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Animal Models of Cardiac Disease and Stem Cell Therapy

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Abstract: Animal models that mimic cardiovascular diseases are indispensable tools for understanding the mechanisms underlying the diseases at the cellular and molecular level. This review focuses on various methods in preclinical research to create small animal models of cardiac diseases, such as myocardial infarction, dilated cardiomyopathy, heart failure, myocarditis and cardiac hypertrophy, and the related stem cell treatment for these diseases

Keywords: Animal model, myocardial infarction, dilated cardiomyopathy, heart failure, myocarditis, cardiac hypertrophy, stem cell

INTRODUCTION

Cardiovascular disease is considered the major cause of morbidity and mortality throughout the world. Over the past several years, great achievement has been made in the treatment/management of cardiovascular diseases, which have depended on the use of experimental animal models. With the use of disease models in preclinical research, a large amount of information has been generated, which has outlined the pathogenesis, progression and mechanisms underlying cardiovascular diseases at the cellular and molecular level. This has allowed the development of many effective treatment strategies.

Cardiovascular disease models have been developed in many species, including large animals such as swines and dogs [1, 2], as well as, small animals such as rats and mice [3-5]. Small animal models are more applicable to research work compared to large animal models due to their inexpensiveness, convenience in handling and the vast amount of scientific literature available [6]. In this review, we mainly focus on various methods used by investigators to create small animal models of cardiac disease, such as myocardial infarction (MI), dilated cardiomyopathy (DCM), heart failure (HF), myocarditis and cardiac hypertrophy (CH) and the related stem cell treatment for these diseases.

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1. ANIMAL MODEL OF MYOCARDIAL INFARCTION (MI)

1.1. Introduction

MI is one of the leading causes of death in the world, induced by a blockage in coronary arteries as a result of atherosclerosis or thrombosis [7]. It is characterized by necrosis of myocardiocytes due to a reduction in blood supply. The conventional clinical treatments, such as percutaneous coronary intervention, coronary-artery bypass graft surgery and anti- or dissolution- thrombotic therapy can reduce death rate to a certain extent [8]. Heart transplantation is greatly restricted due to the limited source of donor hearts. Therefore, more effective approaches are urgently needed to treat this disease.

On the basis of animal models established in experimental research, the mechanisms underlying the development of cardiovascular diseases at the cellular and molecular level have been clarified and the potential treatment options using protein, gene and stem cell therapy have been proposed, which have achieved satisfactory results [9-17].

1.2. Animal Models of MI

MI in animal models can be mainly achieved by two methods. The first is to fully block or partially narrow the coronary artery, which often leads to acute ischemia. This can be achieved by a surgical procedure or by drug intervention. The other method is to induce atherosclerosis in coronary arteries, which would more closely mimic the disease progression in humans; however, this approach is rarely adopted in research studies, since it is time-consuming [18].

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In this section we focus on the commonly used methods to create MI in small animals.

1.2.1. Surgical Ligation Model

Occluding different regions of the coronary arteries *via* a thoracotomy to induce MI has been used for decades [19]. Ligation of the left anterior descending coronary artery (LAD) to create anterior wall infarction of the left ventricle (LV) has been described by many workers [19-23]. The surgical procedure can be divided into three steps. In brief, the heart of an animal under anaesthesia is exposed following a left thoracotomy at the fourth intercostal space. The pericardium is carefully broken and the LAD ligated with a suture placed just distally (1mm) from tip of the left auricle. The procedure is considered successful if the electrocardiogram (ECG) shows ST-segment elevation and the anterior wall of the left ventricle becomes whitish. Finally, the lungs are inflated and the chest closed.

This permanent ligation of the LAD can cause irreversible damage to the myocardium, which is stable and easily reproduced. It has been extensively employed in studies on MI therapy using techniques such as; cell implantation, genetic modification and the administration of cytokines [24-28]. Further ligation of the LAD can also produce a HF model or an ischemia–reperfusion model by subsequently removing the occlusion [29, 30]. However, the difficulty in operating on small rodents, particularly mice and the relatively high surgical mortality, due to the size of the wound created has to be addressed. In addition, the coronary ligation procedure often gives rise to apical aneurysmatic infarcts of variable size.

