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**Optimizing stem cells for cardiac repair: Current status and new frontiers in regenerative cardiology**

Der Sarkissian S *et al*. Optimizing stem cells for regenerative cardiology

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**Abstract**

Cell therapy has the potential to improve healing of ischemic heart, repopulate injured myocardium and restore cardiac function. The tremendous hope and potential of stem cell therapy is well understood, yet recent trials involving cell therapy for cardiovascular diseases have yielded mixed results with inconsistent data thereby readdressing controversies and unresolved questions regarding stem cell efficacy for ischemic cardiac disease treatment. These controversies are believed to arise by the lack of uniformity of the clinical trial methodologies, uncertainty regarding the underlying reparative mechanisms of stem cells, questions regarding the most appropriate cell population to use, the proper delivery method and timing in relation to the moment of infarction, as well as the poor stem cell survival and engraftment following administration especially in a diseased microenvironment which is collectively acknowledged as a major hindrance to any form of cell therapy. Indeed, the microenvironment of the failing heart exhibits pathological hypoxic, oxidative and inflammatory stressors impairing the survival of transplanted cells. Therefore, for any significant therapeutic benefit to be observed, there is a need to increase resilience of stem cells to death in the transplant microenvironment while preserving or better yet improving their reparative functionality. Although stem cell differentiation into cardiomyocytes has been observed in some instance, the prevailing reparative benefits are afforded through paracrine mechanisms that promote angiogenesis, cell survival, transdifferentiate host cells and modulate immune responses. Therefore, to maximize their reparative functionality, stem cell preconditioning and reprogramming by physical, genetic and pharmacological manipulations have shown promise to “prime” the cells to thrive in the post-ischemic transplant microenvironment. In the present work, we will overview the current status of stem cell therapy for ischemic heart disease, discuss the most recurring cell populations employed, the mechanisms by which stem cells deliver a therapeutic benefit and strategies that have been used to optimize and increase survival and functionality of stem cells including *ex vivo* preconditioning with drugs and genetic modifications.

**Key words**: Stem cell; Regenerative medicine; Cellular cardiomyoplasty; Preconditioning; Myocardial infarction; Heart failure; Viability; Paracrine activity; Transplantation

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**Core tip:** Cell therapy has the potential to improve healing of the ischemic heart, to repopulate injured myocardium and restore cardiac function in ischemic and non-ischemic cardiomyopathy. However, one of the biggest impediments lessening clinical effectiveness of cell therapy is the poor viability, retention and functionality of transplanted cells. This review looks as various stem cell *ex vivo* preconditioning and reprogramming methods aimed at enhancing the therapeutic potential of stem cells for heart failure treatment.

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**STEM CELL THERAPY FOR ISCHEMIC HEART DISEASE**

Considering the elevated morbidity and mortality of ischemic heart diseases, there is a pressing need to develop new therapeutic solutions to reduce ventricular remodeling, improve cardiac function and prevent development of heart failure (HF) following myocardial infarction (MI). For many of the patients, heart transplantation is a last resort option and its use is limited due to the scarcity of available donors. Therefore, myocardial stem cell therapy or cellular cardiomyoplasty is an approach that aims at inducing neoangiogenesis and even generating new functional myocardium. Many preclinical studies have involved transplanting cells in the border region of the infarcted myocardium to improve vascular supply, increase or preserve cardiomyocytes and repair damaged ones, and based on many positive findings, cell therapy has long been proposed as a potential treatment for HF[1-3]. However, recent clinical trials have reported much less remarkable results with meta-analyses reporting a mean increase in ejection fraction (EF) of approximately 3% to < 6%, with better results in patients with low EF, or if cell infusion is delayed at least 5 d after MI[4-7]. Randomized trials have also shown that the composite end point of death, infarction, revascularization, is significantly decreased at 12 mo, others have reported sustained benefits up to 5 years with reduced death and infarct size, improved myocardial perfusion and global cardiac function, whereas some have not found any profound long-term clinical benefit thereby advocating for cautious optimism in regards to cell therapy[5,8-10].

