

Use of mesenchymal stem cells in an experimental model of metabolic syndrome complicated with cardiomyopathy

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Abstract

Obesity is a major global health issue. Most obese patients develop metabolic syndrome, a cluster of clinical features characterized by hypertension, insulin resistance and dyslipidemia this pre-diabetic condition has recognized as an independent risk factor for cardiovascular diseases, particularly hypertension, atherosclerosis and diabetic cardiomyopathy. MSC can differentiate into many mesenchymal cells as cardiomyocytes. The application of MSCs in the treatment of DC in recent years offers promising results. Stem cell therapy has emerged as a promising strategy for the treatment of dead myocardium, directly or indirectly, and seems to offer functional benefits to patients. Recently, a substantial number of clinical trials have proven that stem cell therapy is safe. Infusion of bone marrow-derived stem cells (BMCs) represents the greatest number of clinical studies for MI. This review highlights the use of mesenchymal stem cells in metabolic syndrome and diabetic cardiomyopathy

Introduction

Metabolic syndrome is regarded as a complex cluster of obesity-related complications, and, in recent years, this syndrome has become a global health problem [1–3]. Dyslipidemia, hypertension, and diabetes or glucose dysmetabolism are the major factors constituting metabolic syndrome, and these factors are interrelated and share underlying pathophysiological mechanisms [1–3]. Severe obesity predisposes individuals to metabolic syndrome and affected patients have an increased risk of cardiovascular disease and mortality [1–3].

Heart disease remains a major cause of worldwide morbidity and mortality. Despite advances in clinical and surgical care of cardiac patients, current therapies are able to treat symptoms, delay clinical deterioration, and increase survival but are not effective in repair induction in a diseased heart. This is the case of cardiomyopathy

caused by metabolic diseases like diabetes. Therefore, a major effort is under way to develop therapies aiming at regenerating the myocardium or to stimulate endogenous repair programs [4]. Both types of DM increase the progression of atherosclerosis and the development of macrovascular complications, with clinical manifestations such as coronary artery disease (CAD), peripheral artery disease (PAD), and stroke, and these patients have a two to four fold increased risk of fatal myocardial infarction (MI) [5].

Development of ventricular dysfunction in patients with DM in the absence of CAD, valvular heart disease or hypertension is defined as diabetic cardiomyopathy (DC) [6]. DC caused by hyperglycemia causes changes in the diabetic myocardium such as hypertrophy, apoptosis of cardiomyocytes, and abnormal myocardial matrix deposition.

Specifically in DC, there are changes in the activity of matrix metalloproteases MMP-2 and MMP-9. Reduced MMP-2 activity results in increased collagen accumulation and increased activity of proapoptotic MMP-9 and subsequent cell apoptosis, capillary density reduction, and poor myocardial perfusion. Other pathological consequences include microcirculatory defects, and interstitial fibrosis [7].

Mesenchymal stem cells

Mesenchymal stem cells (MSCs) have been highlighted as a new emerging regenerative therapy in recent years. MSCs are progenitors of all connective tissue cells. The International Society for Cellular therapy has defined three minimum requirements for classification of cells as MSC; they must be plastic adherent in normal culture conditions, differentiate into osteoblasts, adipocytes, and chondroblasts in vitro and express a defined population of cell surface markers [8].

MSCs have the capacity of self-renewal and are multipotent, having the potential to differentiate into multiple cell types such as adipocytes, chondrocytes, and osteoblasts, but also differentiation into myocytes and neurons has been proposed [9]. They can be derived from many different organs and tissues such as bone marrow, adipose tissue, nervous tissue, amniotic fluid, umbilical cord, placenta, menstrual blood, and dental pulps [10].

MSCs are a subset of cells that express on their surface CD54/CD102, CD166, CD49 as well as CD73 and CD90. They also express CD44, CD105, whereas they do not express CD34, CD14, CD45, CD11a/LFA-1, and CD31, which are surface markers of hematopoietic cells and/or endothelial cells [11]. The application of MSCs in the treatment of DC (in addition to other CVDs) has received much attention in preclinical and clinical environs in recent years and MSCs do offer promising

treatments due to their direct differentiation to cardiomyocytes but also due to the secretion of potent trophic and paracrine mediators, capable of inducing cardio regeneration and cardio protection [12].

Metabolic syndrome

Obesity is a major global health issue [13]. Changes in lifestyle, predominantly hypercaloric diet ingestion and sedentary habits, produce a dramatic increase in its prevalence. Most obese patients develop metabolic syndrome, a cluster of clinical features characterized by hypertension, insulin resistance and dyslipidemia [14]. This pre-diabetic condition has recognized as an independent risk factor for cardiovascular diseases, particularly hypertension, atherosclerosis and diabetic cardiomyopathy [15]. Diabetic cardiomyopathy was described in 1972 as a heart failure without signs of hypertension, coronary artery disease or valvular or congenital heart disease [16]. During the last decade it has gained relevance because it leads to heart failure [17], its pathophysiology is still not well understood. However, it has been reported that lipid accumulation of cardiomyocytes changes their energy metabolism, increasing oxidative stress, impairing calcium handling and mitochondrial dysfunction, which promote cardiomyocyte death and interstitial fibrosis [18].

At present, clinical treatments for diabetic cardiomyopathy are aimed at delaying its progression, mainly by improving metabolic alterations using hypoglycemic agents, and cardiac performance using β -blockers and angiotensin-converting enzyme inhibitors [19]. Therefore, new therapies intended to reverse heart failure in obese individuals would have a significant impact on the health system [20]. In both pre-clinical and clinical studies promising results were obtained when cell-based therapies were tested for the management of cardiac diseases [21].

Bone marrow multipotent stromal cells, also referred to as mesenchymal stem cells (MSC), appear as an appropriate tool for treating cardiomyopathy, since they manage oxidative stress, down regulating inflammation, secrete anti-apoptotic and mitogenic factors and might differentiate into cardiomyocytes [22].

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Stem cells in metabolic syndrome and cardiomyopathy

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aiming at regenerating the myocardium or to stimulate endogenous repair programs by stem cells [25].

Both types of DM increase the progression of atherosclerosis and the development of macrovascular complications, with clinical manifestations such as coronary artery disease (CAD), peripheral artery disease (PAD), and stroke, and these patients have a two to four fold increased risk of fatal myocardial infarction (MI) [26]. Development of ventricular dysfunction in patients with DM in the absence of CAD, valvular heart disease or hypertension is defined as diabetic cardiomyopathy (DC) [27].

DC caused by hyperglycemia causes changes in the diabetic myocardium such as hypertrophy, apoptosis of cardiomyocytes, and abnormal myocardial matrix deposition. Specifically in DC, there are changes in the activity of matrix metalloproteases MMP-2 and MMP-9. Reduced MMP-2 activity results in increased collagen accumulation and increased activity of proapoptotic MMP-9 and subsequent cell apoptosis, capillary density reduction, and poor myocardial perfusion. Other pathological consequences include microcirculatory defects, and interstitial fibrosis but these changes reversed by using stem cells in both preclinical and clinical studies [28].

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