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Review Article

Research Progress of Myocardial Tissue Engineering Materials in the Treatment of Myocardial Infraction

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Abstract

Myocardial Infraction (MI) remains one of the leading causes of death and disability worldwide. Although drugs and interventional therapy can restore blood supply to the heart in time, the extremely low self-regeneration ability of cardiomyocytes cannot rescue acutely damaged myocardial tissue. Severe cases can lead to heart failure and even death. In recent years, cardiac tissue engineering has been widely used to treat ischemic heart disease, using stem cells to repair the lost parts of the heart. Mesenchymal Stem Cells (MSCS) have been widely used in cardiac tissue engineering in recent years. The development of mesenchymal stem cells has brought breakthroughs in the treatment of different cardiovascular diseases. Therefore, due to its significant benefits, stem cell therapy has attracted attention in recent years as it provides patients with a drug and surgical free treatment and provides a safer and more feasible modality of cardiac repair. After reviewing the pathophysiology of MI, this study addresses the role of tissue regeneration using various materials, including different types of stem cells. This article introduces different transplantation methods and looks forward to the future of this scientific therapy.

Keywords: Myocardial Infraction; Cardiac Tissue Engineering; Stem Cells; Tissue Regeneration

Introduction

Ischemic Heart Disease (IHD), which mainly manifests as Myocardial Infraction (MI), is one of the factors with the highest mortality in patients worldwide [1,2]. Myocardial infraction is a pathological state in which the heart dies of myocardial cells due to insufficient blood supply in the ischemic state [3]. Under the chronic hypoxic conditions of IHD, some cardiomyocytes are replaced by scar tissue and others try to reduce their energy requirements, so their contractility is reduced [4]. At the cellular level, the inflammatory response after ischemia is also complex. Endothelial dysfunction, vessel-wall inflammation, and lipid accumulation are important factors in the development and progression of atherosclerosis, the most common cause of myocardial ischemia. Atherosclerosis is usually caused by the accumulation of Low-density Lipoprotein (LDL) and inflammation of the arterial wall. Atherosclerosis in the coronary arteries is the cause of this. In the inflammatory response, the expression of vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), P-selectin and E-selectin, atherogenic factors and the persistence of the inflammatory response promote the activation of T and B cells, more macrophages and mast cells. Their activation increases vasculopathy, releases cytokines [such as interleukin (IL) -6, Il-1β, interferon (IFN)-α, tumor necrosis factor (TNF)-α], and enhances the migration of monocytes into the subintimal region [5] (Figure 1).

