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Review

Application of stem cell/growth factor system, as a multimodal therapy approach in regenerative medicine to improve cell therapy yields

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ABSTRACT

Stem cells hold a great promise for regenerative medicine, especially for replacing cells in infarcted organ that hardly have any intrinsic renewal capacity, including heart and brain. Signaling pathways that regulate pluripotency or lineage-specific gene and protein expression have been the major focus of stem cell research. Between them, there are some well known signaling pathways such as GF/GFR systems, SDF-1α/CXC4 ligand receptor interaction and PI3K/Akt signaling, and cytokines may regulate cell fate decisions, and can be utilized to positively influence cell therapy outcomes or accentuate synergistic compliance. For example, contributing factors in the progression of heart failure are both the loss of cardiomyocytes after myocardial infarction, and the absence of an adequate endogenous repair signaling. Combining cell engraftment with therapeutic signaling factor delivery is more exciting in terms of host progenitor/donor stem cell survival and proliferation. Thus stem cell-based therapy, besides triggering signaling pathways through GF/GFR systems can become a realistic option in regenerative processes for replacing lost cells and reconstituting the damaged organ, as before.

1. Introduction

1.1. Desirable application of chemotactic factors during the recovery processes

Despite advances in medical and surgical procedures, cardiovascular diseases remain the leading cause of cardiovascular morbidity and mortality. The death of large numbers of cardiomyocytes results in development of heart failure; thus, restoring lost myocardium would be desirable for the treatment of cardiomyopathy.

Human stem cell-derived cardiomyocytes (hSC-DCMs) hold a great promise for myocardial regeneration after infarction. However, existing strategies are restricted by low cell survival and engraftment, and significant obstacles still exist with consistent derivation of hSC-DCMs populations [1]. It was found that long-term culture increases mesenchymal stem cell (MSC)-cellular stress and causes expression of more cell cycle inhibitors, p16(INK), p21 and p19(ARF), whereas the presence of vascular endothelial growth factor (VEGF) reduces cellular stress besides improving MSC viability in infarcted hearts, by increasing pro-survival factors such as phosphorylated-Akt and Bcl-xL. Co-injection of MSCs with VEGF to MI hearts increases cell engraftment and results in better improvement of cardiac function than alone injection of VEGF or MSCs [2–4].

It has been also reported that MSCs overexpressing insulin-like growth factor (IGF)-1 not only improved survival and engraftment in the infarcted heart, but also promoted stem cell incorporation through paracrine release of stromal cell-derived factor (SDF)-1α. The presence of IGF-I has a pivotal role in attracting stem cells to the injured heart and their differentiation via release of paracrine factors, besides activating molecular pathways of cell survival [4,5].

On the other hand, MSCs overexpressing IGF-1, exhibit massive stem cell mobilization via SDF-1α signaling and culminate in extensive angiomyogenesis in the infarcted heart. Clusters of stem cell-like cells have been identified in the human adult heart, which contribute to organ regeneration, as well. These cells express stem cell markers such as Sca-1 and c-Kit, and also harbor telomerase activity which is only present in replicating cells [3,4].

Tissue injuries are also associated with local increases in mediators, the chemotactic factors particularly relevant to bone marrow mesenchymal stem cell (BMMSC) mobilization and homing for tissue repair. BMMSCs are able to migrate in response to a large set of chemotactic factors, including both growth factors (GFs) and chemokines [6,7].

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Some of the GFs have been known to be produced by MSCs and known for their autocrine activity, promigratory, proliferating, or differentiating activity on MSCs. The most chemoattractive GFs have been reported to be platelet-derived growth factor (PDGF-AB), insulin-like growth factor-1 (IGF-1), hepatocyte growth factor (HGF), epidermal growth factor (EGF), and angiopoietin-1 (Ang-1), which are already reported as potent chemoattractants for MSCs [7–9].

Data also indicate that the migration capacity of stem cells is under the control of tyrosine kinases and CXC chemokine receptors (a large family of G protein-linked receptors that are known as seven transmembrane). One of the parameters that have to be taken into account in cell therapy protocols, is that the chemokines are mostly effective on tumor necrosis factor-α (TNF-α)-primed stem cells and MSC subsequent homing to injured tissues depends on the systemic and local inflammatory state [6,10,11].

MSCs pre-incubation with inflammatory cytokines such as TNF-α, lead to increased MSC mobilization towards chemokines especially RANTES (regulated on activation, normal T cell expressed and secreted/CCL5, a chemotactic cytokine that plays an active role in recruiting leukocytes into inflammatory sites) [12]. Notably, MSC's pre-incubation with inflammatory cytokines does not change the migration capacity of cells in response to the major GFs; VEGF, PDGF, IGF-1, HGF and EGF. For example, VEGF as a potent angiogenic agent underlining a major chemotactic activity of MSCs and endothelial cells is not responding to TNF-α. Whereas the growth factor Ang-1 not only promotes angiogenesis from pre-existing blood vessels, but has also been shown to respond to proinflammatory conditions, Ang-1 is a crucial chemotactic factor for endothelial cells through its receptor Tie-2 [13–15]. BM-derived hematopoietic stem cells (HSCs) and MSCs express Tie-2 and Tie-1, respectively and respond to Ang-1 under proinflammatory conditions (i.e., in the presence of TNF-α) [7,14].