1.2.2. Cauterization and Cryo-Injury Model

The surgical procedures for cauterization or cryo-injury-induced MI have been previously studied using various animal models. In brief, the heart is exposed following intercostal thoracotomy. Cauterization or cryo-injury is induced with an electrocoagulation knife for 1 to 2 seconds or a cryoprobe for 10s, respectively, on the anterior LV free wall [31, 32]. The position of the probe can be set accurately using the pulmonary artery as an anatomical landmark.

The MI caused by cauterization or cryo-injury is stable and easily produced in a short period of time, without the interference of the coronary arteries collateral circulation [31]. It is particularly suitable for use in small animal such as the mouse. The necrosis of myocardiocytes is ascribed to tissue damage caused by burning or the ultra-low temperature. Unfortunately, cauterization or cryo-injury is not guaranteed to induce myocardium ischemia [33] or tissue damage that closely mimics the natural ischemia-initiated infarction. In fact, myocardial injury from cauterization or cryo-injury shows pathophysiological changes that are not associated with myocardial infarction [33].

1.2.3. Balloon Occlusion Model

The balloon occlusion model was developed from percutanous translaminal coronary angioplasty and was applied in large animal models [6, 34]. Cohen *et al*. developed this occlusion model in small animals by encircling a superficial branch of the rabbit left coronary artery with a balloon occluder [6]. Briefly, after left thoracotomy, the open end of a balloon occluder is placed around the branch of the exposed left coronary artery (LCA). The occluder is connected to a vacuum pump or compressed air to control balloon inflation and coronary occlusion. The use of this model reduces mortality and the size of the surgical wound when compared with LAD ligation-induced MI. The procedure is reliable and reproducible, allowing the accurate positioning of the balloon, making it the first choice model to induce post-infarct reperfusion. However, balloon angioplasty requires a high level of surgical expertise and is not easily applicable in small animals without extensive training [35-38].

1.2.4. Pharmacologically-Induced Model

Drug-induced myocardial ischemia is a convenient procedure, since it does not require complicated surgery. Isoproterenol, adriamycin and ergonovine have been often used to induce MI. Signal *et al*. induced myocardial ischemia in rats with isoproterenol (a synthetic β-adrenergic agonist) [39]. Similarly, Chagoya *et al*. developed a rat MI model by utilising isoproterenol [40]; and Arteaga de Murphy and his group successfully duplicated the MI model in rats with a subcutaneous injection of isoproterenol [41]. While, Arnolde *et al*. created an ischemia model in rabbits by the intraperitoneal injection of adriamycin [42].

Drug-induced ischemia can be easily achieved, since it increases myocardial oxygen consumption or induces coronary artery spasm to reduce blood flow; however, drug safety and the difficulty in accurately positioning the infarct region make this model rarely used in clinical research.

1.3. The use of Stem Cells to Study MI

Studies using myocardial infarct animal models have indicated that transplantation of mesenchymal stem cells (MSC) [23, 43-45], umbilical cord blood cells [46, 47], bone-marrow-derived haematopoietic stem cells [32, 48], skeletal myoblasts [49], endothelial progenitor cell (EPC) [50], cardiac stem cells [51, 52], embryonic stem cells (ESC) [25], or induced-pluripotent stem cell [53] have the potential to improve the function of ventricular muscle after MI. Clinical trials have also produced some encouraging results. However, the current experimental evidence suggests that the benefits of cell therapy are modest. Several recent reviews have summarized systematically the application of stem cell following MI [54, 55]. The past decade has shown that translating the potential benefit of stem cell therapy into actual clinical practice still needs a lot of work and many barriers would need to be overcome before this therapy can attain its full potential.

