

## Host tissue response in stem cell therapy

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### Abstract

Preclinical and clinical trials of stem cell therapy have been carried out for treating a broad spectrum of diseases using several types of adult stem cells. While encouraging therapeutic results have been obtained, much remains to be investigated regarding the best cell type to use, cell dosage, delivery route, long-term safety, clinical feasibility, and ultimately treatment cost. Logistic aspects of stem cell therapeutics remain an area that requires urgent attention from the medical community. Recent cardiovascular trial studies have demonstrated that growth factors and cytokines derived from the injected stem cells and host tissue appear to contribute largely to the observed therapeutic benefits, indicating that trophic actions rather than the multilineage potential (or stemness) of the administered stem cells may provide the underlying tissue healing power. However, the capacity for trophic factor production can be aberrantly downregulated as seen in human heart disease. Skeletal muscle is a dynamic tissue with an impressive ability to continuously respond to environmental stimuli. Indeed, a relation exists between active skeletal muscle and low cardiovascular risk, highlighting the critical link between the skeletal muscle and cardiovascular systems. Adding to this notion are recent studies showing that stem cells injected into skeletal muscle can rescue the failing rodent heart through activation of the muscle trophic factor network

and mobilization of bone marrow multilineage progenitor cells. However, aging and disease can adversely affect the host tissue into which stem cells are injected. A better understanding of the host tissue response in stem cell therapy is necessary to advance the field and bridge the gap between preclinical and clinical findings.

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### INTRODUCTION

Stem cell therapy has entered the realm of clinical trials evaluating several types of adult stem cells and targeting a broad spectrum of diseases ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)). These investigations have generally demonstrated the safety of stem cell administration. However, consistent and reproducible beneficial effects of stem cells, as might be inferred from various animal studies, have not been demonstrated. In cardiac repair, mixed results have been reported without a clear consensus on the best cell for tissue regeneration<sup>[1,2]</sup>. Interestingly, although the multilineage differentiation potential (stemness) of stem cells was originally thought to mediate their cardiovascular therapeutic attributes, it has now become clear that the secretion of multiple growth factors and cytokines (trophic action) by the injected stem cells is primarily responsible for many of the observed therapeutic benefits<sup>[3-8]</sup>. These recent findings have necessitated a revised view on the action of the exogenously delivered stem cells, and prompted us to adopt a more

integrative approach in optimizing stem cell therapeutics. Specifically, a better understanding of the cross-talk mechanism, mediated by the injected stem cells and host tissue, may prove insightful in transitioning toward future routine clinical use of adult stem cells.

Infection or injury typically triggers an inflammatory response in the host, and resolution of the inflamed state is an actively executed program. Similarly, implantation of large numbers of stem cells, whether autologous or allogeneic, is expected to elicit some host tissue immune response at least during the acute phase, and the duration and extent of this response may dictate the outcome of the cell therapy. Even in the case of implantation of medical devices possessing an inert and nonimmunogenic surface, a sequence of host inflammatory events can lead to fibrous capsule development, which can greatly compromise the device performance<sup>[9]</sup>. Although this consideration is particularly relevant for *ex vivo*-expanded stem cells, which may harbor xenoantigens resulting from the use of animal components (such as fetal bovine serum) in the culture medium, the topic has been discussed previously<sup>[10]</sup>, and thus will not be covered here. Implanted stem cells are metabolically and functionally active, capable of interacting with the host tissue microenvironment and producing bioactive trophic factors, some of which may intervene in the host immune cascade. As elaborated below, these paracrine mediators can exert profound effects on the well-being of the host through modulation of tissue response. The focus of this editorial is to dissect this molecular cross-talk between the host tissue network and implanted bone marrow mesenchymal stem cells (MSCs) in the context of cardiovascular therapy.

