Apelin 13: A novel approach to enhance efficacy of hypoxic preconditioned mesenchymal stem cells for cell therapy of diabetes

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ABSTRACT

Recent studies have proposed cell therapy as an alternative therapeutic strategy for many disease states such as diabetes mellitus. Among different cell types mesenchymal stem cells (MSC) have attracted a significant attention based on their intriguing potentials. However MSC therapy is limited as a large portion of transplanted cells undergo apoptosis after transplantation. Therefore, proposing a strategy to overcome this obstacle may be of great value. Recent studies have shown that hypoxia preconditioning (HPC) may improve cell viability after transplantation. Both HPC and hyperglycemia are reported to exert effects by different levels of ROS overproduction. Overdose of ROS in this case would trigger the apoptosis and thereby decreased cell viability after transplantation. Apelin; the endogenous ligand for the previously orphaned G protein–coupled receptor APJ is shown to exert anti apoptotic effects on oxidative stress-induced apoptosis in MSCs via MAPK/ERK1/2 and PI3K/AKT signaling pathways. Accordingly it has been hypothesized that pretreatment of HPC-MSC, with apelin 13 would be an effective approach to modify and possibly enhance the efficacy of MSCs in cell therapy of diabetes.

Introduction

Cell therapy is a therapeutic alternative for many disease states. Although cell therapy is performed by a number of different cell types, MSCs have appeared as attractive alternative due to their interesting potentials. A number of clinical trials are underway to test the efficacy of MSC, in treating various diseases including type 1 diabetes mellitus (T1D). Recent studies have demonstrated that almost 99% of transplanted MSC are lost within the first 24 h after transplantation [1]. This is thought to be mostly mediated by apoptosis [2]; therefore the idea of protecting MSC against apoptosis in pro-apoptotic microenvironments of hypoxia seems critical for improving the efficacy of cell therapy [2]. A few studies investigating the protective effects of HPC on the post transplantation viability of MSC have found that HP increases expression of pro-survival genes such as AKT via hypoxia inducible factor-1α (HIF-1α) pathway and thereby increased stem cell survival [3]. It is known that ROS is required for intermittent hypoxia (IH) induced HIF-1α accumulation [4]. Interestingly recent studies have shown that increased MSC capacity to repair infarcted myocardium induced by HPC is almost attributable to attenuated cell death and apoptosis of implanted cells [5].

Diabetes mellitus, a chronic syndrome characterized by elevated levels of blood glucose, referred to as hyperglycemia. So when MSC are administered to a DM individual, they are exposed to a high glucose condition which together with hypoxia cause excess ROS production to toxic levels [6]. Increased oxidative stress is one of the major factors responsible for cell stress/death. Increased oxidative stress proceeds in impaired cell function and subsequently reduced cell viability [7–9].

Apelin has been newly identified as the endogenous ligand for the previously orphaned G protein–coupled receptor APJ [10]. The cytoprotective effects of apelin are proved by both in vitro and in vivo studies [11–15]. It has been shown to enhance survival of cardiomyocytes and neuronal cells during ischemia [15]. Recent articles even shown that exogenously administrated apelin protected the ischemic myocardium against I/R injury [11–14]. Interestingly another study performed by Wei et al. have revealed the cytoprotective potential of apelin in MSC exposed to stress such as serum deprivation [15].

Hypothesis and evaluation of the hypothesis

It is hypothesized that pretreatment of HPC-MSCs with apelin would be an effective approach to modify HPC-MSC therapy for diabetes. But is there any clinical evidences supporting the idea? Wang et al. have shown that HPC have a protective effect against MSC apoptosis induced by hypoxia-reoxygenation (H/R) via
stabilizing mitochondrial membrane potentials, up regulating Bcl2 and VEGF and promoting AKT phosphorylation [2].

High glucose is also found to induce oxidative and nitrosative stress in many cell types which leads to the generation of species such as superoxide and peroxynitrite and their derivatives [16]. Interestingly it is found that experiments related to the complications of diabetes such as nephropathy and cardiovascular diseases [16]. Interestingly it is found that experiments using proteasomal and prolyl hydroxylases inhibitors indicate that diovascular diseases [16]. Interestingly it is found that experiments related to the complications of diabetes such as nephropathy and cardiovascular diseases [16]. Interestingly it is found that experiments using proteasomal and prolyl hydroxylases inhibitors indicate that diovascular diseases [16]. Interestingly it is found that experiments related to the complications of diabetes such as nephropathy and cardiovascular diseases [16]. 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