2. ANIMAL MODEL OF DILATED CARDIOMYOPATHY (DCM)

2.1. Introduction

DCM is a primary myocardial disease characterized by chamber dilation associated with impaired systolic and diastolic function [56, 57]. It starts from asymptomatic LV dilatation or impaired systolic function, exercise-induced symptoms, and finally to overt congestive heart failure (CHF). The onset of DCM can be linked to viral infection, genetic abnormalities, and autoimmune mechanisms [58]. A number of animal models of DCM have been developed to elucidate the mechanism responsible for the pathophysiological features of DCM and to establish potential treatment strategies.

This section of the review focuses on viral infection, genetic abnormalities, and autoimmune animal model and the application of stem cells to treat DCM.

2.2. Immunization Model of DCM

Increasing evidence shows that a large proportion of DCM cases are mediated by autoimmune processes [59, 60]. Various antimyocardial antibodies circulating in the serum are associated with myocyte injury, which is detected in 85% of DCM patients [61]. Furthermore, familial occurrence of DCM with the presence of autoantibodies and abnormal cytokine profiles in relatives with asymptomatic LV enlargement can account for 20–30% of cases [62, 63], suggesting the involvement of abnormal humoral and cellular immunity in the early development of the disease.

β1-ECII the anti-β1-adrenergic receptor antibody against the second extracellular receptor loop represents a potent "self-antigen" that induces DCM [64, 65]. Matsui *et al*. using a rabbit model were the first to presented data on the development of biventricular dilatation. They found an upregulation of total cardiac β-AR (β-adrenergic receptor) following immunization with β1-ECII-homologous peptide [66]. Intraperitoneal injection of blood lymphocytes either from immunized anti- β1-ECII-positive rabbits [67], or from anti-β1-AR-positive DCM patients [68] into immunodeficient mice can avoid the expected immune reaction against rabbit or human non-self proteins, which can lead to the early stage of cardiac dilatation. Treatment of mice with certain human leukocyte antigen alleles can also induce autoimmune myocarditis followed by the subsequent development of DCM [69]. Daniel *et al*. induced DCM in a mouse model with the application of KXXS-motif [70]. The autoimmune DCM model can also be created by viral infection, immunization with heart-specific autoantigens, or from genetically predisposed strains.

2.3. Viral Infection Model of DCM

Viral myocarditis is a common cause of acquired DCM in humans. The pathogenesis of viral myocarditis and the pathophysiological features of DCM depend on the viral strain and the genetic background [71].

Transduction of Coxsackie virus genomic constructs with a cardiac-specific promoter in transgenic mice induced DCM with features consistent with human cardiomyopathy [72]. Recent evidence showed that Coxsackie virus myocarditis can lead to DCM [73]. Acute coronavirus infection can also results in virus-induced myocarditis and CHF. After infection, nearly half of the rabbits showed an increased heart weight and heart weight-to-body weight ratios, biventricular dilation, myocyte hypertrophy, myocardial fibrosis, and myocarditis similar to the development of DCM [74]. LP-BM5 murine AIDS (MAIDS) retrovirus induced DCM in the absence of chronic cardiac inflammation, suggesting MAIDS retroviral infection can lead to DCM without myocarditis [75].

2.4. Genetic Abnormality Models of DCM

Approximately 20% of DCM patients have a gene mutation [62], which affects the myosin heavy chain [76], cardiac actin [77], tropomyosin [78], or troponin [79], inducing a functional impairment of the referred proteins. Recent investigations have focused on the genetic mechanisms and stress pathways [76], cytoskeletal abnormalities [77] and signaling pathways for CH and HF in DCM [77]. Yasuhiro *et al*. focused on the mouse models of DCM, together with commentary on the naturally occurring DCM in the hamster [80] based on the subcellular localization and the potential functional importance of the gene products involved.

