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Current Status of Stem Cell Therapy in Heart Failure

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Abstract

Inspired by studies demonstrating the potential for new myocyte formation within adult mammalian hearts, an ongoing explosion of research is elucidating the biology of cardiac myogenesis and angiogenesis. Multiple lines of research suggest that disease-associated activation of endogenous cardiac repair processes are often insufficient to overcome the cell death resulting from myocardial infarction and chronic heart failure. In this context, this review highlights current evidence supporting endogenous cardiac repair mechanisms in human hearts, recent progress with clinical application of myocardial cell therapy, and complementary efforts to manipulate endogenous myocardial repair processes using a variety of tissue engineering strategies. The goal of this overview is to demonstrate that the insights and opportunities derived from each of these lines of inquiry are mutually complementary for ultimately achieving the goal of therapeutic cardiac regeneration.

Keywords

Stem cell therapy; Bone marrow cells; Progenitor cells; Tissue engineering; Endogenous cardiac repair

Introduction

Heart failure (HF) is a leading cause of disability and death that accounts for approximately 1 million hospitalizations, over 50,000 deaths, and almost \$35 billion in health care costs in the United States each year [1]. Despite therapeutic advances in the treatment of myocardial infarction (MI), hypertension, valvular heart disease, and cardiomyopathies, the prevalence of HF continues to grow. Mortality rates remain high, with 50% of HF patients dying within 5 years of initial diagnosis.

Progressive loss of cardiac myocytes, due to MI and/or programmed cell death (apoptosis), is a feature of most causes of HF. Therefore, therapies to increase the number of functional cardiac myocytes could improve the course of this syndrome. Propelled by iconoclastic studies demonstrating the potential for new myocyte formation within adult mammalian hearts, there has been an explosion of research aimed at promoting therapeutic cardiac regeneration during the past decade. In this context, this review highlights current evidence

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supporting endogenous cardiac repair mechanisms in human hearts, recent progress with clinical application of myocardial cell therapy, and complementary efforts to manipulate endogenous myocardial repair processes using a variety of tissue engineering strategies. This perspective reveals a number of potentially productive synergies among these ongoing inquiries, as illustrated in Fig. 1.

Endogenous Cardiac Repair

Increasing evidence supports the existence of endogenous cardiac renewal and repair mechanisms that could contribute to normal homeostasis and the responses to pathologic insults. In humans, some of the strongest data comes from sex-mismatched transplanted hearts (male recipient, female donor) in which Y chromosome-positive cardiac myocytes (as well as endothelial cells and smooth muscle cells) have been found within the cardiac allografts obtained from a female donor. Although the rates of this phenomenon vary considerably in different reports [2, 3], higher rates of allograft chimerism were observed when the donor hearts suffered acute ischemic events [3], suggesting that host-derived progenitor cell recruitment may be injury responsive. In addition, Urbanek et al. [4] reported increases in endogenous cardiac stem/progenitor cells (S/PCs) in hearts from patients who died from acute MI and, to a lesser extent, in patients with end-stage chronic post-MI cardiomyopathy.

In animal models, recent reviews highlight studies demonstrating activation of endogenous cardiac repair processes in response to experimental cardiac injury [5, 6]. Some studies used bone marrow ablation and reconstitution with cells expressing green fluorescent protein (GFP), and then reported GFP-labeled cardiac myocytes, vascular cells, and fibroblasts within and around the infarcted myocardium [7]. Other studies used direct myocardial injection of enriched and labeled S/PCs derived from autologous sources [8] or from allogeneic donors, including humans [9]. Most studies indicated that local myocardial injury augments cell engraftment into the recipient myocardium, but other studies suggested a high rate of attrition for these newly engrafted cells [10].

The degree to which endogenous S/PCs contribute to the native response to myocardial injury and failure in the adult mammalian heart remains a key unresolved question. Studies in mice by Fazel et al. [11] indicated that MI triggers homing of bone marrow-derived progenitors expressing the stem cell surface marker c-kit to the murine heart. This homing of bone marrow stem cells to the heart was associated with angiogenesis and reduced post-infarct dilation [11]. Because very few mature cardiac myocytes or blood vessels were derived from the GFP-labeled bone marrow cells (BMCs), this report concluded that secretion of angiogenic cytokines by bone marrow-derived c-kit⁺ cells was responsible for their beneficial impact [11]. However, subsequent studies by Hsieh et al. [12], using a fate-mapping approach in mice, reported that early increases in myocardial c-kit⁺ cells following experimental MI or pressure overload, were correlated with new cardiac myocyte formation. Together, these studies in animal models indicate that myocardial injury and failure induce a demonstrable, but relatively minor, endogenous repair response [11, 12].