## TROPHIC ACTIONS OF MESENCHYMAL STEM CELLS

Bone marrow-derived MSCs have been extensively used in preclinical and clinical studies primarily because of the ease of cell isolation in large scale and their inherent immune privileged status<sup>[3,10,11]</sup>. Although MSCs can be used for therapeutic tissue engineering by virtue of their ability to differentiate into specialized cells, the beneficial effects of MSCs in treating cardiomyopathy, stroke, and osteoarthritis have been attributed mainly to their trophic activities<sup>[5,12-16]</sup>. We have used quantitative polymerase chain reaction (qPCR), flow cytometry, enzyme-linked immunosorbent assay, and Western blotting to show that bone marrow MSCs produce a diverse array of growth factors and cytokines such as angiopoietin-1, BDNF, BMP-7, FGF-1, FGF-2, FGF-5, FGF-7, FGF-9, G/M-CSF, GDF-9, HGF, IGF-1, IGF-2, IL-6, IL-11, LIF, MCP-1, NGF- $\beta$ , SCF, SDF-1, TGF- $\beta$ 1, and VEGF<sup>[13,17,18]</sup>. While various single growth factor therapeutic regimens have been attempted with FGF, HGF, IGF, and VEGF, demonstrating impressive beneficial results in cardiac regeneration<sup>[19-22]</sup>, the MSC therapy is unique in its engagement of functionally synergistic trophic factors<sup>[5,23]</sup>, which may be required for efficient activation of the endogenous stem cell repair

mechanism and a more sustained therapeutic effect. Therapeutically, the repertoire of MSC trophic factors can act in synergy to (1) inhibit apoptosis and limit tissue injury; (2) attenuate pathologic fibrotic remodeling; (3) promote angiogenesis and vasculogenesis; (4) activate resident tissue stem cells; and (5) modulate host immune response and reduce inflammatory oxidative stress<sup>[3]</sup>.

Previous studies have shown that cells that are directly injected into the skeletal muscle bed are largely trapped in the local musculature<sup>[24]</sup>. To demonstrate that the trophic actions of MSCs underlie their cardiovascular therapeutic effects, we injected MSCs into the hamstrings of cardiomyopathic hamsters away from the myocardium, and confirmed that the intramuscularly injected MSCs were retained in the local muscular bed<sup>[25]</sup>. qPCR and histological cell-tracking assays revealed little, if any, cell migration from the injected site to other tissues, indicating that the vast majority of the injected MSCs were trapped in the musculature as expected. Despite this finding, the intramuscular MSCs significantly improved cardiac function by promoting heart cell regeneration<sup>[12]</sup>. Further, MSC-conditioned medium upon intramuscular injections was also found to be therapeutically effective for treating hamster heart failure, thus providing the ultimate proof for the critical role of trophic factors in stem cell therapy<sup>[12,13]</sup>.

## PARACRINE RESPONSE OF MUSCLE TISSUE

Skeletal muscle is a dynamic tissue with an adaptive capacity to continuously respond to environmental stimuli<sup>[26]</sup>. Its impressive ability to regenerate after injury or ischemic insult is coupled with the ability to produce many cardioprotective growth factors and cytokines. Indeed, the ability of skeletal muscle to function as a trophic factor-producing organ has increasingly been recognized<sup>[27-30]</sup>. Cytokines and growth factors produced and released by skeletal muscle, collectively designated as myokines, can potentially exert numerous trophic actions on other organs. Using both *in vivo* muscle injection and *in vitro* C2C12 skeletal myocyte culture, we have demonstrated muscle expression of several trophic factors such as HGF, IGF-2, NGF, and VEGF in response to trophic factor injections<sup>[31]</sup>. In addition, implanted stem cells have been found to stimulate host muscle cells to produce angiogenic factors, resulting in neovascularization<sup>[32,33]</sup>.

Delivery of MSCs by intramuscular injection offers a relatively noninvasive strategy as skeletal muscle, being the most abundant tissue in the body, is amenable to repeated injection of large numbers of stem cells. This approach if validated clinically is expected to facilitate future stem cell therapy. The intramuscular injection regimen for heart failure treatment draws significant comparison to the relation between active skeletal muscle and low cardiovascular risk, and highlights the critical link between the skeletal muscle and cardiovascular systems. Exercise training can promote muscle production of trophic factors including HGF, IGF, IL-6, and VEGF<sup>[27,28,34,35]</sup>, some of which have been

used in pre-clinical or clinical studies for cardiovascular therapy<sup>[19,20,36]</sup>. These effects of exercise have been shown to induce angiogenesis, mobilize bone marrow progenitor cells, and protect myocardium after infarction. Indeed, we found that the skeletal muscle in response to MSC injections produced many trophic factors in a more sustained fashion. The hallmark of this unique and relatively noninvasive cardiac repair regimen thus lies in the trophic cross-talk mechanisms mediated initially by the exogenous short-lived MSC-derived trophic mediators and subsequently by the myriad of endogenous muscle-derived trophic factors. These trophic factors collectively activate several signaling transduction pathways well known for their regulatory roles in cell growth, differentiation, and survival, e.g. those mediated by PI3K/AKT, ERK1/2, and JAK/STAT3. These data together indicate that skeletal muscle actively produces growth factors, and the trophic capacity can be further boosted in response to stem cell signaling *in vitro* and *in vivo*.