Clearly evidence shows there is much room for improvement that can only be achieved through the fundamental understanding of the stem cell biology and mechanisms for the therapeutic benefit afforded by these cells. We now understand that only a small portion of cells are retained in the myocardium and that their paracrine activity will promote cardiac repair through production of anti-inflammatory, pro-survival and angiogenic factors[11]. Indeed studies have shown that injection of stem cell conditioned media rich in these factors improve cardiac repair in HF models[12]. These factors are able to attenuate tissue injury, inhibit fibrotic remodeling, stimulate recruitment of endogenous stem cells and reduce oxidative stress[13]. Therefore, cell-mediated therapy may be viewed as providing “cytokine factories” for a sustained beneficial effect[14]. This is true of course only if the cells are retained long enough and remain viable in the transplant environment for this to occur.

**STEM CELLS USED IN REGENERATIVE MEDICINE**

Stem cells possess the capacity for prolonged proliferation, multilineage differentiation as well as trophic functions which enables tissue and organ repair[15-17]. Cell types used for cardiac repair include unfractionated bone marrow cells (BMCs) and mononuclear cells (BMMNCs), mesenchymal stem cells (MSCs), hematopoietic stem cells (HSCs), endothelial progenitor cells (EPCs), skeletal myoblasts (SkMbs), cardiac progenitor cells (CPCs), fetal cardiomyocytes, and embryonic stem cells (ESCs)[18-20]. Each cell type has its advantages and disadvantages for cell therapy applications. Therapeutic injection of stem cells into a host requires accurate cell selection based on differentiation potential, relative ease of isolation, availability in large quantities, *in* *vitro* expansion[21,22]. These cells are isolated from various sources. For instance, SkMbs are isolated by skeletal muscle biopsies and expanded *in vitro*. EPCs identified by the CD34 antigen which have shown the greatest potential for angiogenesis[23], can be isolated from the blood. Resident cardiac stem cells or cardiospheres could be isolated from biopsies, clonally expanded *in vitro* and differentiated into cardiomyocytes[24]. Bone marrow contains a heterogeneous cell population that includes differentiated cells and stem cells, such as HSCs, MSCs and EPCs. Due to its relative ease of accessibility and processing, as well as its ability to transdifferentiate into myocardial or vascular cells, BMCs have been readily used in clinical trials. However, contradictory benefits have been reported mainly since either unfractionated or sub-populations of BMCs with or without *in vitro* culture steps have been employed in various studies[25,26].

**MSCs**

MSCs are one of the best candidates for heart disease cell therapy due to their easy isolation, rapid expansion and safety[27]. MSCs retain their growth potential over several passages[28,29] and have the ability to differentiate into osteoblasts, chondrocytes, myocytes, fibroblasts, adipocytes and other mesenchymal phenotypes *in vitro* and *in vivo*[28,30-32]. In addition, MSCs are also immune-privileged because they express low levels of MHC II compared with MHC I[33]. They display immunosuppressive effects allowing successful allogenic transplantation. Many reports have shown improved recovery of ventricular function following MI with transplantation of MSCs in animal models[34] as well as an improvement in cardiac function and infarct size in human trials[29,35-38].

The safety and feasibility of intra-coronary MSC infusion and intra-myocardial delivery during coronary bypass grafting in post-MI patients has been demonstrated[33,39]. However, MSC-based therapy has the fatal limitation of poor viability of MSCs after cell transplantation[31]. Only approximately 5% of transplanted MSCs survive for 14 d in the infarcted porcine heart[40], whereas survival rate of human MSCs transplanted in an uninjured mouse heart is less than 0.5% at 4 d[31]. Similar results were obtained from studies using different cell types. For instance, about 7% of SkMb, 15% of smooth muscle cells, and 6% of unfractionated BMCs survived at 3 d to 1 wk in infarcted animal hearts[41-43]. Consequently, cell viability is likely a common barrier for any cell therapy approach for MI.

**HEMATOPOIETIC AND ENDOTHELIAL PRECURSOR STEM CELLS**

HSCs count for perhaps as few as 1:10000 bone-marrow cells and are known for their positivity for the CD34 cell surface marker. EPCs also residing in the bone marrow, have originally been defined by their expression of the CD133, CD34, and the vascular endothelial growth factor receptor-2 (VEGFR-2) markers. CD133 or prominin-1 is a highly conserved stem cell glycoprotein antigen described as marker for identification of early immature EPCs[44]. CD133+ cells migrate upon gradients of vascular endothelial growth factor (VEGF) and stromal-derived factor (SDF) *in vitro* and *in vivo*[45-47]. CD133+ cells *in vitro* differentiate into endothelial cells and release paracrine angiogenic cytokines. Differentiated CD133+ are capable of inducing capillary tubes *in vitro*[46,48-51] and several clinical trials have reported promising effects following infusion or direct intramyocardial injection of autologous CD133+ cells into ischemic hearts[52-56].