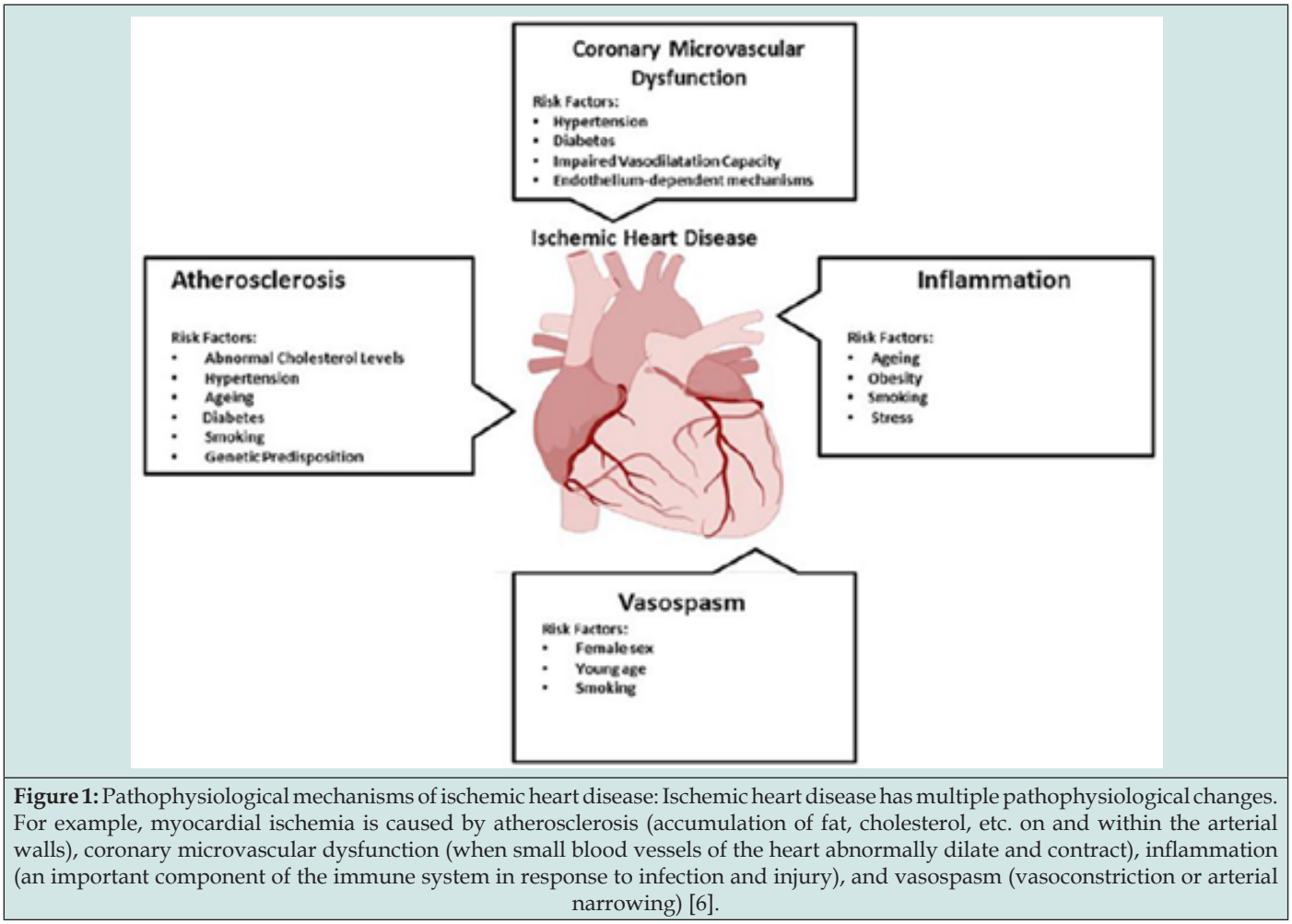

Figure 1: Pathophysiological mechanisms of ischemic heart disease: Ischemic heart disease has multiple pathophysiological changes. For example, myocardial ischemia is caused by atherosclerosis (accumulation of fat, cholesterol, etc. on and within the arterial walls), coronary microvascular dysfunction (when small blood vessels of the heart abnormally dilate and contract), inflammation (an important component of the immune system in response to infection and injury), and vasospasm (vasoconstriction or arterial narrowing) [6].

Cardiac tissue engineering has a great impact on the recovery of cardiac function in patients with myocardial infraction. Different from traditional interventional therapy and coronary artery bypass grafting (CABG), the most advantage of cardiac tissue engineering is that it can provide a treatment plan for patients with chronic pain and severe injury without drugs or surgery [7]. In the field of IHD, studies have suggested the use of stem cells for treatment. Stem cells have multi-directional differentiation potential, which is the reason why cardiac tissue engineering is based on stem cells today. Among all kinds of stem cells, Mesenchymal Stem Cells (MSCs) are more important in the application of IHD treatment and have been studied in many preclinical and clinical studies. Basic studies have shown that MSCs transplantation in the treatment of MI mainly through paracrine effects. It can promote angiogenesis, inhibit fibrosis and improve immune regulation [8,9]. However, current clinical studies have shown that the repair effect of MSCs on damaged myocardium is limited, which is mainly related to the low homing rate of myocardium and the low survival and retention rate of transplanted cells after transplantation.

In order to improve the therapeutic effect, many methods have been studied, including appropriate increase in the dose of MSCs transplantation, intramyocardial injection, and transendocardial transplantation. The emergence of the above methods has brought a new dawn for the development of stem cell transplantation therapy [10,11]. MSCs come from a wide range of sources, including bone marrow, fat, umbilical cord, placenta, and dental pulp [12]. The most promising is Bone Marrow Mesenchymal stem cells (BM-MSCs) derived from bone marrow. BM-MSCs have a high pro-angiogenic activity and there is no ethical controversy. Other mesenchymal stem cells such as umbilical cord mesenchymal stem cells (UC-MSCs) and Adipose-Derived Mesenchymal stem cells (AD-MSCs) also have broad application prospects.

