in [30]). Abnormally high production of ROS has also been reported for dystrophic cardiac tissue and isolated cardiomyocytes (reviewed in [26]). Similar to the findings in dystrophic skeletal muscle, treatment of mdx mice with NAC significantly improved cardiac pathophysiology.

It is agreed that there are two major sources of ROS in dystrophic cardiac tissue: NAD(P)H oxidase (NOX) and mitochondria. The contribution of these sources to the oxidative stress varies during development of the disease. Whereas NAD(P)H is the major source of ROS at early (pre-clinical) stages of dystrophic cardiomyopathy and during acute mechanical stress, mitochondria become a substantial contributor at later pathological stages (see chapter 4.5 below). Expression levels of several subunits of membrane-bound NOX2 isoform are elevated in hearts of dystrophic animals and DMD patients, and the activity of the enzyme is increased. At early stages of the disease, the ROS production in mdx hearts can be normalized by the NOX inhibitors DPI and apocynin, as well as by the specific peptide gp91ds that prevents the assembly of NOX2 subunits, but not by rotenone (an inhibitor of the mitochondrial respiratory chain). It is clear that NOX2 is a potentially important target for the therapeutic interventions in DMD, but currently small-molecule NOX2 inhibitors are not clinically available. Additional approaches are needed to identify new isoform-selective drugs (for review see [31]).

Relocalization of neuronal nitric oxide synthase (nNOS), which is a member of the dystrophin associated protein complex, from the plasmalemma to the cytosol along with the dysregulation of the NO signaling pathway was initially held accountable for the development of skeletal muscle pathology in DMD. Later, defective NO signaling has been also reported for dystrophic heart. A significant downregulation of nNOS activity has been shown [32]. NO serves as an important signaling molecule. In particular, it activates guanylyl cyclase to produce cGMP, a

second messenger with multiple targets in heart including protein kinase G and proteins directly involved in intracellular Ca2+ homeostasis. Reduced NOS activity in dystrophic heart may down regulate the cGMP-signaling pathway. Consistent with this possibility, dystrophic mdx mice with overexpression of constitutively active guanylyl cyclase were found to have improved cellular integrity, myocardial contractility and energy metabolism. Moreover, treatment of young mdx mice with the phosphodiesterase 5 inhibitor sildenafil, which slows down cGMP breakdown, had a similar beneficial effect on cardiac function. Several clinical trials of sildenafil (and tadalafil) for treatment of DMD are currently underway.

It should be noted that progressive development of dystrophic cardiomyopathy is accompanied by enhanced in inflammatory processes, which in turn stimulate the activity of inducible iNOS. The latter can also have consequences on intracellular Ca^{2+} signaling and redox balance.

Augmented intracellular Ca^{2+} signaling in DMD

There is solid evidence that in addition to enhanced transplasmalemmal Ca^{2+} entry into mdx cardiomyocytes, cells also exhibit augmented cytosolic Ca^{2+} signaling. Changes in intracellular Ca^{2+} cycling that are either causal or adaptive were observed in diverse models of cardiac disease, including several forms of heart failure. Frequently, Ca^{2+} signaling proteins show altered levels of expression, most notably the SR Ca^{2+}-ATPase (a.k.a. SERCA pump), which is typically underexpressed in diseased cardiac muscle. In addition, functional changes in Ca2+ handling were often linked

to posttranslational modifications of Ca
2+
signaling proteins, most importantly of the SR Ca
2+
release channel (a.k.a. RyR), which can undergo various modifications, such as oxidation, S-nitrosation S-glutathionylation, and phosphorylation. All these modifications increase the open probability of RyR and therefore sensitize intracellular Ca
2+
signaling and most of these modifications have been found in RyR of dystrophic cardiac myocytes.

As it was mentioned above, the development of dystrophic cardiac disease is associated with early oxidative and late nitrosative stress. These conditions favor the oxidative and nitrosative modification of various proteins, including RyR. Moreover, oxidation of the intracellular environment modifies the activity of various kinases, one of which, CaMKII kinase becomes directly activated. Direct oxidation or CaMKII phosphorylatyon of RyR results in an increase of its sensitivity to Ca^{2+}, promoting CICR and thus contributing to intracellular Ca
2+
overload.