Extending the fate-mapping studies by Hsieh et al. [12] to humans, Bergmann et al. [13] used an analogous approach to demonstrate and quantify the cardiac myocyte renewal that occurs in adult human hearts. Recognizing that an era of nuclear bomb tests between 1955 and 1963 (when the Nuclear Test Ban Treaty was signed) produced a spike in atmospheric carbon-14 (¹⁴C), these investigators used cardiac-specific markers (cardiac troponin I and cardiac troponin T) to identify and isolate cardiac myocytes from hearts obtained at the time of autopsy. Because the ¹⁴C content of myocyte DNA should reflect the atmospheric ¹⁴C level at the time of cell formation, differences between the actual ¹⁴C content of DNA and

the predicted level based on atmospheric ^{14}C levels provide a means of identifying net cell replacement. Higher than expected ^{14}C myocyte DNA levels observed among those born before 1955 and the lower than expected ^{14}C myocyte DNA levels observed among those born after 1963 supported the replacement of some myocytes during adult life. Even after accounting for previously described myocyte nuclear division up to the age of 10, these investigators estimated that about 1% of cardiac myocytes are replaced annually at the age of 25 and that this rate gradually decreases to about 0.45% annually by age 75. These findings demonstrate low rates of durable cardiac myogenesis in the adult heart, but do not define whether these new cardiac myocytes are derived from the adult cardiac myocytes re-entering the cell cycle or from an S/PC pool from within or outside the heart.

Studies isolating viable cardiac progenitors complement these observations and affirm the existence of functionally relevant, although usually insufficient, native cardiac repair mechanisms in adult human hearts. In one type of study, typified by the work of Smith et al. [9•], S/PCs were isolated from multicellular aggregates, termed cardiospheres, that were derived by culturing fragments of human endomyocardial biopsies. These cardiac-derived human S/PCs typically expressed c-kit, were capable of in vitro proliferation, and were passaged in vitro. Although in vitro culture and expansion requires weeks to months, these cells retained the capacity to undergo differentiation into cardiac myocytes during co-culture with neonatal rat cardiac myocytes and contribute to new cardiac myocyte and endothelial cell formation when engrafted into the regions bordering a new MI in the hearts of immunotolerant mice. Complementary studies from our laboratory isolated c-kit⁺ cardiac S/PCs from human hearts within hours of their explant during organ donation and cardiac transplantation [14•]. Consistent with previous studies using histologic approaches, we observed three- to fourfold more S/PCs in severely diseased versus nonfailing hearts, and these c-kit⁺ cells were capable of undergoing cardiac myocyte differentiation during co-culture with neonatal rat cardiac myocytes. Although functionally immature, these newly differentiated human cardiac myocytes exhibited action potentials that are clearly distinct from those of rodent myocytes and are also capable of in vitro electrical coupling. In contrast with previous studies using S/PCs expanded in vitro [9•], freshly isolated human S/PCs usually expressed the pan-leukocyte marker CD45, suggesting their possible bone marrow origin [14•].

Taken together, these findings indicate that cardiac S/PCs, often expressing the c-kit stem cell marker, can be identified within virtually all human hearts. Acute MI and/or HF promotes increases in the abundance of c-kit⁺ cells in human hearts, and c-kit⁺ cardiac-derived progenitor cells can be induced to differentiate into new cardiac myocytes that display electrophysiologic characteristics suggesting immaturity. While ^{14}C fate-mapping studies (and sex-mismatched heart transplants) suggest a low net rate of cardiac myocyte replacement in the absence of physiologic stress, greater cardiac S/PC abundance in diseased hearts suggests increased homing and/or proliferation of extracardiac S/PCs to the heart in the setting of injury or heart failure. At the same time, the observation that MI often leads to progressive myocardial dysfunction and pump failure also indicates that the recruitment, differentiation, and/or survival of endogenous progenitors and new myocytes is insufficient in many failing hearts. This general inadequacy of native myocardial repair responses combined with a recognition that new myocyte formation is possible in the adult mammalian heart has propelled a robust effort within the clinical research community to develop effective stem cell therapy for infarcted and/or failing human hearts.