## ACTIVATION OF MUSCLE STEM CELLS

Whereas most tissue-specific stem cells are difficult to identify, muscle satellite (stem) cells can be readily identified based on their unique location between the plasma membrane and the ensheathing basal lamina<sup>[37,38]</sup>. In undamaged skeletal muscle, the majority of satellite cells are quiescent. Activated satellite cells caused by injury or exercise are able to proliferate, differentiate, and fuse to augment existing muscle fibers and to form new fibers<sup>[37,38]</sup>. Critical roles of stem cell niches have also been established for hematopoietic and intestinal crypt stem cells that can be recruited for tissue repair when required<sup>[39]</sup>. Stem cell activity is controlled by supporting extracellular matrix and cells in the immediate vicinity<sup>[40]</sup>. These influences can be mediated by direct cell contact or secretion of soluble products. Among the multiple trophic factors produced by MSCs, FGF-2, HGF, IGF-1, SDF-1, and VEGF have been shown to activate muscle satellite cells<sup>[41-45]</sup>. In this context, we have demonstrated that MSC injections causes activation of muscle satellite cells, which mediates effective formation of new myofibers and capillaries in both injected and non-injected muscles<sup>[25]</sup>. In addition, cell tracking studies revealed that the injected MSCs could directly participate in *de novo* capillary formation, although the extent to which this process might take place *in vivo* is probably limited<sup>[46]</sup>. Trophic factor actions further lead to the expansion of myocardial progenitor cells expressing c-kit, CD31, or CD133 markers<sup>[12,31]</sup>. Expansion of these cardiac progenitor cells in the diseased myocardium are thought to critically contribute to *de novo* cardiomyogenesis and angiogenesis necessary for cardiac regeneration<sup>[47]</sup>.

## MOBILIZATION OF BONE MARROW PROGENITOR CELLS

Mobilization of bone marrow progenitor cells plays an important role in tissue repair<sup>[48]</sup>. The MSCs used here have

been shown to express trophic factors such as HGF, LIF, G/M-CSF, SDF-1, and VEGF<sup>[13,17,18]</sup>, which are capable of mobilizing bone marrow progenitor cells. It should be noted that administration of G-CSF has been proposed as a potential new therapy for myocardial infarction<sup>[49]</sup>, and intramuscular injection of LIF plasmid DNA has been found to be cardioprotective<sup>[50]</sup>. Indeed, we detected elevated levels of circulating HGF, LIF, and M-CSF along with increased circulating c-kit<sup>+</sup>, CD31<sup>+</sup>, and CD133<sup>+</sup> bone marrow progenitor cells after MSC therapy<sup>[12]</sup>. The mobilized progenitor cells subsequently repopulate the diseased myocardium, and participate in endogenous cardiac repair mechanisms. Notably, we have obtained evidence that this cell mobilization mechanism becomes impaired in the old cardiomyopathic hamster, which may explain at least in part why the MSC therapeutic regimen fails to rescue the aging heart (see below). The molecular cross-talk between the injected MSCs and the bone marrow compartment illustrates the dynamic and functionally relevant signaling cascade involved in stem cell repair. The signaling cascade depicted here further activates myocardial expression of growth factor genes, highlighting an additional cross-talk mechanism between the injected MSCs and myocardium.

The effect of MSC administration on mobilization of bone marrow progenitor cells can be mimicked by administration of statins<sup>[51]</sup>, which are a class of HMG-CoA reductase inhibitors currently used clinically to lower cholesterol levels, retard the progression of atherosclerosis, and reduce death from cardiovascular disease<sup>[52]</sup>. Both MSCs and statins appear to mobilize bone marrow cells harboring the CD133 and/or c-kit surface markers, which are also expressed by some cardiac stem cells<sup>[12,51]</sup>. These circulating progenitor cells are thus likely to play a major role in contributing to myocardial regeneration, although detailed cellular and molecular mechanisms underlying this tissue repair process remain to be elucidated. It would be of interest to determine whether a combined MSC and statin therapy may more potently recruit bone marrow progenitor cells, resulting in a more effective cardiac therapeutic regimen.

