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Stem cells in the diabetic infarcted heart

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Abstract

Diabetes mellitus is one of the leading causes of death, and the majority of these deaths are associated with cardiovascular diseases. Development and progression of myocardial infarction leading to heart failure is much more complex and multifactorial in diabetics compared with non-diabetics. Despite significant advances in pharmacological interventions and surgical techniques, the disease progression leading to diabetic end-stage heart failure remains very high. Recently, cell therapy has gained much attention as an alternative approach to treat various heart diseases. However, transplanted stem cell studies in diabetic animal models are very limited. In this review, we discuss the pathogenesis of the diabetic infarcted heart and the potential of stem cell therapy to repair and regenerate.

Keywords

Diabetes; Embryonic stem cells; Myocardial infarction; Oxidative stress; Hyperglycemia

Introduction

Diabetes mellitus is responsible for a host of conditions such as heart disease and stroke, nephropathy, retinopathy, blindness, neuropathy, gastroparesis, and periodontal disease. Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in patients with diabetes, accounting for an estimated 80% of all diabetic deaths in North America [1,2]. Three quarters of these deaths are attributable to coronary artery disease (CAD) leading to myocardial infarction (MI) and heart failure. Acute MI, in the condition of diabetes, results in coagulative necrosis of the myocardium, myocyte cell loss, and infiltration of neutrophils. Cardiac myocyte cell loss in the infarcted region occurs via necrosis or apoptosis and has long been thought to be irreversible. Moreover, cardiac hypertrophy is considered to be a major mechanism to meet increased demands under pathophysiological conditions. Other means to restore cardiac function of the diabetic MI heart may have a great therapeutic potential. Current treatment strategies for diabetic infarcted heart and subsequent heart failure include drugs (aspirin, angiotensin converting

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enzyme inhibitors, and *β*-blockers), angioplasty, thrombolytic therapy, ventricular assist devices, and, ultimately, heart transplantation [1,3]. However, recent advances in cell transplantation in the injured myocardium have enhanced the reality of improved cardiac function in the diseased myocardium [4–6].

Cell transplant studies in the infarcted hearts have reported differentiated heart cell types from transplanted adult and embryonic stem (ES) cells [4,7]. Thus, cell transplantation may be applicable in the regeneration of diabetic infarcted myocardium. In this review, we first highlight differences in the pathophysiology of diabetic versus non-diabetic infarcted hearts. This is followed by a discussion of the mechanisms in the development of cardiac pathogenesis in the diabetic infarcted heart. Finally, the review focuses on the potential of stem cells as a future therapeutic intervention.

Incidence of myocardial infarction in diabetic versus non-diabetic patients

At present, the rate of hospitalized MI is about 180 per 100,000, and ~25% of these MI patients have also been diagnosed with diabetes [8,9]. Furthermore, patients with diabetes without prior history of MI have as high a risk of MI as non-diabetic patients with history of MI [10,11]. Following MI, a greater risk of morbidity and recurrent ischemic events is observed in the diabetic population compared with non-diabetic equivalents [12,13]. The GUSTO-1 angiographic study revealed that diabetes is an independent determinant of 30-day acute MI mortality with a rate of 11.3% in diabetic versus 5.9% in non-diabetic subjects [3]. The MONICA study, comparing diabetics to non-diabetics, determined that the overall mortality following MI was 4 and 7 times higher in diabetic men and women, respectively [12]. Additionally, patients with diabetes following non-fatal MI encounter more severe complications than their non-diabetic counterparts including larger infarcts, increased frequency of post-infarction angina, and enhanced susceptibility to congestive heart failure [3,14,15]. Although the source of these differences in outcomes has yet to be fully understood and delineated, the current evidence suggests diabetic MI pathogenesis is more complex and multi-factorial.