Cell Therapy Clinical Trials

Encouraging results from animal studies prompted dozens of clinical trials for stem cell therapy. Debate continues over the optimum cell sources, cell processing, delivery methods,

timing, and other variables. Nevertheless, this section highlights the overall effectiveness of alternative myocardial cell therapy strategies that have been explored to date. It also highlights several ongoing trials using new sources of S/PCs that will provide new insights into which therapeutic strategies are most promising for achieving cardiac regeneration in clinical settings.

Autologous Skeletal Myoblasts

The first attempts to use autologous stem cells to repair the human heart focused on skeletal myoblasts introduced through myocardial injection after an MI. After several pilot studies suggested that skeletal myoblasts could improve contractility [15], the MAGIC trial was the first randomized controlled trial (RCT) to evaluate myoblast therapy. At the time of coronary bypass grafting, 97 patients were randomized into three groups: low-dose myoblasts, high-dose myoblasts, and control (cell-free injection) via direct myocardial injection (~30 sites). This study failed to demonstrate efficacy with skeletal myoblast therapy while reporting a doubling in rate of arrhythmias among patients receiving the myoblasts. Although interest in skeletal myoblasts as an autologous cell therapy waned after these results were reported, recent results from a double-blind, controlled pilot study of autologous skeletal myoblasts in patients with healed MI (MARVEL-1) have rekindled interest in this approach. In this 20-patient pilot study, patients receiving transvascular injection of autologous myoblasts into an area of established scar had a mean increase of 91 m during a 6-minute walk test at 6 months after treatment compared with a mean decrease of 4 m in the vehicle-treated controls [16]. An increase in ventricular arrhythmias among myoblast-treated patients was usually suppressed with amiodarone. Based on these encouraging preliminary results, a larger follow-up trial has been initiated.

Mobilization of Bone Marrow Progenitors

The vast majority of clinical trials of cardiac cell therapy have focused on autologous bone marrow progenitor cells (BMPCs). The first BMPC trials delivered granulocyte colony-stimulating factor (G-CSF) to the bloodstream post-infarction in an effort to stimulate progenitor cell release from the bone marrow, but did not involve administration of BMPCs directly. This strategy was shown to temporarily increase circulating progenitor concentration, as defined by concentration of CD34⁺ cells [17]. However, placebo-controlled, double-blind clinical trials such as STEMMI [18] found no improvement for G-CSF treatment over controls. A meta-analysis of four blinded and six non-blinded trials found no statistically significant improvement in ejection fraction (EF) or decrease in infarct size when using G-CSF [19]. For this meta-analysis, G-CSF doses ranged from 2.5 to 10 µg/kg per day for delivery periods of 4 to 10 days. Delay between coronary angioplasty and treatment ranged from 90±35 min in the FIRSTLINE-AMI trial to 5 days for the MAGIC-Cell and REVIVAL-2 trials. Based on these findings, direct cell administration to the heart has emerged as the dominant therapeutic approach in recent clinical trials, although G-CSF may be used in conjunction with other interventions.

Direct Delivery of Unfractionated BMCs

Following a series of small interventional trials, several larger RCTs have been performed using the direct injection of BMCs into the coronary arteries or myocardium. Several studies showed modest but consistent improvements in cardiac performance and overall mortality, although the mechanism for their benefit remains uncertain. REPAIR-AMI, the largest RCT to date, included 204 patients and found that delivering bone marrow S/PCs 4 days post-MI increased left ventricular EF (by 3.2%±1.3%) at 4 months. Although the difference compared with placebo was lost by 12 months, a subanalysis focusing on patients with a baseline EF below the median of 48.9% had statistically significant increases in EF compared with placebo throughout the experiment [20]. These results mirrored the BOOST