Generally, the chemotactic activity of chemokines on stem cells is appeared to be less efficient than that of GFs. Exceptionally, three chemokines RANTES/CCL5, SDF 1/CXCL12 and macrophage-derived chemokine (MDC)/CCL22 display clearly a significant activity. Although, in comparison to PDGF-AB and IGF-1 which have the most potent activity on stem cells, the three mentioned chemokines, display limited effects [16]. MDC, as an active chemokine on mature hematopoietic cells, and also as a potent chemoattractant for BMMSCs, even displays the strongest activity among the chemokines tested on steady state cells [7,16].

A dramatic increase has been observed in MSC sensitivity to RANTES, MDC, and SDF-1, after TNF-α stimulation. It was indicated that MSCs express the receptors for RANTES (CCR3, CCR4, and CCR5, but not CCR1), MDC (CCR4), and SDF-1 (CXCR4).

Some cytokines like granulocyte-colony stimulating factor (G-CSF) and SCF cause an increase in the release of stem cells from the bone marrow into the peripheral blood circulation. The administration of G-CSF and/or SCF could contribute to myocardial regeneration, if circulating stem cells accumulate in the myocardium and differentiate into cardiomyocyte [7]. Notably, the migration capacity of MSCs clearly stands in contrast to that of HSCs whose migration is induced mainly by the single chemokine, SDF-1 [17], whereas hematopoietic GFs display little or no chemotactic activities [12].

Consider that MMPs and CD26/DPPIV proteases are able to favor cell locomotion and tissue reconstitution by breaking down the extracellular matrix and also by degrading locally a number of chemokines. Their local administration along the chemotactic factors can accentuate MSC homing and incorporation into the injured tissue through the extracellular matrix, as recently reported with IGF-1, HGF, or PDGF after myocardial damage [18]. Consider that systemic administration may also trigger endogenous MSC mobilization towards tissue injuries, while avoiding ex vivo stem cell amplification. In addition, the local or systemic administrating of inflammatory mediators might influence not only MSC mobilization [19], but also MSC proliferation and differentiation [20] and MSC engraftment [7,21].

1.2. The IGF-1/IGF-1R system poses a greater degree of angiogenesis in the heart

IGF-1 is an autocrine/paracrine growth factor that circulates at high levels in the plasma and is expressed in most cell types. IGF-1 has major effects on development, cell growth and differentiation [22,23]. Intramyocardial transplantation of MSCs overexpressing IGF-1/GF-1R during the acute phase of MI in some studies has ensured optimal participation of IGF-1/IGF1R system for enhanced cardiac repair [24]. Through IGF-1/IGF1R system, significant progress has been made to promote donor cell survival, engraftment and differentiation in the transplanted heart [25–27].

The main function of IGF-1 in the heart is known to stimulate cardiac growth and contractility [28]. Although there are reports showing left ventricular (LV) hypertrophy caused by IGF-1 administration [29], decreased level of IGF-1 has been indicated in different pathological conditions and implies its critical roles in tissue protection and repair [30]. IGF-1 has distinct beneficial effects on cardiomyocytes including their survival and proliferation. Besides activating molecular pathways of cell survival, IGF-1 accelerates stem cell migration and plays a pivotal role in attracting stem cells toward the heart. Part of its function is through potent activation of paracrine factors. It was reported that MSCs overexpressing IGF-1, showed improved survival and engraftment in the infarcted heart and promoted stem cell recruitment through the paracrine release of SDF-1α. The autocrine and particularly paracrine bioactivity of IGF-1 released from stem cells in terms of cytoprotection has been determined under sever conditions [5].

1.3. IGF-I signaling pathways play a pivotal role in cell survival and homing

MSCs secrete a plethora of angiogenic and mitogenic cytokines, as well as growth factors in normoxic conditions. The secretion of these factors is increased significantly in response to anoxia for reducing the infracted size. The findings imply that MSCs play a crucial role in improving regional blood flow in scar tissue. Indeed, this therapeutic effect of MSCs was overlooked by most studies which then are emphasizing multipotential characteristics of the cells [31].

It has also been shown that concomitant overexpression of Ang-1 and Akt in MSCs promotes their survival in the infarcted heart. It is important to note that the IGF-1/IGF-1R system has a wide distribution in the heart inside the myocytes, cardiac progenitor cells (CPCs), and cardiac fibroblasts, and its activation regulates many functions such as telomerase activity, hinders replicative senescence, and preserves functionally competent CPCs [32].

IGF-1 promotes multiple growth factor expression and releasing, including hepatocyte growth factor (HGF), basic fibroblast growth factor (b-FGF), and vascular endothelial growth factor (VEGF), besides SDF-1α, which stimulate bone marrow and endothelial progenitor cell mobilization towards the ischemic area [5]. Although multiple signaling pathways have been reported downstream of IGF-1/IGF-1R interaction, the phosphoinositide 3-kinase (PI3K)/Akt signaling pathway plays a major role in cytoprotection. IGF-1/IGF1R interaction activates PI3K to the cell membrane that in turn, activates the Akt kinase, thus activating its downstream substrates such as Bcl.xL and inhibiting glycogen synthase kinase (GSK)3β in stem cells (Fig. 1).

In other words, overexpression of Akt increases Akt phosphorylation (pAkt) level which in turn brings on the release of bioactive molecules such as SDF-1α to act in a paracrine/autocrine fashion to exert cytoprotective and ionotropic effects [5,33]. Besides its role in cell survival, pAkt negatively regulates the kinase activity of GSK3β (a negative regulator of cell growth). These intracellular changes, for example inactivation of GSK-3β are associated with the expression of muscle specific proteins and potentiate myogenesis, in addition to their pivotal role in cell survival.

SDF1-α/CXCR4 ligand/receptor system is a potent activator of stem cell mobilization and homing [34], as well as a modulator of several