The main mechanism of MSCS transplantation in the treatment of myocardial infraction

Promote The Formation of New Blood Vessels

MSCs promote the formation of new blood vessels in the area of myocardial infraction and the repair of injured myocardium by secreting bioactive factors [13,14]. Vascular endothelial growth factor and fibroblast growth factor secreted by MSCs play an important role in promoting the repair of damaged myocardium. In animal experiments with MSC treatment, the levels of Vascular

endothelial Growth Factor (VEGF) and Fibroblast Growth Factor (FGF) in animals were significantly increased. Moreover, normal MSC showed a stronger protective effect on damaged myocardium than L-VEGF expressing MSC [15]. The effect of BM-MSCs combined with VEGF on angiogenesis and myocardial repair in MI rats was significantly better than that of BM-MSCs alone, and the number of transplanted cells surviving was also significantly increased [16]. In conclusion, MSCs promote neovascularization by secreting VEGF, FGF and other factors, thereby repairing the damaged myocardium after MI.

Immune Regulation

When MI occurs, the integrity and barrier function of vascular endothelial cells are impaired, accompanied by a large number of myocardial cell death or apoptosis, leading to changes in the microenvironment, and then activating the immune system to trigger immune responses. At the same time, chemokines released by injured cardiomyocytes bind to their corresponding receptors to promote immune cell infiltration, while the rise of chemokines (tumor necrosis factor, interleukin, etc.) enhances the adhesion between inflammatory cells and endothelial cells, leading to the transfer of a large number of inflammatory cells to the infarcted myocardium. This suggests that immune factors may become important targets for the treatment of acute myocardial infraction and the prevention of heart failure [17,18].

When BM-MSCs were co-cultured with T cells, the PD-L1 and PD-L2 ligands expressed by BM-MSCs activated the PD-1 receptor on T cells, leading to reduced production of proinflammatory cytokines such as interferon-γ, tumor necrosis factor-α, and interleukin-2. At the same time, MSCs can block the maturation of B cells in the G0/G1 phase and reduce the chemotactic activity of these cells, thereby reducing the occurrence of inflammatory responses [19]. In conclusion, MSCs play a very important role in regulating immune cells in the area of myocardial infraction, inhibiting adverse cardiac remodeling, and promoting the repair of cardiac function by inhibiting inflammatory response and reducing myocardial fibrosis.

Protection of Cardiomyocytes

Recent studies have shown that transplanted MSCs perform endogenous repair mainly through paracrine effects. For example, bone marrow mesenchymal stem cells exosome (BM-MSC-Exo) can inhibit H2O2-induced cardiomyocyte apoptosis. Furthermore, it can stimulate the proliferation of rat cardiomyocytes and improve the damaged cardiac function [20]. In conclusion, transplanted MSCs can protect host cardiomyocytes from apoptosis by improving the microenvironment of the infarct area.

The Effect of Transplantation Method on the Efficacy

An important factor determining the success of MSCs therapy is the mode of cell transplantation, which will directly affect the survival, proliferation and functional effect of transplanted cells, and then affect the therapeutic effect. The application of tissue engineering materials in ischemic heart disease has some problems, such as low cell survival rate and poor target positioning. Several methods have been developed to prolong the viability of grafts, including (1) seeding cells on prefabricated scaffolds, (2) assembling stem cells in hydrogels, and (3) cell patches [21-23].

The Stem Cells were Assembled in the Hydrogel

In this technique, 3D networks are formed using hydrophilic structural hydrogels made of synthetic or natural polymers. There are a number of conditions to be met in this 3D network: in addition to including growth factors and other molecules to mediate cross-links between cells, oxygen, nutrients, and metabolites all need to be exchanged through their pores [24,25].

Engineered Myocardial Tissue

There are two main approaches to the application of tissue engineering in the cardiac field. One of these aims to promote cardiac function and the other is to develop 3D in vitro models capable of mimicking native myocardium. These approaches need to consider a number of features: (1) biochemical mechanisms, electrophysiological and mechanical extracellular matrix and cell-cell interactions; (2) in vivo dynamic conditions such as fluid flow and shear stress; (3) correct cell characteristics, morphology and structural microstructure [26].