**TRANSPLANT CELL DEATH IN THE INFARCTED HEART**

One of the prime challenges of stem cell therapy consists in the survival, retention and differentiation of cells delivered in the harsh microenvironment of diseased tissues or organs[31,57-59]. Poor retention and survival of transplanted cells in the heart which can decrease to 39% at 1 h following injection as seen in human studies[60-64] or reach at most 21% in animal models following intramyocardial injection[65,66], further decrease exponentially thereafter due to apoptosis[31,57,67,68]. The increased cell death is swayed by various inflammatory response mediators, mechanical injury, hypoxia and ischemia-reperfusion stressors, and influenced as well by the donor cell source and quality[69]. Indeed, the cause of death of implanted cells may begin during the preparation step where MSCs for example, which are normally grown attached, are prepared in suspension in order to be injected. The loss of matrix attachments causes programmed cell death called “anoikis”[69-73]. Adhesion of cells to the matrix predominantly *via* integrin molecules represses apoptotic signaling, whereas detachment has the opposite effect. This effect is compounded by the hostile microenvironment of diseased myocardium which includes deprivation of nutrients and oxygen, upregulation of inflammatory mediators and low pH leading to poor transplant survival[70,74,75]. Moreover, myocardial injury generates an inflammatory response involving neutrophils and macrophages[76] which themselves produce inflammatory cytokines and reactive oxygen species (ROS) that may intensify the inflammatory response and anoikis signals and lead to cell death as well[77-79]. Indeed, co-injection of SkMbs with the ROS scavenger superoxide dismutase (CuZn-SOD) increases graft survival[43].

**MECHANISMS OF INFARCT REPAIR BY STEM CELLS: PARACRINE MODULATION OF ISCHEMIC ENVIRONMENT**

Several studies have shown that recruitment of endogenous stem cells or their delivery to injury sites results in structural regeneration and functional improvement[80]. While the original thesis regarding the beneficial mechanism pointed to stem cells and their differentiation within the host myocardium, we now understand that few if no exogenously administered cells engraft and differentiate[81-84]. It is rather the paracrine biomolecules produced by stem cells which account for the bulk of observed functional repair and these molecules also reduce cell death in cardiomyocytes and other populations thereby benefiting the diseased host tissue[85-89]. Stem cells secrete an array of cytokines, growth factors and extracellular matrix (ECM) components that act in an autocrine or paracrine manner. Cytokines are signaling and immune-modulating agents involved in cellular communication, whereas chemokines also produced by stem cells are involved in chemotaxis, while growth factors stimulate cell growth, proliferation and differentiation. Moreover, antioxidants, anti-apoptotic, anti-inflammatory or immunosuppressive molecules also secreted by stem cells can protect the cellular niche and transplant microenvironment from damaging mediators such as ROS. Finally, angiogenic and antifibrotic factors secreted by stem cells are responsible for tissue repair. In view of the numerous bioactive molecules produced and secreted by stem cells, current research using transcriptomic and proteomic technologies is poised at identifying the precise beneficial mediators and developing ways to harness these powerful pathways and mechanisms of repair[80,90-94].

The cardioprotective panel of stem cell secreted factors include bFGF/FGF-2, IL-1β, IL-10, PDGF, VEGF, HGF, IGF-1, SDF-1, thymosin-β4, Wnt5a, Ang-1 and Ang-2, MIP-1, EPO and PDGF[21,85-89,95]. FGF-2 reduces ischemia-induced myocardial apoptosis, cell death and arrhythmias, and stimulates increased expression of anti-apoptotic Bcl-2[96,97]. HGF, bFGF, Ang-1 and -2, and VEGF secreted by BMMSCs lead to augmented vascular density and blood flow in the ischemic heart[91,98,99], whereas SDF-1, IGF-1, HGF facilitate circulating progenitor cell recruitment to injury sites thereby promoting repair and regeneration[100-103]. Stem cells also secrete ECM components including collagens, TGF-β, matrix metalloproteinases (MMPs) and tissue-derived inhibitors (TIMPs) that inhibit fibrosis[104-106] and may thereby benefit cardiac tissue remodeling post-MI.