Animal models

Appropriate animal models are powerful tools for understanding the pathogenesis and preventative strategies in diabetes research. There are several chemicals (streptozotocin (STZ) and alloxan) and genetically induced mouse and rat animal models as listed in Table 1. MI can be generated in these diabetic animal models using a coronary artery ligation technique, which closely mimics several features of the diabetic infarcted human heart (Table 1). Moreover, Table 1 lists various type 2 diabetic (T2D) animal models and their use in MI studies [16–34].

Factors responsible for pathophysiologic mechanisms

The development and progression of MI in diabetes is multifactorial including metabolic syndrome, insulin resistance, hyperglycemia, and oxidative stress (Fig. 1). However, due to multifaceted factors, there is no clear understanding of the precise pathophysiologic mechanisms of the infarcted diabetic heart.

Metabolic syndrome

The metabolic syndrome, a complex disorder that encompasses several risk factors including impaired glucose regulation, insulin resistance, hypertension, obesity, dysli-pidemia, and microalbuminuria, is associated with the infarcted diabetic heart [35]. In diabetic MI patients, the metabolic syndrome is associated with the prothrombotic state, which develops

by decreased endothelial thrombo-resistance, platelet hyperactivity, increased plasmatic coagulation, and hypofibrinolysis [36,37]. Moreover, atherogenic dyslipidemia is also closely associated with the metabolic syndrome and T2D. Atherogenic dyslipidemia is comprised of 3 constituents including elevated low-density-lipoproteins (LDL), reduced high-density-lipoproteins (HDL), and increased triglyceride levels [38]. Importantly, it has been reported that accumulated LDL particles are associated with oxidation, impairment of endothelial cell function, inflammation and adhesion, and promotion of vascular smooth muscle cell anomalies that may lead to MI. High levels of LDL are associated with an increased risk for the development of MI as much as observed in post-MI [2,38].

Insulin resistance

Insulin, an anabolic hormone, plays an essential role in carbohydrate and lipid homeostasis and protein metabolism. Additionally, insulin has pertinent non-metabolic functions including thrombosis, homeostasis, and modulation of vascular tone and blood flow [39–41]. Insulin's cellular actions are impaired in insulin-resistant conditions including obesity, T2D, stress, metabolic syndrome, hypertension, and MI. Hyperinsulinemia and insulin resistance give rise to hyperglycemia, decreased lipolysis, increased adipose mass, dysfunctional energy balance and appetite, and an imbalance in the signaling pathway downstream of the insulin receptor. In turn, these pathogenic components induce hypertension, increased thrombophilia and inflammation, endothelial dysfunction, and, ultimately, atherosclerotic cardiovascular disease [40,42]. Furthermore, previous investigations have shown that the extent of insulin resistance is directly related to the incidence of MI and stroke in diabetes [2].

Hyperglycemia

Elevated plasma blood glucose level, hyperglycemia, is now established as a major contributor in the pathogenesis of cardiovascular diseases including MI leading to heart failure and death [2,43,44]. Hyperglycemia has been shown to be associated with increased oxidative stress, enhanced inflammatory processes, non-enzymatic and enzymatic glycosylation of proteins, delayed endothelial cell replication, increased cellular apoptosis, and accelerated atherosclerosis [2,43]. Chronic elevated glucose induces vasculature and cardiac myocyte cell death through several processes including formation of advanced glycation end-products (AGE) via non-enzymatic glycosylation of proteins and lipids, activation of protein kinase C (PKC), increased polyol pathway flux, and enhancement of flow through the hexosamine pathway [2,43,45,46].

One of the most deleterious effects of chronic hyperglycemia is glycation of proteins and lipids. AGEs are formed as a result of non-enzymatic reactions of reducing sugars with free amino groups of proteins, lipids, and nucleic acids. AGEs contribute to the development of some pathological modifications associated with various CVDs through multiple mechanisms: interrupting normal function of proteins and lipids, diminishing ligand/receptor recognition of proteins and lipids, releasing inflammatory cytokines and growth factors from macrophages, and altering enzymatic activity, extracellular matrix (ECM) permeability, and circulating lipoproteins [2,43,47]. These mechanisms initiate a continuous cycle of cellular insult and vascular complications, which potentiate and contribute to the development of diabetic vasculopathy and CVDs [2,43,47].

