Arrhythmia in Stem Cell Transplantation

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KEYWORDS

• Arrhythmia • Stem cell • Coupling • Cardiomyocyte • Regeneration • Paracrine • Electromechanical

KEY POINTS

- Candidates for cardiac cell therapy include autologous sources such as bone marrow progenitor cells, skeletal myoblasts, and resident cardiac stem cells. Human pluripotent stem cells, including embryonic stem cells and induced pluripotent stem cells, are additional candidates with vast differentiation potential, although no clinical trial has yet tested their efficacy.
- Cell coupling and engraftment are vital to improved myocardial function.
- Mechanisms for arrhythmia in stem cell transplantation include reentrant rhythms, automaticity that is at least in part dependent on host heart rate, noncardiac graft contaminates and noncellular features involving nerve sprouting and increased sympathetic innervation.
- Paracrine effects may serve a protective role.
- The method of stem cell transplantation also contributes to arrhythmogenicity, in that intramyocardial injection carries a higher rate of arrhythmia caused by disruption of the native architecture of the heart.

INTRODUCTION

The human heart has limited regenerative capacity, and there is an unmet demand for improved therapies for cardiovascular disease. Both adult stem cells (ASCs) and human pluripotent stem cells (hPSCs) have the potential to facilitate development of cell-based therapies. ASCs have been used in clinical trials,[1,2] and hPSCs have been used extensively to regenerate injured mammalian hearts, including a recent report of nonhuman primates.[3] However, full clinical translation of stem cell–based therapies has been limited by numerous challenges, including the proarrhythmic nature of stem cell–derived cardiac grafts. The potential arrhythmic risk may be attributed to differences in electrophysiologic maturity,[4–6] gap junction isotypes, cell orientation, and wave propagation between graft and the host myocardium. In vivo, the normal myocardial architecture has a unique three-dimensional extracellular matrix, offering cyclic mechanical stress (from rhythmic heart beating), electric stimulation, cell-cell signaling, and topographic cues among the cardiomyocytes (CMs). On injury, the normal architecture is disrupted, and CMs are replaced by scar tissue and proliferating fibroblasts, which in turn results in compromise of the structural integrity

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and adverse remodeling of the heart. These structural changes cause anisotropy, which provides substrates for reentrant arrhythmias. In addition, the action potential duration prolongation may potentially produce early afterdepolarizations or delayed afterdepolarizations. Any attempt to introduce exogenous cells for regenerative purposes should take into consideration the hostile environment, the lack of normal myocardial structure, and the potential for the introduction of cells in a microenvironment in which normal CM fibers are replaced by scar. The electromechanical integration of the transplanted cells into such an environment may be a far-fetched reality but warrants critical analysis and intense research.

In the following sections, candidates for stem cell therapies, the mechanisms of stem cell cardiac graft–induced arrhythmogenicity, and the requirements for successful integration and electrophysiologic coupling of the hPSC cardiac graft to the damaged heart are discussed.

CANDIDATES FOR CARDIAC REPAIR

There are 2 schools of thought regarding cell therapy for cardiac regeneration: (1) delivery of cells into the heart with the goal of survival, maturation, and integration of the transplanted cells for regeneration and replacement of the scar tissue, and (2) delivery of therapeutic cells into the heart, where cells may not survive to physically replace the damaged tissue, but which leads to regeneration via a paracrine effect and recruitment of endogenous cells to repair the scar. Although both scenarios could introduce arrhythmia, survival and engraftment of transplanted cells may dangerously serve as a nidus for arrhythmias.

Potential cell candidates to replace CMs in the injured heart must generate an action potential, couple this electrical stimulus to contraction, and form the necessary gap junctions for action potential propagation and integration with host myocytes.[7] A variety of cell types have been studied as potential candidates for cardiac regeneration (**Table 1**). Properties such as propensity for electromechanical integration, arrhythmogenicity, and risk of teratoma formation are important considerations in selecting the appropriate cell. Cell sources for cardiac cell therapy include skeletal myoblasts (SMs), bone marrow progenitors, resident cardiac stem cells (CSCs), human embryonic stem cell (hESCs) and induced pluripotent stem cells (iPSCs).[7–9] Human ESCs, iPSCs, and resident cardiac progenitor cells have all been reported to differentiate into CMs in both in vivo and in vitro studies, whereas bone marrow mesenchymal stem cells (MSCs) and SMs rely on transdifferentiation.[10]

In addition to selecting the appropriate cell candidate for transplantation, other concerns include the quantity of transplanted cells needed to achieve a clinically reasonable graft size, potential for proliferation in vivo and the degree of cell retention.[7] Methods for transplantation include intracoronary and direct intramyocardial via a surgical or catheter-based approach.[11] The degree of cell retention is largely dependent on the method of transplantation, whereas cell viability and survival after transplantation also depend on the cell type and the microenvironment. Widimsky and colleagues[11] reported that after intracoronary injection of bone marrow cells (BMCs) into large-animal models and humans, retention rates ranged 1.3% to 5.3% 2 hours after transplantation. Various methods of transplantation may also directly influence the arrhythmogenicity of stem cell therapy, as discussed in later sections.

Another aspect important for successful hPSC integration is graft alignment. If not patterned correctly, engrafted cells have a propensity to integrate randomly into the host heart and thereby increase electric heterogeneity and arrhythmogenic foci. Applications such as tissue engineering need to be used to ensure optimal graft alignment.

Skeletal Myoblasts

SMs are a reservoir for skeletal muscle cell regeneration in cases of muscle injury.[12,13] A major source of SMs is satellite cells, resident muscle stem cells responsible for muscle growth, repair, and homeostasis.[14] The potential for in vitro amplification of satellite stem cells and their ability to self-renew make SMs a desirable target for CSC therapy. There are several features unique to SMs. These cells are committed to a myogenic lineage and become functional myocytes regardless, or rather despite, environmental cues.[12] Further, SMs continue to proliferate in vivo with a high degree of resistance to tissue ischemia, leading to larger graft sizes. In early mice studies, grafts were shown to be viable for as long as 3 months after transplantation.[15]

SMs were used in some of the first clinical trials for cardiac regeneration. Despite modest improvements in left ventricular ejection fraction, the increased incidence of sustained ventricular tachycardia in cell-treated patients led to increased concerns regarding cardiac cell therapy.[13,16,17] SMs do not express the gap junctions, connexin-43 (Cx43) in particular, necessary for electrical coupling with host CMs[18–20] discussed in more detail later. Roell and colleagues[20] have