trial in which BMCs administered 5 days after percutaneous coronary intervention (PCI) were associated with a 6.7% absolute increase in EF in the bone marrow group compared with a 0.7% increase in the control group ($P=0.0026$) [21]. Here again, intergroup differences were no longer significant during later follow-up (18 months), suggesting that the benefit of infused BMCs may be in delaying pathologic remodeling. A meta-analysis of 13 RCTs (811 patients) determined that intracoronary injection of BMCs improves EF by 2.99 points ($P=0.0007$) over 3 to 6 months, although not all trials have been positive [22•, 23]. Supplementing these findings are several other recent trials including the unblinded BALANCE study, which reported that delivery of BMCs 7 days after acute MI decreased 5-year mortality (2.35% vs 0.35% annual mortality rates, $P=0.03$) and increased EF (4.6% improvement over baseline for BMC delivery vs a decrease of 5.8 points for controls) [24]. In patients with an EF less than 45%, the MYSTAR ($n=60$) study found no difference in the improvement in EF and reduction in infarct size when a dual-cell introduction method (intramyocardial and intracoronary injection) was used at 3 to 6 weeks versus 3 to 4 months post-MI, although MI size was smaller in treated hearts than in controls [25].

Direct Delivery of Specific Marrow-Derived Cells

Chen et al. [26] evaluated mesenchymal stem cells (MSCs) in a placebo-controlled trial of 69 patients and reported the largest increases in EF for trial groups over controls when delivering 8 to 10 billion MSCs via intracoronary injection at about 18 days after PCI. At 3 and 6 months, the study reported an average EF of $67\% \pm 11\%$ and $67\% \pm 3\%$ in MSC-treated patients, compared with $53\% \pm 18\%$ and $54\% \pm 5\%$ in placebo-treated controls. Several other cardiac performance measurements supported these results [26]. Two additional reports describing the effects of enriched BMC subsets reported rather modest benefits. In a blinded study of 22 patients reported by Katritsis et al. [27], in 1 to 2 million BMCs enriched for MSCs ($\sim 33\%$) and endothelial progenitor cells ($\sim 66\%$), improved wall motion score indices and tissue viability were observed without significant improvement in EF. A clinical trial using intracoronary delivery of AC133⁺-enriched BMCs 2 weeks after MI reported significant improvements in EF and perfusion defects when compared with control patients receiving no cell therapy [28]. Two ongoing clinical trials are also evaluating the therapeutic potential of MSCs. The PROMETHEUS trial is a placebo-controlled study of intracardiac injection of expanded autologous MSCs in patients who require coronary artery bypass surgery with an EF between 20% and 50%. Efficacy will be assessed by quantitative evaluation of myocardial wall motion, tissue perfusion, and infarct size as measured by serial cardiac MRI over 18 months following surgery. The TAC-HFT is a similar study in which autologous MSCs or autologous whole bone marrow are delivered percutaneously by means of the BioCardia delivery system (BioCardia, San Carlos, CA).

Delivery of Cardiac-Derived Stem Cells

Based on reports suggesting particularly potent myogenic potential for c-kit⁺ (CD117⁺) cells isolated from human hearts during co-culture [14•] or xenotransplantation studies [9•], a new open-label clinical trial (SCIPIO) involving intracoronary delivery of expanded autologous c-kit⁺ cardiac-derived progenitors has been initiated in patients with a prior MI with persistent scar. A similar study using autologous cardiosphere-derived cells (CADUCEUS) is examining the effects of intracoronary delivery of cardiac-derived progenitor cells following MI with a patent infarct-related coronary artery.

Although the cardiac cell therapy investigations described above have and will continue to yield new insights into the potential for cardiac repair and regeneration, a high degree of redundancy and an excessive focus on end points with too little attention to mechanisms of benefit have undoubtedly slowed progress in the field. An expansion of direct comparisons between alternative cell types, cell delivery methods, alternative dosing, and adjuvant

strategies would hasten progress toward effective therapeutic myogenesis. Likewise, greater attention to defining rates of stem cell retention and differentiation will provide mechanistic clues that will further accelerate the optimization of regenerative strategies. Finally, it is possible that alternative approaches may be required for alternative clinical settings such as recent versus remote MI. In particular, the timing of cell delivery that is most suitable for stem cell-mediated repair, and the features of a fertile myocardial microenvironment have not yet been determined. In this context, rapidly progressing advances in tissue engineering and local manipulations of the cardiac microenvironment are providing new insights and tools to augment the ultimate efficacy of cardiac regeneration strategies. These manipulations are discussed in the next section of this review.