## HOST TISSUE AS A MAJOR COMPETENCE FACTOR IN STEM CELL THERAPY

Aging and disease can greatly affect the environment in which stem cells are injected. Genomic, cellular, and structural damage elicited by reactive oxygen species increase with age and translate into impaired tissue function, and oxidative stress triggered by inflammation has been implicated in the pathogenesis of many diseases<sup>[53,54]</sup>. A major challenge encountered in stem cell therapy is rapid loss of most of the injected cells after implantation<sup>[25]</sup>. This is presumably caused in part by hostile diseased tissue environments usually infiltrated with inflammatory, fibrotic, fatty, and calcified components, making it difficult for the exogenously delivered stem cells to engraft and survive. Studies have suggested that old brains are less able to support

the expansion and differentiation of neuronal progenitor cells<sup>[55]</sup>. Although it is not clear if this is due to an intrinsic age-related deficit in neuronal progenitor cells, studies of endothelial progenitor cells have revealed disease- and age-associated functional impairment<sup>[56,57]</sup>. Interestingly, the degree of regeneration of the bone marrow stroma is inversely related to chronological age<sup>[58]</sup>, and while the basal hematopoietic capacity is maintained throughout life, the ability of hematopoietic stem cells to respond to stress and differentiation cues appears to decrease with age<sup>[59,60]</sup>.

Satellite cells of aging muscle exhibit a markedly impaired ability to produce myoblasts, which is associated with insufficient up-regulation of the Notch ligand Delta<sup>[61]</sup>. Increased Wnt signaling during aging further diverts satellite cells toward a fibrogenic lineage, contributing to increased tissue fibrosis with age<sup>[62]</sup>. Although the adult heart contains resident cardiac stem cells capable of supporting limited myocardial regeneration<sup>[47]</sup>, age-associated senescence of cardiac stem cells leads to a decreased number of cardiomyocytes and heart failure<sup>[63]</sup>. Consistent with these demonstrations, aged tissue has been found to be more refractory to stem cell therapy<sup>[64]</sup>, which may be associated with inadequate cell-matrix interaction and the presence of inhibitory elements. For instance, the extra lamina caused by the deposition of collagen in older dystrophic muscle<sup>[65]</sup> can potentially impede stem cell engraftment and survival. The presence of degraded fibronectin and elastin products can cause necrotic cell death<sup>[66]</sup>. Since the Notch signaling cascade in muscle satellite cells is mediated by myofiber expression of Delta, which is impaired in aged muscle<sup>[61]</sup>, changes in aged myofibers are expected to impact significantly on the efficacy of the intramuscularly implanted MSCs. Given that stem cell therapy primarily targets age-associated tissue dysfunction and degeneration, host tissue competence will need to be taken into consideration in future cell therapeutics.

## PERSPECTIVE

Stem cell therapeutics is entering into the clinical realm with much enthusiasm and optimism. Recent cardiovascular trial studies have demonstrated that growth factors and cytokines derived from the injected stem cells and host tissue appear to contribute largely to the observed therapeutic benefits. Thus, trophic actions rather than multilineage potentials (or stemness) of the administered stem cells are taking the center stage. Also emerging from these studies is that host tissue competence can greatly influence the outcome of stem cell therapy. Logistic aspects of stem cell therapeutics remain an area that requires urgent attention from the medical community. In cardiac repair for instance, intracoronary infusion or intramyocardial injection are mostly used for cell delivery. These delivery methods are invasive, often clinically unsuitable, and can introduce harmful scar tissue, arrhythmia, calcification, or microinfarction in the heart<sup>[67-70]</sup>. As demonstrated here with intramuscular injections of MSCs, stepping outside of the heart and taking an integrative therapeutic approach can offer an

innovative cardiac repair regimen, which, if validated clinically, could minimize many perceived side effects of stem cell therapy and reduce the treatment cost. Skeletal muscle can be a major source of therapeutic trophic factors due to the large body mass of the tissue, and activation of the skeletal muscle trophic factor network can potentially be an attractive therapeutic strategy for regenerative medicine. A better understanding of host tissue response in stem cell therapy is thus likely to provide additional insights for formulating logistically sound and therapeutically effective stem cell therapeutics.

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