**STRATEGIES TO ENHANCE STEM CELL SURVIVAL**

It is clear that the injected stem cells must survive and thrive in the injured or diseased transplant environment for any significant repair to occur. Acute cardiac ischemia results in a hypoxic and inflammatory microenvironment which makes it extremely difficult for the injured area to be functionally repaired[107-109]. Consequently the injected cells will need to be tolerant of these deleterious conditions[110-113]. For this, *ex vivo* manipulation of cells has been used to overcome cell survival issues as well as to enhance metabolic characteristics in order to confer cells with a powerful advantage in the critical early days after transplantation. Preconditioning, or pre-treating and reprograming cells by physical/environmental, pharmacological, genetic manipulations or with cytokine and growth factor treatments has shown great potential to prime cells to withstand the rigors of the transplant microenvironment post-ischemia and maximize the cells’ biological and functional properties. In addition, there are strategies to modify the transplant environment through immune modulation and even by increasing cell retention with bio-scaffolds.

**PRECONDITIONING STEM CELLS USING PHYSICAL/ENVIRONMENTAL CHALLENGES**

Beneficial effect of preconditioning was first demonstrated by treating healthy heart with intermittent cycles of non-lethal ischemia followed by reperfusion. This manipulation protected the myocardium from a subsequent important ischemic episode[114]. Subsequently, various strategies including hypoxic, oxidative and thermal conditioning challenges have been studied in an attempt to improve stem cell survival[115-118]. Low oxygen culture conditions (0.5% O2 for 24 h) have been shown to trigger survival pathways in MSCs before their engraftment *in vivo*[119]. MSCs exposed to hypoxia *in vitro* showed upregulation of Bcl-2 and Bcl-XL survival genes, promoting reduced infarct size and enhanced cardiac function[119]. Hypoxia preconditioning also increases *in vitro* expression of antiapoptotic genes such as Akt and eNOS[81,88,116]. Hypoxia treated cells show significantly improved survival post-engraftment in the infarcted heart[119]. Also, during ischemic preconditioning, hypoxia inducible factor-1α (HIF-1α), a master regulator of genes responsible for low oxygen survival signaling[119-121], stimulates the transcription of VEGF and erythrogenin that increase cellular oxygen availability by promoting angiogenesis and erythropoiesis[122,123]. In addition to VEGF, temporary exposure to hypoxia increases expression of many growth factors including bFGF, HGF, IGF-1, and thymosin-β4[124,125] which are implicated in cell mobilisation and apoptosis.

In addition to promoting pro-survival and cytoprotective effects, hypoxic preconditioning supports cells to preserve their stemness and promote their differentiation and proliferation potential post-engraftment[116,126-129]. Furthermore, BMMSCs exposed to anoxic conditions and transplanted into infarcted myocardium have been shown to exert increased protective effects on cardiomyocytes[130]. Thus, hypoxic treatment may lead to enhanced donor and host cell survival in ischemic environments and provide functional benefits.

Burst exposure to low levels of oxidative stress *in vitro* also increases stem cell viability as seen for example by the exposure of CPCs *in vitro* to low concentration of H2O2 prior to implantation in ischemic rat hearts[131]. Similarly, NPCs exposed to non-cytotoxic low dose treatment of H2O2 demonstrated improved resistance to lethal oxidative stress[132], and MSCs preconditioned with H2O2 and transplanted in the ischemic heart display increased viability and functional improvement[133].

Heat shock treatment is also an interesting approach to enhance cell survival. Heat shock protein (HSP) generation can be achieved by exposing cells to elevated temperatures (39 °C to 45 °C). Thermal shock of primary cardiomyocytes has been shown to result in increased expression of HSP70 thereby protecting the cells from *in vitro* and *in vivo* oxidant stress[134,135]. Transplantation of human ESC-derived cardiomyocytes treated by 30 to 60 min of 43 °C heat upregulates HSPs such as HSP60, 70, and 90 has been shown to improve graft functionality in a rat model of MI injury[136,137]. Exposing MSCs to elevated temperature (43 °C) also induces secretion of HSPs, including HSP27 and HSP70[138] which may contribute to increased cell survival. Similarly, culture of CPCs at 42 °C has been shown to reduce apoptosis, increase functionality, and reduce fibrosis of mouse ischemic myocardium[139]. Considering the role of HSPs in cell protection and immune modulation, thermal conditioning represents an easy and effective means of increasing cell viability, retention and consequently improving stem cell graft function.