Cardiac Tissue Engineering

Although the research reviewed above supports both the need and the therapeutic potential for advances in new cardiac repair strategies, a widening diversity of tissue engineering research has begun to yield new insights that are highly relevant for the development of myocardial repair and regeneration strategies. In general terms, recent tissue engineering research has been targeting three fundamental biological challenges for cardiac cell therapy: how to increase the number of S/PCs available for myogenesis and angiogenesis; how to promote differentiation and maturation of S/PCs; and how to assure structural and functional integration with the host myocardium. This section highlights how tissue engineering strategies are helping to address these challenges while simultaneously providing new insights into the biology of myocardial regeneration.

Increasing the Number of Progenitor Cells

One of the major challenges when using cell therapy is to provide a sufficient number of multipotent cells to achieve meaningful myogenesis and angiogenesis to restore cardiac function. Although often ignored, retention of viable progenitors within the myocardium remains a major challenge for cell therapy. In the BOOST study, one of the few cell therapy trials using cell labeling, investigators found that fewer than 3% of unselected BMCs were retained in the heart at 30 days after their administration [29]. Recent animal studies using positron emission tomography imaging and quantitative mRNA expression (with reverse transcriptase polymerase chain reaction) demonstrated that only 40% of injected cells are retained in the heart by 5 h after injection, that half of these cells die within the first 24 h after injection, and that stem cell proliferation within the heart can more than counterbalance this early attrition by 1 week after injection [30•]. Thus, in addition to the number of cells administered, rates of retention, proliferation and death are important factors determining the number of cells available for therapeutic myogenesis or angiogenesis. Recruitment of endogenous progenitors to the heart represents another relevant strategy to increase the effectiveness of cell therapy.

Based on these considerations, engineered constructs demonstrated the potential to improve the overall engraftment rates of cardiac S/PCs. In particular, constructs containing extracellular matrix (ECM) constituents appear to provide signals that favor retention, proliferation, and survival. For example, a myocardial patch made of lyophilized ECM from the porcine urinary bladder in a dog model improved regional stroke work and doubled myocyte content after 8 weeks [31]. Complementary studies using a fabricated collagen matrix demonstrated reduced MSC relocation to other organs [32]. In a hindlimb ischemia model, combining collagen with sialyl Lewis(X), which binds L-selectin, resulted in increased recruitment of endothelial progenitor cells in vitro and increased mobilization of endogenous circulating precursor cells in vivo, together with a decrease in apoptosis [33]. Further augmentation of S/PC number was achieved by using engineered constructs as vehicles to deliver substances favoring their viability and/or survival. Recognizing that

insulin-like growth factor-1 (IGF-1) significantly enhances proliferation and reduces apoptosis of cardiomyocytes in vitro, Padin-Iruegas et al. [34••] recently reported that injected nanofibers slowly releasing IGF-1 improve myocardial regeneration after MI in association with reduced cell death and increased proliferation of injected and endogenous S/PCs.

Promoting Differentiation and Maturation of Cardiac Progenitors

Engineering approaches were also used to examine and manipulate the factors affecting the differentiation and maturation of S/PCs. Previous studies demonstrated that application of cyclic mechanical force regulates growth and contractile physiology in engineered myocardial [35] and vascular structures [36]. Moreover, in vitro studies demonstrated that the stiffness of the microenvironment affects the commitment of multipotent stem cells to a particular lineage with the same cell differentiating into neuron, myocyte, or osteocyte depending on the stiffness of the cell culture substrate [37]. Recent studies further demonstrated that the configuration of the ECM regulates cell morphology by imposing restrictions to its geometry or size which, in turn, modulates internal cytoskeletal and sarcomeric architecture [38]. Beyond these physical factors, growth factors and other biochemical stimuli within the myocardium clearly affect S/PC differentiation and maturation. For example, the study by Padin-Iruegas et al. [34••] demonstrated that newly formed myocytes reached a more advanced level of cell differentiation after treatment of infarcted myocardium with IGF-1-containing nanofibers. Similarly, vascular differentiation can be improved by including growth factors, such as vascular endothelial growth factor, into the scaffolds [39]. Thus, the ability to control the physical characteristics of engineered constructs and/or their ability to release particular cytokines has provided a versatile means of elucidating factors affecting stem cell fate while providing potential therapeutic adjuvants for clinical applications.