Cell Sheets

This method uses temperature to affect the polymer surface, enabling the release of cell monolayers. These free-floating sticky cell sheets can be placed on the epicardium with or without suture. Similarly, a single layer of 3-4 layers can fuse to a degree of necrosis without touching the myocardial core. Different cell types can be used in this approach, such as cardiomyocytes for contractile support and non-muscle cells for delivery of secreted factors [27-29]. Some disadvantages of this approach include the thin and brittle nature of the myocardial patches themselves and the limited number of sheets that can be stacked on top of each other without causing cell death [30].

Biofabrication

In this approach, a suitable cell scaffold is required in order to provide a cellular microenvironment as a structural platform. Our aim is to provide biochemical factors that provide a suitable environment for cell adhesion, migration and differentiation. The main limitation of this approach is that only uneven cell density can be achieved because cells tend to stay on the scaffold surface, so only weakly contracting heart tissue can be used for manufacturing methods, so 3D printing technology can be used for gene editing technology and multiple cell layers can be generated from different cell types. There are some standardization problems with this method, such as correct cell composition, localization of various types of cells and materials, vascularization, and incorporation of bioactive substances [31] (Figure 2).

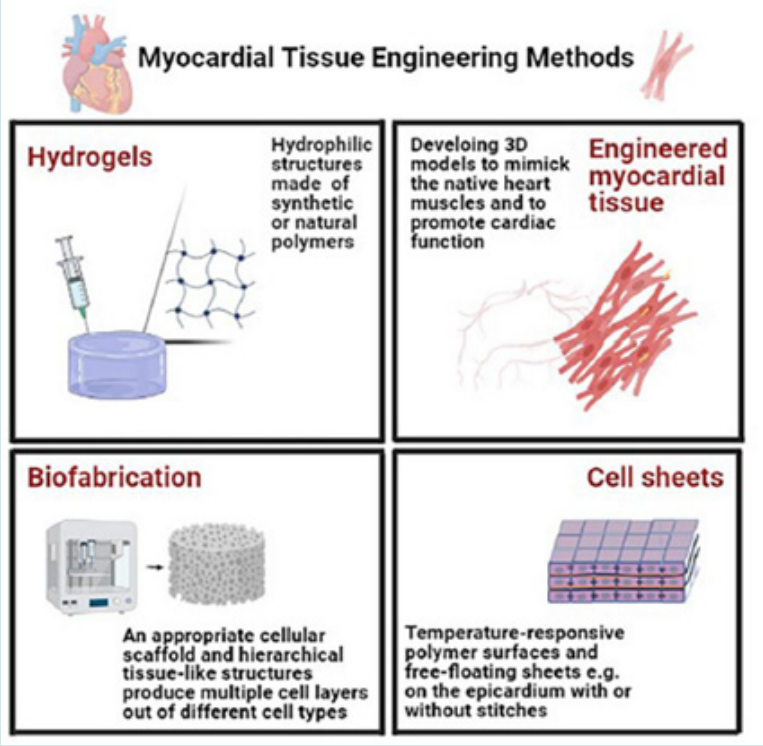

Figure 2: Several approaches have been proposed to prolong graft activity for tissue engineering in ischemic heart disease, including the use of hydrogels (synthetic or natural polymers using hydrophilic structures), engineered cardiac tissue (development of three-dimensional (3D) in vitro models to mimic native cardiac muscle), cell sheets (the use of a temperature-responsive polymer surface that enables the release of a cell monolayer, and the development of a new model of cardiac muscle. For example, it can be placed on the epicardium with or without suture) and bioediting technologies (which require appropriate cell scaffolds to provide a cellular microenvironment as a structural platform) [31].

Future Development

Ischemic heart disease remains one of the leading causes of human mortality. Cell therapy and regenerative medicine have opened up new approaches for the treatment of IHD. It seems necessary to find the best source of stem cells and the most efficient way to introduce them into the damaged myocardial region. The use of biomaterials alone as a cardiac therapy has been widely discussed in recent years, and more research is needed to demonstrate the effectiveness of this approach. Studies have shown a significant increase in the demand for the discovery of molecular mechanisms that can be used in clinical practice due to the low cell adhesion of grafts. In addition, researchers are working to improve the effectiveness of regenerative medicine by combining cell and gene therapy. In addition, cell sheet therapy is another novel approach that can increase the number of transplanted stem cells in cardiac tissue. Drug treatment may also affect molecular pathways associated with improving the quality of cell therapy.

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