Mechanistic activation of PKC pathway contributes to a myriad of pathogenic consequences by altering expression of angiotensinogen II (AT-II), activator protein-1 (AP-1), endothelial nitric oxide synthetase (eNOS), endothelin-1 (ET-1), vascular endothelial growth factor (VEGF), transforming growth factor-β (TGF-β), and production of increased reactive oxygen species (ROS). These alterations in signaling pathways lead to vasoconstriction,

capillary occlusion, pro-inflammatory gene expression, hypertension, vascular smooth muscle cell growth, and protein functions [45,46].

Moreover, hyperglycemia further causes vascular/cardiac complications by inducing oxidative stress via increased polyol pathway flux. Generation of reactive oxygen species (ROS) is attributable to two enzymes within the pathway. The first, aldose reductase, utilizes NADPH to reduce glucose to sorbitol. Under non-pathological conditions, this reaction is a minute percentage (<3%) of total glucose use, whereas in a hyperglycemic environment, glucose metabolism by aldose reductase is increased by 30–35% [48]. This leads to a decrease in NADPH availability, reducing glutathione regeneration and NO synthase activity, and ultimately augments oxidative stress [46,49]. Sorbitol dehydrogenase (SDH), the second enzyme, oxidizes sorbitol to fructose with simultaneous production of NADPH, which may be used to produce superoxide [46,49]. Taken together, ROS generated within the polyol pathway in the presence of elevated glucose concentrations has been shown to play an important role in the development of diabetic vascular complications [50].

Additionally, previous studies suggest hyperglycemia-dependent activation of the hexosamine pathway impairs various nuclear and cytoplasmic protein activity through O-linked glycosylation modification (O-GlcNAcylation) leading to endothelial and cardiomyocyte dysfunction [46,51,52].

Oxidative stress in the diabetic heart

Oxidative stress is responsible for a myriad of diabetic complications including cardiomyopathy [53], impaired wound healing [54], retinopathy [55,56], bone disorder [57], endothelial dysfunction [58], nephropathy [59], neuropathy [60], and MI [61]. Oxidative stress is an imbalance between production of reactive oxygen species (ROS) and its breakdown by enzymes including superoxide dismutase (SOD), glutathione peroxidase, catalase, and vitamins C and E. ROS include a variety of oxygen and nitrogen derivatives including superoxide ($O_2^{\bullet -}$), hydroxyl ($OH^{\bullet}$), hydrogen peroxide (H_2O_2), and peroxynitrite ($ONOO^-$). Detailed reviews of ROS generation in the cardiovascular system have been previously published [62–64]. However, potential sources of ROS generation include dysfunctional mitochondrial electron transport chain, arachidonic acid metabolism, neutrophil infiltration and activation, xanthine-xanthine oxidase, and catecholamines [65,66]. A perturbance in the balance of ROS activates mitochondrial pathways, caspases, and mitogen-activated protein kinases (MAPKs), which ultimately have been implicated in the onset and progression of many cardiovascular diseases such as diabetic MI [65,66].

Apoptosis in the diabetic heart

Apoptosis is programmed cell death mediated through a succession of biochemical events including cell blebbing and shrinkage, chromatin condensation, and DNA fragmentation. Collected evidence suggests apoptosis occurs in cardiovascular diseases and plays a significant role in the development of heart failure [5,67,68]. Despite intense investigation into apoptosis in cardiovascular diseases, the exact stimulus for apoptosis remains controversial. The balance between endogenous apoptotic stimuli and inhibitors decide the fate of the cell, i.e. death versus survival.