More complicated tissue engineering strategies have incorporated supporting cells into particular scaffolds designed to improve cell differentiation and functionality. For example, Kobayashi et al. [40•] developed sandwich-like constructs engineered by stacking of the co-cultured cell sheets containing endothelial progenitor cells together with fibroblasts. Application of these constructs in rat MI models resulted in local cytokine secretion and increased de novo blood vessel formation that reduced scarring and improved overall contractility. Extending this approach, a tri-culture model using human embryonic stem cell-derived cardiomyocytes, human endothelial cells, and embryonic fibroblasts seeded on a porous scaffold was transplanted to the in vivo rat heart and was reported to increase vascularity and general graft integration [41]. These and other studies highlight how myogenesis and improved contractility are dependent on concomitant revascularization. Myogenesis without parallel angiogenesis will not be successful, although angiogenesis alone could promote enhanced salvage following ischemic insults by reducing adult myocyte attrition or by enabling endogenous repair processes.

Fostering Integration with the Host Myocardium

An important challenge facing any strategy for therapeutic cardiac regeneration is the necessity to integrate the engrafted cells or tissues into a diseased host myocardium that must continue to support the circulation without interruption. A variety of engineering approaches have proved useful for defining the factors required for structural and functional integration of the cells with the host myocardium while providing constructs designed to foster such integration. On one end of the spectrum are approaches creating whole-heart scaffolds via myocardial decellularization protocols, as first reported by Ott et al. [42•]. Following decellularization of rat heart with methods designed to maintain the integrity of the ECM and vasculature, repopulation with neonatal myocytes produced areas of relatively

mature cardiac myocytes capable of organized syncytial beating in response to electrical stimulation and modulation by pharmacologic agonists. These approaches, combined with enhanced decellularization protocols designed to minimize immunoreactivity [43], and seeding with autologous myogenic and angiogenic progenitors might ultimately enable subsequent xenotransplantation in humans.

Complementary approaches, involving artificial scaffolds, are also being developed to promote structural and functional integration of cellular and tissue therapeutics. These artificial scaffolds range from the simplest hydrogel scaffold, into which cells are seeded directly, to matrices with elastic properties [44] or fiber-based structures with a wide spectrum of morphologic and geometric possibilities [45] including cell-sheet/tissue constructs that offer high versatility, biocompatibility, and biodegradability with minimal cytotoxicity [46]. As recently reviewed, engineered cells sheets, fabricated in temperature-responsive conditions and subsequently transplanted in vivo, have already demonstrated the potential to improve cardiac function in animal models [47]. Alternative structural approaches for promoting integration with host myocardium include microspheroids that can be uniformly dispersed to the heart following intravascular delivery [48] and/or self-assembling nanoparticles that favorably modify the local microenvironment following intravascular delivery. Previously discussed studies involving administration of cardiac progenitor cells together with self-assembling nanofibers capable of releasing IGF-1 augmented the expression of connexin 43 and N-cadherin in newly formed cardiomyocytes to foster electrical and mechanical coupling between resident and regenerated myocytes [34••]. The importance of such electrical integration is demonstrated by the increased incidence of ventricular arrhythmias when skeletal myoblasts, which have low capacity to transmit electrical signals, are engrafted into the myocardium [15].

Another method used to promote compatibility of engineered cells and tissues with the host myocardium has been the use of bioreactors to cultivate tissue constructs in conditions that mimic the in vivo environment. During bioreactor cultivation, cardiac tissue constructs may be subjected to mechanical stimulation designed to enhance tissue assembly and contractile properties [49]. Electrical stimulation may likewise improve signal propagation in engineered cardiac constructs [50]. Application of appropriate metabolic and humoral cues can further complement these mechanical and electrical inputs to better prepare engineered myocardial constructs for their integration into the host tissue. While facilitating engraftment, these in vitro conditioning studies using fabricated tissue constructs and specialized bioreactors also reveal fundamental features of cellular adaptation to environmental cues that may inform strategies for cell therapy and augmenting endogenous cardiac repair.

Conclusions

Pathophysiologic stress is often associated with increased abundance of S/PCs within the myocardium. Although these cardiac-derived S/PCs can be induced to differentiate into new myocytes or vascular cells, their in vivo impact is clearly insufficient in many failing hearts. A challenge in studying endogenous repair responses in humans is the lack of labeling, such that new myocytes and other cells may appear indistinguishable from “original” cells in the absence of sex-mismatched transplants or other anomalies that permit post hoc fate mapping. Nevertheless, the general inadequacy of native myocardial repair responses combined with the recognition that new myocyte formation is possible in the adult mammalian heart continues to propel an explosion of research aimed at achieving therapeutic cardiac regeneration. In this regard, we propose that progress will be enhanced by cross-pollination between the distinct lines of inquiry highlighted in this review and summarized in Table 1.