Recently RyRs have been identified as an appealing pharmacological target in cardiac disease (for review see [33]). In particular, there is compelling evidence that abnormal RyR mediated Ca^{2+} release from the SR can lead to both atrial and ventricular arrhythmias, even to subsequent sudden cardiac death. In addition to various posttranslational modifications of the protein, mutations of the RyR molecule or other components of the RyR macromolecular complex can be the underlying cause of the enhanced RyRs activity. As Ca
2+
release from the SR is a key step in cardiac excitation-contraction coupling, some antiarrhythmic compounds are thought to preferentially reduce diastolic RyR Ca
2+
release and not systolic. These compounds may constrain RyR channel activity by reducing its open probability and gating, by decreasing its conductivity, by

regulating channel subunit composition or by modulation of its posttranslational status. The list of the RyR-modifying drugs consists of, but is not limited to, RyR protein stabilizing drugs such as dantrolene, JTV519 (a.k.a. K201) and recently S107 (from the class of drugs called Rycals). Established antiarrhythmic compounds already in clinical use (e.g. flecainide, carvedilol) were recently found to exhibit an off-target effect on the RyRs and modify their gating. Whereas dantrolene, flecainide, and carvedilol are widely used medications, ARM210 (one of the Rycals) just recently received FDA Orphan Drug Designation and Rare Pediatric Disease Designation for the Treatment of DMD. Clinical trials of Rycals are planned by ARMGO Pharma. Because RyR is a subject of various posttranslational modifications in cardiac diseases including DMD, drugs modulating these modifications are currently also under consideration.

Mitochondrial and metabolic dysfunctions in DMD

Under normal physiological conditions, mitochondria use electron transport through the respiratory chain to generate an electrochemical gradient across the inner mitochondrial membrane. This gradient is used by the ATP-synthase to phosphorylate ADP to ATP. Under pathological conditions such as DMD, oxidative stress in combination with intracellular Ca^{2+} overload results in widespread opening of mitochondrial permeability transition pores (mPTP), depolarization of the mitochondrial membrane and dissipation of the proton gradient. This results in reverse operation of ATP-synthase to the point where it consumes ATP instead of producing it. This, in turn, facilitates cell death by apoptotic or necrotic mechanisms [22]. To make things worse, impaired mitochondrial autophagy has been recently demonstrated in DMD [24]. The latter promotes accumulation of damaged mitochondria in cardiac tissue and further deterioration of cardiac muscle.

For quite a time dysfunctional mitochondria have been an appealing pharmacological target to treat DMD. Debio-025 (a.k.a. UNIL-025, Alisporivir), a cyclophilin inhibitor that desensitizes the mPTP and subsequently reduces cellular necrosis, was shown to improve the pathology in several mouse models of muscular dystrophy [34]. Alisporivir is currently under development by Debiopharm for Japan and by Novartis for the rest of the world. Another mitochondria targeted drug is idebenone (a.k.a. Raxone), which is developed and currently trialed by Santera Pharmaceuticals. It is a synthetic cofactor for the enzyme NAD(P)H: quinone oxidoreductase (NQO1), which stimulates mitochondrial electron transport, scavenges ROS, improves cellular energy supply and overall muscle function [35, 36]. Yet another potential group of medications aims to enhance autophagy and removal of damaged cellular components, including mitochondria. As a surprise for the scientific community cholesterol-lowering statins (in particular simvastatin) has been recently shown to improve muscle function in DMD by targeting autophagy [37].

Therapies to restore dystrophin in DMD

Absence of the structural protein dystrophin is the main genetic defect in DMD. The Dystrophin gene is the largest in the human genome, consisting of ~2.3 million base pairs, and it has the highest rate of spontaneous mutations. The restoration of the dystrophin is the ultimate goal of gene-based approaches, but the large size of the gene makes the implementation of the genetic research challenging and tedious (for review see [38]). An exon-skipping approach has been under development for more than two decades. It aims to restore the disrupted open reading frame for dystrophin. This is achieved by antisense oligonucleotides, small pieces of DNA or RNA that are directed against the dystrophin target transcript (exons 47 to 52 of the dystrophin gene). The dystrophin rescue is accomplished by excluding an exon that neighbors a deletion mutation, thus transforming out-of-frame transcript to in-frame-transcript that is capable of transcription of de novo dystrophin in DMD patients. This treatment is