2.5. Stem Cell Therapy for DCM

A number of experimental studies and clinical trials support cellular cardiomyoplasty as a promising therapeutic strategy to improve cardiac function after acute MI [81, 82], however, much less information is available on the therapeutic potential of MSCs for DCM. Noritoshi *et al*. investigated the effect of MSCs on DCM in animals following immunization [83]. The results showed that MSC transplantation increased capillary density and decreased the collagen volume fraction in the myocardium, resulting in decreased LV end-diastolic pressure. Bone marrow-derived mononuclear cell therapy in DCM limited cellular apoptosis, inflammatory and oxidative responses, up-regulated the expressions of Cx43, PKC, and energy transcription factors and improved LV function [84]. In addition, intracoronary administration of bone marrow-derived progenitor cells improved coronary microvascular function in DCM [85]. Hence, stem cell transplantation has great potential as a new therapeutic strategy for the treatment of DCM.

3. ANIMAL MODELS OF HEART FAILURE (HF)

3.1. Introduction

HF is associated with 50% survival at 5 years. The use of animal models is indispensable in understanding the pathophysiology of HF and to evaluate the efficacy and efficiency of novel therapeutic approaches such as gene therapy, the use of mechanical devices and new surgical procedures. This section presents the most common *in vivo* models used to study HF.

3.2 Models of acute HF

3.2.1. Hydraulic Occluder and Ameroid Constrictor

These methods allow complete or partial occlusion of coronary artery branches in animal models. Hence, they are applicable to induce HF [86, 87], and coronary stenosis for the investigation of hibernating myocardium. Briefly, a left anterolateral thoracotomy is performed followed by an incision of the pericardium; a branch of the LCA is exposed and the hydraulic occluder placed around the vessel. The occluder is then inflated to induce partial stenosis or complete occlusion. An ultrasonic flow probe can be placed distally to the occluder to control the degree of occlusion and record the downstream flow through the LCA [88]. An ameroid constrictor can also be implanted in a similar way. At body temperature, the casein plastic ring around the vessel will gradually narrow, due to the hygroscopic property of the material. The complexity of placing the hydraulic occluder and ameroid constrictor mean that these procedures are not appropriate for use in small animal models for investigating MI-induced HF [86, 87].

3.2.2. Coronary Artery Ligation

Pfeffer *et al*. created HF in rats by coronary artery ligation [89]. Rats with an infarction size greater than 46% developed CHF after 21 days, with symptoms of elevated filling pressures, reduced cardiac output, and a minimal capacity to respond to pre- and after-load stress. The impairment of LV function was closely associated with the extent of myocardial loss [89]. Animal mortality from HF seems to be strain-dependent, since Sprague-Dawley and Lewis rats have a mortality rate of 36% and 16%, respectively [90].

3.2.3. Coronary Artery Embolisation

Coronary artery embolisation-induced HF is based on intracoronary embolisation with microspheres [91], agarose or polystyrene beads or the intracoronary injection of thrombin and autogenous blood with fibrinogen [92]. Sabbah *et al*. used dogs that underwent 3 to 9 catheter-mediated intracoronary embolisation 1–3 weeks apart [90]. The embolisation was discontinued when the ejection fraction of the LV was less than 35%. In this model coronary artery embolisation increased the LV end-diastolic pressure, which was accompanied by a significant rise in pulmonary artery wedge pressure and systemic vascular resistance. Three months after the embolisation, patchy myocardial fibrosis and LV hypertrophy were observed in the heart. There was also an increase in plasma levels of atrial natriuretic peptide and norepinephrine, as well as, a reduction in the number of β-AR and L-type calcium channels and the activity and protein levels of SR Ca2+-ATPase [93].

This model can mimic the clinical situation, of patients with HF and acute coronary syndrome, since embolisation-induced atherosclerotic and thrombotic debris are deposited into the coronary microcirculation. However, one disadvantage of the model is the difficulty in accurately controlling the location or the length of coronary artery occlusion.