**PRECONDITIONING STEM CELLS WITH DRUGS**

The effectiveness of preconditioning on cell viability and function can also be achieved by pharmacological treatments[118]. Other than the initiation of survival signaling, treating cells with conditioning mimetics causes release of growth factors and cytokines that exert protective and angiomyogenic effects. Preconditioned cells show greater release of growth factors including VEGF, Ang-1, SDF-1α, HGF, and IGF[118]. Several drugs including mitochondrial potassium channel openers that promote influx of K+ through ATP-sensitive K+ channels (mitoKATP) are useful agents altering the apoptotic cascade by preventing cytochrome c release[140-143]. Pinacidil or Diazoxide, well-known non-selective mitoKATP channel openers have been demonstrated to suppress apoptosis[144-146]. SkMbs and BM-MSCs treated with Diazoxide demonstrated increased cell survival in ischemic environment, and increased secretion of Ang-1, bFGF, HGF and VEGF by preconditioning was proposed to augment angiomyogenesis[146,147].

HMG CoA reductase inhibitors (Statins) appear promising in blocking apoptosis, prolonging stem cell survival and improving organ repair. Treatment with atorvastatin for example enhances cell survival and differentiation into cardiomyocytes, decreases the infarcted area, promotes angiogenesis, and reverses the ventricular remodeling processes[148]. Also, *ex vivo* statin treatment has been shown to prevent impairment of the functionality of EPCs *in vitro* as well as the loss of telomere repeat-binding factor 2 (TERF2), whose expression is reduced in end-stage human HF, and functions to prevent cells from entering in apoptosis or senescence[149,150]. A recent review provides encouraging basis for the use of statins to increase the number and/or function of MSCs and EPCs for cell therapy[151].

Preconditioning cells with naturally occurring hormones such as Oxytocin (OT) or its synthetic analog drug (Pitocin) is another means for stem cell optimization. Indeed, OT preconditioning of various cell types makes them resistant to oxidative stress[152], and primes stem cell differentiation into cardiomyocytes[153] and vascular cells[154]. MSC express a functional OT receptor (OTR) which mediates glucose uptake[155] and cell differentiation[156] it has been shown that OT modulates gene expression for adhesion molecules and MMPs involved in cellular migration[154,157,158]. Our group showed that OT treated MSC respond with rapid calcium mobilization and upregulation of the protective pAkt and pErk1/2 proteins. Functional analyses revealed the involvement of these kinase pathways in cell proliferation, migration, and protection against apoptotic effects of hypoxia and serum starvation. OT preconditioning increased upregulation of genes with angiogenic, anti-apoptotic and cardiac anti-remodeling properties such as HSP27, HSP32, HSP70, VEGF, thrombospondin, TIMPs and MMPs, and co-culture of cardiomyocytes with OT-preconditioned MSC reduced apoptosis[159].

Various other classes of drugs and chemicals have also shown potential for use as stem cell *ex vivo* conditioning agents. Treatment of BMMSCs with trimetazidine (1-[2,3,4-trimethoxybenzyl] piperazine), an anti-ischemic drug for angina treatment has been shown to increase cell viability in response to oxidative stress[160]. Also, treatment of rat BMMSCs with β-mercaptoethanol was shown to upregulate HSP72 resulting in improved resistance to oxidative injury[161] Also, the pan caspase inhibitor ZVAD-fmk has been shown to increase engraftment of HSC during intra-bone marrow transplantation procedure in allogeneic mice[162]. This said, one has to be mindful of the balance between enhancing stem cell survival and enabling unintended carcinogenic effects when selecting compounds in the development of as stem cell pharmaco-enhancers.

Finally, a means to favor stem cell differentiation would constitute an interesting pharmacological conditioning method for improving graft function. Small molecules such as 5-Azacytidine (5-AZA), a DNA demethylating agent[32], have been shown to prime cardiac differentiation in MSCs. Other molecules including the HSP90 inhibitor Geldanamycin[163], the kinase inhibitor Imatinib Mesylate[164] and the proteasome inhibitor Bortezomid[165] have been shown to instruct stem cell commitment to various lineages.