not yet approved, however the intensive clinical development of this approach and ongoing clinical trials gave patients and researchers hope that exon-skipping may work in the nearest future. Read-through therapy is a promising genetic treatment for ~10 % of DMD patients with nonsense mutations of the dystrophin gene. Nonsense mutations generate stop codons, which prematurely terminate translation of the protein. The specific drugs (e.g. aminoglycoside antibiotics) persuade cells to ignore, or “read through”, a premature stop codon in a dystrophin gene. Several clinical trials (phases 2b and 3) with some promising results are currently on the way. Vector-mediated gene therapy aims to deliver functional copies of the dystrophin gene to restore lost protein via vectors. Adeno-associated viruses (AAV), which are not associated with any known pathogenicity, are currently the most commonly used. Mini or micro dystrophins can be directly packaged into the AAV and locally or systemically delivered to the patients. Recent reports also demonstrated a possibility to deliver full-size dystrophin gene via multiple AAV vectors in dystrophic mice by splitting the full coding sequence into segments and package them in different AAV vectors, which can be reconstructed to the larger sequence in-vivo. Similar to the two other approaches described above, the vector mediated therapy is also in clinical trials.

Conclusions

Over recent years, there was a substantial progress in understanding of mechanistic aspects of the cardiac pathology in DMD, as well as in DMD therapy development. At present in the USA alone, there are more than 200 preclinical and clinical trials ongoing (e.g. treatment with antioxidants, PDE inhibitors, ACE and Ang II receptor inhibitors, β-blockers, membrane sealants, RyR stabilizers, mitochondrial stabilizers, etc). Each trial is targeting a specific mechanism thought to be of key importance for muscular dystrophy. However, it might be more prudent to apply combinational therapies targeting multiple cellular pathologies simultaneously, and to adapt the treatment regime to the time-dependent prevalence of each of the pathways. For the development of such multi-pronged

treatment plans a more detailed understanding of the basic pathomechanisms will be decisive. Obviously, gene therapy that ultimately restores dystrophin expression in DMD can be the ultimate solution for treatment of the disease, but the progress in these fields is still limited.

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М’язова дистрофія Дюшена: роль патології у виникненні кардіоміопатії

Резюме. Міодистрофія Дюшена (МД) є летальною х-зчепленою патологією м’язів із серйозними серцевими ускладненнями. Ця стаття підсумовує сучасні відомості щодо клітинної патофізіології дистрофічної кардіоміопатії, виявляє потенційні терапевтичні цілі та описує новітні фармакологічні агенти і генетичні підходи, метою яких є уповільнити прогресування захворювання.

Нині три головні механізми пояснюють розвиток дистрофічної кардіоміопатії. Перший механізм пов’язаний з механічним впливом на сарколему. Відсутність дистрофіново-глікопротеїнового комплексу (ДГК) у МД послаблює зв’язок між екстрацелюлярним матриксом та цитоскелетом під час м’язового скорочення та спричиняє появу в мембрані мікророзривів, як наслідок, – підвищення внутрішньоклітинних рівнів $Na+$ та Ca^{2+}. Другий механізм безпосередньо впливає на порушення регуляції гомеостазу Ca^{2+} всередині клітини та активації ряду патологічних шляхів. Третій механізм асоційований з підвищеною продукцією активних форм кисню та азоту й подальшим стресом.

При патологічних станах, таких як МД, оксидативний стрес разом із інтрацелюлярним перевантаженням Ca^{2+} призводить до поширеного відкриття пор мітохондрій і спадання протонного градієнта. Зрештою, пошкоджені мітохондрії накопичуються в міокарді та зумовлюють його дегенерацію.

Найголовнішим генетичним дефектом при МД є відсутність структурного протеїну – дистрофіну, тому його відновлення є метою генетичного лікувального методу. Метод «пропуску екзонів» розвивається вже понад два десятиліття, а його метою є відновлення пошкодженої рамки зчитування для дистрофіну. Терапія «прочитування» є генетичним лікуванням МД пацієнтів з нонсенс-мутаціями гена дистрофіну, що генерує стоп-кодони, які блокують трансляцію протеїну. Вектор-опосередкована генна терапія має за мету доставку функціональних копій гена дистрофіну для відновлення загубленого протеїну за векторами з використанням адено-асоційованих вірусів.

Ключові слова: дистрофічна кардіоміопатія, мітохондрія, фармакологічні цілі, генна терапія.

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Стаття надійшла в редакцію 09.04.2018 р.