Clinical trials to date support the conclusions that simply increasing the number of circulating bone marrow–derived progenitor cells (via G-CSF) is insufficient to augment endogenous repair processes following MI, and that delivery of bone marrow S/PCs to the heart is generally safe, but has relatively minor overall impact. Interestingly, the minor beneficial effects of myocardial S/PC delivery despite minimal retention of cells with uncertain myogenic capacity suggests that local myocardial responses triggered by cell delivery may indirectly promote favorable remodeling and/or augment endogenous regenerative mechanisms. As the search for the optimal S/PC for cell therapy continues, new insights about endogenous cardiac progenitors in developmental biology are suggesting novel approaches for generating autologous myogenic progenitors. At the same time, versatile tissue engineering strategies are elucidating ways in which the ECM, cytokines, and other cell types within the myocardium can shape the homing, retention, maturation, survival, and integration of endogenous and exogenous S/PCs. We believe that successful therapeutic strategies will leverage both enhanced understanding of native repair processes and creative modifications of the cardiac microenvironment to optimize the overall efficacy of cardiac regeneration with or without exogenous S/PCs.

Clinical Trial Acronyms

BALANCE	Clinical Benefit and Long-Term Outcome After Intracoronary Autologous Bone Marrow Cell Transplantation in Patients With Acute Myocardial Infarction
BOOST	Bone Marrow Transfer to Enhance ST-Elevation Infarct Regeneration
CADUCEUS	Cardiosphere-Derived Autologous Stem Cells to Reverse Ventricular Dysfunction
FIRSTLINE-AMI	Front-Integrated Revascularization and Stem Cell Liberation in Evolving Acute Myocardial Infarction by Granulocyte Colony-Stimulating Factor
MAGIC	Myoblast Autologous Grafting in Ischemic Cardiomyopathy
MARVEL-1	To Assess Safety and Efficacy of Myoblast Implantation Into Myocardium Post Myocardial Infarction-1
MYSTAR	Myocardial Stem Cell Administration After Acute Myocardial Infarction
PROMETHEUS	Prospective Randomized Assessment Of Mesenchymal Stem Cell Therapy in Patients Undergoing Surgery
REPAIR-AMI	Reinfusion of Enriched Progenitor Cells and Infarct Remodeling in Acute Myocardial Infarction
REVIVAL-2	Bone Marrow Stem Cell Mobilisation Therapy for Acute Myocardial Infarction
SCIPIO	Myocardial Regeneration Using Cardiac Stem Cells
STEMMI	Stem Cells in Myocardial Infarction
TAC-HFT	Transendocardial Autologous Cells in Heart Failure Trial

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Fig. 1. Illustrates how mutually complementary studies of endogenous myogenesis/angiogenesis, cardiac cell therapy, and cardiac tissue engineering together can promote optimized myocardial repair. PCs—progenitor cells; S—cardiac stem cells

Table 1

Strengths and weaknesses of alternative myocardial repair inquiries

	Insights	Study deficiencies	Repair deficiencies
Endogenous repair	Native S/PCs are present in all hearts; a native injury repair response exists; cardiac and extracardiac sources of S/PCs are implicated in repair	Biological variability impedes to isolate variables; lack of labeling typically obscures source and magnitude of impact	Insufficient response to prevent pump failure; concerns about defects in native mechanisms (S/PC “senescence”)
Stem cell therapy	Native repair response can be augmented; some cell types are more beneficial than others; cell delivery is not intrinsically toxic; improvement is proportional to initial damage	Tradeoff between using autologous cells and immediate S/PC delivery; weak response lowers signal:noise ratio	Insufficient retention and maturation of cells; many variables to optimize: cell type, delivery method, and timing
Tissue engineering	Mechanical, electrical, and biochemical aspects of microenvironment affect S/PC growth and maturation; both angiogenesis and myogenesis are required for effective repair	Most in vivo applications require surgery; decellularization may unfavorably alter ECM properties	Difficult to integrate into existing tissue; difficult to incorporate all biological cues needed for growth/repair; may not be scalable to larger hearts

ECM extracellular matrix, *PCs* progenitor cells, *S* cardiac stem cells