**A NOVEL PHARMACO-CONDITIONING AGENT**

Celastrol is an antioxidant molecule extracted from the root of a vine (*Tripterygium wilfordii*) which has showed beneficial effects in the treatment of various diseases including cancer, neurodegenerative diseases, autoimmune diseases, and inflammatory conditions[166-171]. We are the first to report Celastrol’s efficacy as a potent infarct sparing agent[172] and we propose its use as a stem cell optimizer considering in part Celastrol’s targeting and activation of two very potent cellular defence mechanisms: The heat shock response (HSR) and the antioxidant response (AR). HSR leads to cell protection against various physiological stresses[173,174] *via* activation of HSP. HSR is regulated at the transcriptional level by the activation of heat shock factors with heat shock factor 1 (HSF1) being the master switch for HSP expression[174]. The AR is mediated by the transcription factor nuclear factor (erythroid-derived 2)-like 2 (NRF2). NRF2 is a key controller of the redox homeostatic gene regulatory network including antioxidant proteins and Phase II enzymes such as glutathione S-transferase, heme oxygenase 1 (HO1), NADPH-quinone oxidoreductase 1 (NQO1), superoxide dismutases 1-3 (SOD1-3), catalase (CAT), thioredoxin (TRX), glutathione peroxidase (GPx), and non-enzymatic antioxidants such as glutathione which exert protective, antioxidant, and anti-inflammatory effects[173-176]. Under homeostatic conditions, HSF1 is bound and silenced by its natural repressor HSP90 chaperone, and NRF2 is similarly repressed by KEAP1 (Kelch-like ECH-associated protein1). During oxidative and electrophilic stress (ROS increase), NRF2 is liberated from KEAP1 and binds to antioxidant response elements (ARE) in the promoter region of genes including HO-1. Similarly, during cellular stress, HSF1 translocates to the nucleus where it binds to heat shock elements (HSE) as a phosphorylated-trimer and drives the transcriptional activity of HSPs[177]

Briefly, Celastrol targets the interaction between HSP90 and its essential cofactors (*i.e.*, Cdc37)[178], and through HSP90 functional inhibition, Celastrol promotes HSF1 release and HSR activation. Similarly, through a ROS/KEAP1/NRF2 pathway Celastrol activates the AR[179]. Together, Celastrol activates the two evolutionary conserved cellular protective mechanisms as detailed above and is able to stimulate a powerful endogenous protective effect that could be harnessed to increase viability and therapeutic efficiency of stem cells.

**PRECONDITIONING STEM CELLS WITH GROWTH FACTORS AND CYTOKINES**

Pre-treating stem cells with growth factor (GF) is a simple and safe strategy to improve cellular survival, proliferation and differentiation. For example, preconditioning EPCs by culturing them in medium supplemented with VEGF, activates Akt and significantly reduces apoptosis in a dose-dependent manner[180]. Also, by exploiting the SDF-1/CXCR4 ligand/receptor interaction which modulates cell growth, proliferation, survival, migration and transcriptional activation[21,181-184], SDF-1 can be used as a preconditioning chemokine[185]. Indeed, treatment with recombinant SDF-1 enhanced vascular density and survival of cells under anoxic condition *in vitro* and following engraftment in the infarcted heart[185]. Also, it has been shown that IGF-1 preconditioning of bone marrow-derived Sca-1+ cells upregulates connexin 43 which improves survival and integration of cells with host myocytes[186]. The anti-apoptotic effects of IGF-1 are mediated by IGF-1/IGF-1R ligand/receptor interaction which involves PI3K/Akt and MAPK/Erk1/2 activation, whereas knockdown of connexin 43 rescinds cell viability to hypoxia *in vitro* and *in vivo* in the infarcted heart.

An additional strategy may consist of preconditioning cells with anti-inflammatory cytokines such as interkeulin-10 (IL-10) which promotes multiple effects including down-regulation of Th1 cytokines such as IL-2, IFN-γ, TNF-α, and increase expression of the cell survival gene Bcl-2 thereby increasing stem cell survival[187]. It also has been demonstrated *in vitro* and *in vivo* that in the presence of IFN-γ, MSCs suppress T-cells and graft versus host disease[188-190].