Evidence of apoptosis has been reported in the pathogenesis of various complications including nephropathy, cardiomyopathy, retinopathy, and neuropathy [69–72]. Several studies have identified hyperglycemia as an independent risk factor for cardiac cell insult, damage, and, ultimately, cell death leading to many cardiovascular diseases including MI [67,69,73]. Additionally, diabetes has been shown to be associated with increased

myocardial cell death in the months following the acute MI phase [67,74]. Adverse cardiac remodeling was observed in the diabetic MI that included cardiomyocyte-apoptotic cell loss, hypertrophy, and fibrosis [75]. Moreover, several mechanisms of hyperglycemia-induced myocardial apoptosis have been identified. However, future studies are necessary to understand the enormity and complexity of the initiation and progression of diabetic cardiomyocyte loss.

Stem cell therapy

Engineered cells and tissues have gained much attention as an alternate method to repair or regenerate injured myocardium following MI. A number of candidate cell types have been transplanted into MI animal models demonstrating their ability to improve the structural and functional capacity of the heart; for example, skeletal myoblasts, bone marrow-derived hematopoietic stem cells, mesenchymal stem cells, endogenous cardiac stem cells, induced pluripotent stem (iPS) cells, embryonic stem (ES) cells [5,6,76–78]. Clinical trials have also been ongoing to study the effects of cell transplantation in patients with MI. The Reinfusion of Enriched Progenitor cells And Infarct Remodeling in Acute Heart Failure (REPAIR-AMI) clinical trial investigated the effects of infused bone marrow stem cells in patients day 4 post-MI and reported improvement in left ventricular ejection fraction (LVEF) [79]. However, the Autologous Stem cell Transplantation in Acute Myocardial Infarction (ASTAMI) clinical trial reported no ventricular function improvement in stem cell transplant–treated group compared to the control group [79]. Overall, the clinical data have reached no conclusive decision regarding the efficacy of adult stem cells for transplantation in MI. However, we are still in search of the optimal cell type for enhanced cardiac repair and regeneration.

Moreover, cell transplantation has also been examined in diabetic cardiomyopathy and infarcted hearts [80–83]. Transplanted MSCs improved cardiac function through increased angiogenesis and matrix metalloproteinase-2 (MMP-2) expression and decreased collagen content and transcription of MMP-9 in diabetic cardiomyopathy hearts [83]. Bone marrow stem cells were also tested in the diabetic cardiomyopathy setting in which improved cardiac function was observed [82]. Govaert et al. transplanted diabetic bone marrow mononuclear cells (BMMCs) and healthy BMMCs into *db/db* mice with ischemic myocardium. They demonstrated diabetic BMMCs were unable to improve cardiac function post-MI, whereas healthy BMMCs were able to preserve fractional shortening [80]. Additionally, transplanted MSCs initiated increased heart rate, left ventricular developed pressure, and contractility index as well as decreased systolic blood pressure in the diabetic animal model [81].

Current adult stem cell transplantation studies in the diabetic heart are very limited and require further investigation. Moreover, as per the best of our knowledge, there is no study performed on either a diabetic infarcted or cardiomyopathy heart using ES or iPS cells. ES and iPS cells possess many desirable traits, making them a more promising approach to attenuate the damaged myocardium. ES cells, derived from the inner cell mass of a blastocyst, are pluripotent, undifferentiated cells. They are capable of self-renewal and are able to differentiate into multiple cell types in the body including functional cardiomyocytes, endothelial cells, and vascular smooth muscle cells [4]. Previous studies have demonstrated the ability of ES cells transplanted into the infarcted heart to engraft, differentiate into cardiomyocytes, contribute to heart regeneration, and improve heart function [4–6]. Although the molecular mechanism of myocardial repair by transplanted ES cells has yet to be elucidated, it remains an active area of continued research. Nevertheless, an optimized ES cell therapy holds great promise for the treatment of diabetic injured myocardium.