3.2.4. Models of Chronic Heart Failure

Incomplete narrowing of coronary arteries similar to that observed in the coronary artery occlusion animal model has been established to mimic chronic HF. In brief, a thoracotomy is performed on the chosen animal model; a probe or copper wire is inserted into the epicardium along the LCA. The LCA is ligated with the probe inside 1-2 mm from its origin. The probe is then removed, resulting in an average reduction in the luminal diameter by 42% [94]. The ST segment of the ECG should be transiently elevated during coronary occlusion if the operation is successful. An excessive coronary artery occlusion may induce persisting ST segment elevation even after removal of the probe. HF may occur as a result of chronic cardiac ischemia [95]. The coronary ligation procedure may inevitably include the ligature of some muscle mass, which could induce vessel stenosis. The maximal resting coronary blood flow can decrease by 43% 5–7 days following the operation [96]. Reparative fibrosis, myocytolytic necrosis, as well as, myocyte hypertrophy can also occur [97].

This model lacks predictability and reliability and the degree and progression of the stenosis cannot be adjusted. After several weeks a complete occlusion of the coronary artery can develop [98]. Interestingly, the gradually increasing stenosis may prompt the formation of collateral vessels, similar to the situation observed in some patients.

3.3. Stem Cells Therapy for HF

Current therapies aim largely to attenuate the pathological remodelling that occurs after injury and to reduce risk factors for HF. Studies in animal models indicate that transplantation of bone-marrow derived stem cells, MSC, EPC or autologous umbilical cord blood mononuclear cells [99] have the potential to improve the function of ventricular muscle after HF. A number of studies showed improvement in cardiac function when bone marrow-derived stem cells were directly implanted. However, limited or no differentiation of bone marrow cells to cardiovascular cell types [100, 101] suggested that the beneficial effect was independent of tissue regeneration [102]. Some groups have shown that EPC has great promise as a potential therapeutic agent [103, 104]. However, further research is required to enhance the therapeutic efficiency of EPCs in HF.

4. ANIMAL MODELS OF MYOCARDITIS

4.1. Introduction

Myocarditis can be defined as inflammation of heart muscle. It resembles a heart attack without the blockage of coronary artery. Myocarditis is often induced by a viral infection such as parvovirus B19 or less commonly non-viral pathogens such as borrelia burgdorferi (Lyme disease) or trypanosoma cruzi, or as a hypersensitivity response to drugs [105]. Myocarditis is, therefore, an infection of the heart, with inflammatory infiltrate, causing damage to the heart muscle [106], which may or may not result in the death of heart tissue.

4.2. Experimental Autoimmune Myocarditis (EAM) Animal Model

EAM can be induced in susceptible mice by immunization with murine cardiac myosin or cardiac myosin peptides [107, 108], or by adoptive transfer of myosin-stimulated T cells [109]. Myosin-induced EAM is a model of inflammatory heart disease initiated by CD4+ T cells [109]. The immune-mediated cardiac damage could play a role in the pathogenesis of a subset of post-infectious human cardiomyopathies [110]. It is also possible to induce myocarditis in Lewis rats by immunization with cardiac myosin [111] or by adoptive transfer of T cells stimulated by specific peptides from cardiac myosin [112].

4.2.1. Induction of EAM by Active Immunization with Cardiac Myosin

The procedure to produce the animal model of EAM by active immunization with cardiac myocin has previously been described [107]. The immunogen is injected subcutaneously into mouse; 7 days later a second dose of immunogen emulsified in Complete Freund's adjuvant (CFA) is administered; 21 days after the first immunization the mouse is euthanized. The heart is immediately removed, fixed in formalin for 24 hours, stained and a histopathological assessment performed to ascertain whether EAM is established. A rapid determination of the induction of EAM can be also made by analyzing specific serum markers for cardiac injury.