***EX VIVO* GENETIC OPTIMIZATION OF STEM CELLS**

***Survival, differentiation and angiogenesis as targets***

Stem cells are excellent vehicles for therapeutic gene delivery and can be genetically engineered for gene overexpression. Transgenes can encode for a myriad of beneficial factors including angiogenic and chemoattractant factors, anti-apoptotic proteins and growth factor(s) of interest[181,191-193] and serve as a continuous source for these to mediate sustained intracrine, autocrine, and paracrine effects. Indeed, molecules secreted by transgene-modified MSCs may have different therapeutic profiles compared with normal MSCs. For example, transformation of stem cells to overexpress IGF-1 promotes donor cell survival, engraftment, and differentiation in cardiac cell therapy[194-196]. IGF-1 induces expression of the pro-survival genes PI3-kinase, Akt, Bcl-xL and SDF-1 which is a potent chemoattractant of stem cells. Indeed, IGF-1 transformed MSC improve EF and fractional shortening in an infarct model[197]. Cells have also been manipulated to overexpress Ang-1, HGF, VEGF and MyoD for post-MI myocardial repair. Results show increased cell engraftment, angiogenesis and commitment to the myogenic lineage in the ischemic region[100,198-205]. Indeed, any therapeutic approach aimed at increasing vascularization within the ischaemic heart tissue will improve functional repair and recovery of the infarcted myocardium. One of the key proteins is VEGF whose overexpression will promote a strong pro-angiogenic signal. VEGF has been shown to promote endothelial cell survival[206,207], and myocardial transfer of VEGF-transfected MSCs lead to better improvement of myocardial perfusion and heart function following ischemia[192,208]. Studies evaluating other angiogenic and myogenic genes with various VEGF isoforms, PDGF and TGF-β1, have also suggested enhancement of cell therapy efficacy[209]. VEGF is itself regulated by the transcription factor HIF-1α which plays a critical role in the stabilization of VEGF transcription during hypoxia[210,211]. Therefore, HIF-1α overexpression has also been evaluated as an means to optimize BMMSCs for increased VEGF expression[212].

Stem and progenitor cells have also been engineered to survive and engraft more effectively in hostile environments[213,214]. Transfection of MSCs with growth factors such as bFGF shows increased survival in hypoxic conditions. These transformed cells also improve neovascularization compared to non-transformed MSCs[215]. Interestingly, Akt-modified BMMSCs exhibit resilience to apoptosis through secretion of growth factors such as bFGF, HGF, IGF-1 and VEGF, as well as secreted frizzled-related protein 2 (Sfrp2) which exerts a beneficial effect on the infarcted heart post-engraftment by antagonizing pro-apoptotic properties of Wnt3a. Together, secretion of these factors known to exert pro-angiogenetic, cardioprotective and inotropic actions[125] is increased under hypoxic conditions[81,125,216]. Transplantation of Akt-modified BMMSCs in the infarcted myocardium safeguards surviving myocardium for up to 2 weeks post-MI at least in part through paracrine actions[217]. In another study, MSCs overexpressing both Ang-1 and Akt provide long-term therapeutic benefits for preventing apoptosis in an ischemic heart up to three months after initial transplantation[218]. This said, it is interesting to note that medium from BMMSCs overexpressing Akt cultured under hypoxic conditions show an increase of many beneficial molecules including VEGF, FGF-2, HGF, IGF-1, and TB4, and trigger an increase in contractile response of cultured rat cardiomyocytes as well as improves ventricular function in a rat infarction model[125]. In addition to Akt overexpression, BMMSCs have been engineered with anti-apoptotic genes such as Bcl-2 and HO-1. Bcl-2 overexpression in BMMSC decrease apoptosis of BMMSCs and increases VEGF secretion and capillary density in the infarct border zone thereby increasing functional recovery in ischemic myocardium[124]. HO-1 exerts potent antioxidant and cytoprotective activity in the ischemic environment[219,220]. HO-1 transfected MSCs are resistant to apoptosis and inflammatory injury and display improved tolerance to ischemia-reoxygenation injury harsh transplant microenvironments[221]. Another opportunity to enhance transplanted cell survival in the damaged heart is to transfect them with recombinant HSPs, that represents a family of inducible and constitutively expressed proteins responsible for potent increase in cell tolerance to environmental stress including ischemia, hypoxia, oxidative injury, heat stress, and ischemia-reperfusion injury[222]. Indeed, cells transfected with HSP encoding genes, namely HSP70, are protected from ischemic injury *in vitro* and *in vivo*[223-226].

In order to procure a holistic coverage of survival and growth effects, combination treatment of stem and progenitor cells can be achieved prior to their transplantation. Combined overexpression of Akt and Ang-1 has been attempted in MSC. Ang-1, a potent modulator of vascular development activates survival signaling[227-229], and co-expression with Akt was shown to be more effective for cytoprotection in the context of lethal anoxia[230]. Simultaneous overexpression of Akt and Ang-1 in MSC transplanted in infarcted rat heart conferred better engraftment, and cells were able to adopt myogenic and endothelial phenotypes. Combination treatments may also be more ambitious by including various components such as a collagen matrix (matrigel) to increase retention and prevent anoikis, Bcl-xL and Cyclosporine A to block mitochondrial death pathways, an inducer of mitoKATP channel opening such as Pinacidil or Diazoxide to mimic ischemic conditioning, a caspase inhibitor such as zVAD-fmk and IGF-1 to activate Akt pathways as previously described[136].