Another emerging approach of cell transplantation therapy is the creation of iPS cells. iPS cells are reprogrammed adult cells exhibiting pluripotent cell characteristics through forced gene expression of Oct 3/4, Sox2, Klf4, and c-myc. These cells can then be directed to differentiate into specific cell types though mechanisms similar to ES cell differentiation. Fibroblast-derived iPS cells have recently been tested in a MI model and demonstrated the ability to engraft into the host myocardium, differentiate into all three major heart cells such as cardiac myocytes, smooth muscle and endothelial cells, repair the ventricular wall, and restore contractile function [78]. Although still in infancy, iPS cell transplantation holds tremendous potential for use in the repair of diabetic MI damaged myocardium.

Future perspectives

Patients with diabetes have improved their lifestyle with strict pharmacological interventions and non-pharmacological management (exercise, weight, smoking, etc.). However, the relative frequency and death occurring from MI remain drastically increased in the T2D patients compared to their non-diabetic counterparts. Thus, there is an eminent need to develop new therapeutic options. Recent studies suggest that stem cells transplanted in the infarcted heart have significantly improved cardiac function along with differentiation into all three major heart cell types. Moreover, transplanted adult stem cells in STZ-induced diabetic cardiomyopathy show improved cardiac function. However, there are no studies that define the role of ES cells for the treatment of infarcted diabetic hearts. More recently, generation of iPS cells and their applications to treat MI with improved heart function has raised new hope to bring stem cell therapy in the clinic. Overall, we propose that ES or iPS cells could have additional beneficial effects for the treatment of diabetic infarcted hearts.

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Fig. 1.
List of various factors involved in the development and progression of heart failure in diabetes

Table 1

T2D models	Description	Type 2 diabetic characteristics	Used in MI/IR studies?	References
ob/ob mouse	Leptin deficient	Obesity, dyslipidemia, insulin resistance, hyperinsulinemia, hyperglycemia, impaired glucose tolerance	Yes/Yes	16,17,18,19
db/db mouse	Leptin resistant	Obesity, dyslipidemia, insulin resistance, hyperinsulinemia, hyperglycemia	Yes/Yes	17,19,20,21
KK/A^{y} mouse	Genetically derived (A^{y} mutation)	Obesity, insulin resistance, hyperinsulinemia, islet cell hyperplasia, hyperglycemia, impaired glucose tolerance	No/No	16,20,22
Zucker (fa/fa) rat	Leptin resistant	Obesity, dyslipidemia, insulin resistance, hyperinsulinemia, hyperglycemia, impaired glucose tolerance, hypertension	Yes/Yes	20,31,32,34
Goto Kakizaki rat	Spontaneous diabetes by selective breeding	Insulin resistance, hyperinsulinemia, hyperglycemia, impaired glucose tolerance	Yes/Yes	16,20,23,32,33
NZO mouse	Polygenic diabetes model by selective inbreeding	Obesity, insulin resistance, hyperinsulinemia, hyperglycemia, impaired glucose tolerance	No/No	20
NSY mouse	Spontaneous diabetes by selective inbreeding	Insulin resistance, hyperglycemia	No/No	16
OLETF rat	Spontaneous diabetes by selective inbreeding	Mild obesity, dyslipidemia, hyperinsulinemia, hyperglycemia, impaired glucose tolerance	No/Yes	16,20,30
Cohen diabetic rat	Diet-induced diabetes	Hyperinsulinemia, hyperglycemia, hypertension	No/No	20,24,25
Low dose ALX- or STZ-treated rodents	Chemical ablation of β cells	Dyslipidemia, hyperglycemia, hyperinsulinemia	Yes/Yes	20,28,29
C57BL/6J	High fat diet-induced	Obesity, dyslipidemia, insulin resistance, hyperglycemia, impaired glucose tolerance	Yes/Yes	20,26,27

NZO New Zealand obese, *NYS* Nagoya-Shibata-Yasuda, *OLETF* Otsuka Long-Evans Tokushima fatty, *ALX* alloxan, and *STZ* streptozotocin, *IR* ischemia/reperfusion