Cardiac troponin I (cTnI) and cardiac troponin T (cTnT), are two proteins associated with the myocyte contractile apparatus, which will be released into the serum when myocytes are injured and can serve as markers of myocyte injury. cTnI is highly sensitive and specific for myocarditis in mice 17 – 21 days after immunization. The sensitivity of cTnT measurement is maximal at day 16. Both cTnI and cTnT measurements are superior to the measurement of CK-MB for the detection of murine EAM.

4.2.2. Induction of EAM by Adoptive Transfer of Cardiac Myosin-Stimulated T Cells

The protocol for EAM induction with adoptive transfer of cardiac myosin-stimulated T cells has been reported [113, 114]. In breif, the donor mice (6 to 8 weeks old) is immunized with cardiac myosin emulsified in CFA, the spleens are harvest from these mice 12-14 days after the first immunization. The spleens are incubated in sterile tissue culture flasks for 72 hours at 37°C. Lymphocytes are separated from the red blood cells and dead cells by Ficoll-Hypaque gradient centrifugation. The T cells are enriched and the B cells removed by cytotoxic elimination using an anti–MHC class II antibody and complement. T cells are injected intravenously into the tail veins of recipient SCID mice; 21 days after the first immunization the mouse is euthanized. The heart is immediately removed, fixed in formalin for 24 hours, stained and a histopathological assessment performed to ascertain whether EAM is established.

This model is ideal for studying the role of specific cellular effectors on the induction and pathogenesis of EAM, but it is only applicable to SCID mice, which have no functional B and T cells.

4.2.3. Induction of EAM by Active Immunization with Bordetella

The protocol to induce EAM by active immunization with bordetella is known [111]. In brief, an emulsion of the selected immunogen (cardiac myosin or cardiac myosin peptide) is prepared. On day 0 and 7, an appropriate volume of immunogen is subcutaneously injected into female Lewis rats. A solution of B. pertussis is prepared in PBS and injected into the rats intravenously on day 1 and 3; 21 days after the first immunization the rat is euthanized. The heart is immediately removed, fixed in formalin for 24 hours, stained and a histopathological assessment performed to ascertain whether EAM is established.

The injection of cardiac myosin and B. pertussis is the only way to induce EAM in rats, allowing the comparative study of the mechanism underlying disease development.

4.3. Virus-Induced Myocarditis Animal Model

Humans infected with common viruses such as; adenovirus, enterovirus, Epstein-Barr virus, human herpes virus 6, parvovirus B19 and cytomegalovirus may have activated T-cells and associated cytokine mechanisms, [115] resulting in autoimmune myocarditis [116]. Viruses induce the initial myocardial injury, and can cause continuous low grade inflammation and enduring myocardial damage and reparative fibrosis. Inflammatory cells also produce matrix-degrading proteases [117, 118], leading to LV dilatation and cardiac dysfunction [119].

Similar to autoimmune myocarditis, direct virus injection can cause myocarditis in three phases. The initial phase frequently passes without symptoms, since the initial damage is often prevented by the innate immune response [120]. The second phase results from immune dysregulation, triggered by the initial cardiomyocyte injury. The initial cellular and humoral immune responses may improve the outcome during phase 1; conversely, they are responsible for the harmful effect during phase 2. This is in part due to molecular mimicry [121], which is caused by mimicked epitopes shared between the viral and cardiac antigens [122]. Finally, in the third phase, a typical DCM develops as a result of extensive myocardial injury.

It is, however, difficult to determine the virus dose/ concentration required to induce myocarditis and detect the inflammation of the myocardium during the first phase, limiting its application in preclinical research.