***Adhesion as a target***

Adhesion is necessary for cell survival and is a key factor for MSC differentiation. Disruption of cell-ECM contact with trypsinization may facilitate apoptosis once cells are transplanted. Therefore, over-expression of adhesion molecules may enhance cell retention and improve viability. For example, tissue transglutaminase (tTG) over-expression in MSC leads to increased survival *via* an integrin-dependent mechanism[231]. tTG also acts as a coreceptor for fibronectin (Fn)[232,233] and enhances adhesion by bridging integrins and Fn or by mediating formation of ternary complexes[234]. Compared to simple MSC transplantation, tTG transformed MSCs have been shown to better restore cardiac function of infarcted myocardium[231]. Also, transfection of the integrin-linked kinase (ILK), a 59-kDa Ser/Thr kinase that binds to the cytoplasmic domain of -integrin and participates in cell adhesion, growth, and ECM assembly, activates Erk and Akt phosphorylation which play important roles in cell survival during hypoxia[77,235-238]. Transplantation of ILK-MSCs has been shown to further reduce infarct size, improve left ventricle function and increase microvessel density[239].

***Stem cell rejuvenation as a target***

Increasing evidence supports the concept of senescence affecting tissue resident stem cells and diminishing regenerative capacity of organs[240-242]. Cellular senescence is induced by multitude of stressors including hypoxia and oxidative conditions[243-245] which reduces the cell’s proliferative, differentiation and metabolic potential, and upregulates apoptotic markers[246-255]. At the genomic level, aging appears associated with increase in p53-associated genes in addition to modulation of telomere, mitochondrial and apoptotic process[255,256]. These age related changes limit the ability of stem cells to secrete angiogenic factors thereby reducing their regenerative potential. It has been shown that MSCs from old patients are less effective in preventing ventricular remodelling and inducing new vessel formation post-MI[248]. Old donors exhibit reduced tolerance to ischemia and decreased transplant survival within ischemic muscle[251]. Similarly, older recipients have a diminished therapeutic response to receiving stem cells from donors of any age[251,254]. To overcome these effects related to cellular senescence, many strategies are being developed as recently reviewed[257]. In this regard, modifications to improve regenerative capacity have been sought[30,81,258,259] and include genetic modification of human CPCs with Pim-1, a pro-survival downstream effector of cytokine signalling pathways[260] including Akt[261], in order to improve cellular metabolic activity[262]. The wingless integration (WNT)/β-catenin pathway has also been studied as a potential target for MSC rejuvenation[263]. While increasing age is associated with reduced MSC proliferation, differentiation capacity and WNT/β-catenin signalling, lithium treatment which increases β-catenin bioavailability restores the impaired function of these cells[257].

**CONCLUSION**

The use of stem cells to regenerate heart muscle has revolutionized the clinical practice for ischemic heart disease treatment. While safety and feasibility of cell therapy has been demonstrated in experimental and clinical studies, and the technology is making its way from bench to bedside, in order to reap the full regenerative potential afforded by stem cells, there is a necessity to develop the tools and the understanding required to ameliorate clinical efficacy. Most importantly, in order to harness the full therapeutic potential of these cells for cell therapy or any regenerative medicine application, optimization of cell viability, retention and functionality are of utmost importance. As summarized here, many groups are currently investigating various avenues of stem cell optimization. These methods include cell preconditioning using environmental stressors, genetic manipulations to enhance survival pathways, increase angiogenesis and cell adhesion, as well as preconditioning methodologies involving *ex vivo* stimulation of stem cells with growth hormones, cytokines and pharmacological agents such as statins and conditioning mimetics. The latter pharmacological method may be one of the safest, quickest, most reproducible, reliable and readily transferable method to the clinic used for producing optimized cell populations for patients. It is also foreseeable that in order to further enhance the therapeutic quality of these cells, multiple cellular pathways and effectors may be targeted, drug cocktails may be developed, or even conditioned cells may be combined with hydrogel technologies to encapsulate cells in a favorable environment to further promote retention, limit anoikis and facilitate cell-cell and cell-matrix interactions. All of these upcoming advances in stem cell optimization will greatly benefit patients and the promising field of regenerative medicine in the coming years.

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