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Therapy with mesenchymal stromal cells or conditioned medium reverse cardiac alterations in a high-fat diet–induced obesity model

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Abstract

Background. Obesity is associated with numerous cardiac complications, including arrhythmias, cardiac fibrosis, remodeling and heart failure. Here we evaluated the therapeutic potential of mesenchymal stromal cells (MSCs) and their conditioned medium (CM) to treat cardiac complications in a mouse model of high-fat diet (HFD)–induced obesity. *Methods.* After obesity induction and HFD withdrawal, obese mice were treated with MSCs, CM or vehicle. Cardiac function was assessed using electrocardiography, echocardiography and treadmill test. Body weight and biochemical parameters were evaluated. Cardiac tissue was used for real time (RT)-polymerase chain reaction (PCR) and histopathologic analysis. *Results/Discussion.* Characterization of CM by protein array showed the presence of different cytokines and growth factors, including chemokines, osteopontin, cystatin C, Serpin E1 and Gas 6. HFD-fed mice presented cardiac arrhythmias, altered cardiac gene expression and fibrosis reflected in physical exercise incapacity associated with obesity and diabetes. Administration of MSCs or CM improved arrhythmias and exercise capacity. This functional improvement correlated with normalization of GATA4 gene expression in the hearts of MSC- or CM-treated mice. The gene expression of connexin 43, troponin I, adiponectin, transforming growth factor (TGF) β, peroxisome proliferator activated receptor gamma (PPARγ), insulin-like growth factor 1 (IGF-1), matrix metalloproteinase-9 (MMP9) and tissue inhibitor of metalloproteinases 1 (TIMP1) were significantly reduced in MSCs, but not in CM-treated mice. Moreover, MSC or CM administration reduced the intensity of cardiac fibrosis. *Conclusion.* Our results suggest that MSCs and CM have a recovery effect on cardiac disturbances due to obesity and corroborate to the paracrine action of MSCs in heart disease models.

Key Words: *cardiac dysfunction, cell therapy, mesenchymal stromal cells, obesity*

Introduction

Obesity and excessive consumption of dietary fats have deleterious consequences to the metabolism and heart function, being strongly linked to the progression of type 2 diabetes mellitus (DM2) and heart disease [1,2]. Obesity has been associated with structural and functional changes in the heart, including arrhythmias, cardiac fibrosis and subclinical impairment of left ventricle systolic and diastolic functions. Some cardiac alterations associated with structural and electrical remodeling are irreversible and can lead to heart failure, increasing the risk for sudden death through mechanisms that are not completely elucidated [3].

In addition to the electrical remodeling and severe arrhythmias, long-standing obesity is also associated with structural remodeling, characterized by eccentric hypertrophy and followed by diastolic dysfunction and fibrosis, despite coronary disease or hypertension [4–6]. When isolated from other cardiac

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impairments, this disease state is referred to as diabetic cardiomyopathy [7].

Cell-based therapies are currently under investigation and hold promise to treat cardiac diseases. Mesenchymal stromal cells (MSCs) are among the most-studied cell types in the cardiovascular field. MSCs are multipotent cells easily isolated from different tissues in the adult, being expandable *in vitro* as plastic-adherent cells with fibroblast-like morphology, with potential for differentiation into tissues of mesodermal origin and displaying immunomodulatory properties [8,9]. Pre-clinical and clinical studies have shown beneficial effects of MSCs in injured hearts, leading to reduction of fibrosis [10], stimulation of angiogenesis [11] and restoration of contractile function [12]. In cardiac diseases, the beneficial effects of MSCs are primarily explained as the result of release of paracrine factors [11,13–15], which regulate several biological processes. This hypothesis is further supported by the observation that MSC conditioned medium (CM) also enhances cardiac tissue repair [16,17], being used for treatment of cardiac ischemia lesions, as previously shown [17,18].

Despite the growing body of evidence, there are no reports showing the effects of cell therapy and cardiac remodeling in the presence of arrhythmias and physical disability due to obesity. In the present study, we investigated the therapeutic effects of bone marrow–derived MSCs and its CM in an experimental model of cardiac alterations by obesity induction in C57Bl/6 mice fed with a diet enriched with lard saturated fat.

Materials and methods

Animals and obesity induction

Six-week–old male C57Bl/6 mice were housed at the animal facility of the Center for Biotechnology and Cell Therapy, São Rafael Hospital (Salvador, Brazil), in a room with constant temperature (20 ± 2°C), controlled humidity (50%), free access to food and water *ad libitum* and exposure to a constant light–dark cycle of 12 h and 12 h. All animal protocols were approved by the Ethical Committee for Animal Research of Gonçalo Moniz Institute, Oswaldo Cruz Foundation.

All mice were fed a standard mouse chow for up to 6 weeks of age. Mice were then divided into two groups: standard diet (Nuvital; n = 10) and high-fat diet (HFD; Pragsoluções Biociências; n = 28) for 36 weeks, for obesity induction. The composition of the diets is shown in Table I. The time of exposure to HFD was based on our previous study [19] in which we standardized the model of obesity and DM2 in C57BL/6 mice.

Treatment with MSCs and CM

After 36 weeks of obesity induction, HFD was withdrawn and replaced by regular chow. Obese mice were randomly divided into three subgroups depending on treatment administered: (i) MSCs (n = 10), in which intravenous (i.v.) administrations of MSCs (5×10^5 cells/mouse), suspended in 100 µL, were performed through the tail vein, on 2 consecutive days; (ii) MSC CM (n = 10) or (iii) Dulbecco's Modified Eagle's

Table I. Composition of standard diet and HFD.

HFD 60% integral			Control diet		
	g %	kcal %		g %	kcal %
Protein	23.4	17.5	Protein	16.8	16.4
Carbohydrate	33.2	24.69	Carbohydrate	74.3	73.1
Fat	34.6	57.9	Fat	4.8	10.5
Total Kcal/g	3.87	100	Total Kcal/g	4.07	100
Ingredients	g	kcal	Ingredients	g	kcal
Dry matter	95.7	0	Casein, 30 mesh	228	912
Gross fiber	4.2	0	DL-methionine	2	0
Corn starch	—	928	Maltodextrin 10	170	680
Sucrose	10.0	400	Corn starch	835	3340
Soybean oil	8.6	774	Sucrose	0	0
Lard	24.7	2223	Soybean oil	25	225
Mineral mix	4.6	0	Coconut oil, hydrogenated	40	360
Sodium	2.1	0	Mineral mix S10001	40	0
Potassium	4.60	0	Sodium bicarbonate	10.5	0
Calcium	4.76	0	Potassium citrate, 1 H_2O	4	0
			Vitamin mix V10001	10	40
			Choline bitartrate	2	0
			FD&C yellow dye #5	0.1	0
Total	159.26	4325		1366.6	5557

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