4.4. Stem Cell Therapy for Myocarditis

Stem cells play a critical role in the pathogenesis and outcome of myocarditis. Recent studies have described the role of different stem cell types and subtypes and their products in mediating cardiac dysfunction in myocarditis. Kania G *et al. in vitro* culture-expanded a specific population of bone marrow-derived prominin-1-expressing progenitor cells from healthy heart tissue and injected these cells intravenously into autoimmune-myocarditis animal model [123]. MSCs also have angiogenic, myogenic, and paracrine actions in the treatment of EAM. Okada H *et al*. determined whether MSC transplantation attenuated EAM [124]. Their results showed that MSC transplantation reduced the severity of EAM by inducing neovascularization and inhibiting inflammatory cytokine production. Weener *et al.* investigated the effect of delivering spleen-derived EPC into a rat model of inflammatory-mediated myocardial damage [125]. They found that EPC caused a functional improvement in cardiac performance evident by higher fractional shortening, reduced scar tissue and thickened ventricular walls. Wang *et al.* used ESC to attenuate viral myocarditis [126]. They found that a tail vein injection of ESC significantly increased the survival of viral myocarditis mice and decreased the necrosis and infiltration of inflammatory cells. These studies taken together, demonstrate the potential stem cell therapy has in treating myocarditis.

5. ANIMAL MODEL OF CARDIAC HYPERTROPHY (CH)

CH is an adaptive response of the heart to pressure overload. However, long term hypertrophy of cardiomyocytes can not maintain normal function and eventually HF will develop. CH is a common feature of the failing myocardium in the progression of some cardiovascular diseases (e.g. hypertension, MI and HF) and is closely related to the pathological changes [127-130].

Many investigators have studied the mechanism underlying CH [131-133]. Recent research has showed that CH is a complicated and dynamic process. It is associated with many genetic and molecular changes related to the regulation of a series of signaling pathways, expression of some cardiac fetal genes, and enhanced of protein synthesis. Interestingly,

the increase in cardiac protein synthesis directly causes the enlargement of cardiomyocytes [134,135].

Various chemical factors, as well as, mechanical stimulation contribute to the development of the hypertrophic response, which is also the basis of establishing cell and animal models [136-138]. Many laboratories induce hypertrophic phenotypes on neonatal or adult cardiomyocytes using mediators such as endothelin-1, angiotensin II and leptin [139-142]. Akimasa Koga and his group constructed an adenovirus vector carrying human wild-type caveolin-3 gene, which was able to prevent phenylephrine and endothelin-1-induced hypertrophic responses [143]. While, Galindo and his colleagues compared the transcriptional difference between isoproterenol-induced and exercise-induced CH in mice [144].

There have been a few reports on stem cell therapy following CH. In general, CH can be suppressed as an accompanying symptom following ischemic injury or HF during treatment. Our team has found that the post-infarct hypertrophic phenotype can be inhibited after erythropoietin treatment, which activated stem cell mobilization and migrate to the infarcted heart [145].

SUMMARY

With the use of small animal disease models in preclinical research, workers have aquirred a large amount of information on the pathogenesis/progression of cardiovascular disease, which has aided the development of effective treatment options. These animal models are effective scientific tools to study the molecular mechanisms of stem cell based therapies for cardiovascular diseases, which potentially provide a powerful approach for discovering new drugs.

ABBREVIATIONS

CH = Cardiac hypertrophy

cTnI = Cardiac troponin I

cTnT = Cardiac troponin T

CFA = Complete Freund's adjuvant

CHF = Congestive heart failure

CK-MB = Creatine kinase-MB

DCM = Dilated cardiomyopathy

ECG = Electrocardiogram

EPC = Endothelial progenitor cell

EAM = Experimantal autoimmune myocarditis

ESC = Embryonic stem cell

HF = Heart failure

LAD = Left anterior descending coronary artery

LCA = Left coronary artery

LV = Left ventricle

MHC = Major histocompatibility complete

MSCs = Mesenchymal stem cells

MAIDS = Murine acquired immune deficiency syndrome

MI = Myocardial infarction

PBS = Phosphate buffered saline

PKC = Protein kinase C

SCID = Severe combined immunodeficiency

SR Ca^{2+} ATPase = Sarcoplasmic reticulum Ca^{2+} ATPase

β1-ECII = Anti-β1-adrenergic receptor antibody against the second extracellular receptor loop

β-AR = Beta adrenergic receptor

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