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Heart to heart: Cardiospheres for myocardial regeneration

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Cardiac regenerative therapies seek to grow new myocardium after "irreversible" injury such as myocardial infarction. Various cell types and delivery techniques have been used in experimental models of human disease and clinical trials. When selecting a candidate stem cell type for clinical use, multiple factors need to be taken into consideration. The ability to regenerate myocardium without potentiating arrhythmogenesis is a critical property. Skeletal myoblasts engraft, differentiate, and are arrhythmogenic; in contrast, bone marrow-derived cells do not engraft long-term and have not been associated with excess arrhythmias. Neither cell type, however, achieves true myocardial regeneration. Recognition of the existence of cardiac stem cells and of the ability of mature myocytes to reenter the cell cycle and proliferate has motivated the development of new approaches to cardiac regenerative medicine. Cardiosphere-derived cells decrease scar mass and regenerate viable myocardium both in animal models and in the CADUCEUS (Cardiosphere-Derived Cells For Heart Regeneration After Myocardial Infarction) clinical trial. Although cardiosphere-derived cells fulfill the criteria for stem cells, their stemness appears not to mediate the therapeutic benefit; instead, indirect mechanisms lead to proliferation of the host myocardium. Being of endogenous origin, the newly grown heart muscle is electrically and mechanically well integrated with preexisting myocardial tissue. We hypothesize that cardiac arrhythmias are less likely to complicate cell therapy when the mechanisms of benefit involve secondary proliferation of endogenous myocardium. Conversely, arrhythmias will more likely bedevil therapeutic approaches (such as transplantation of skeletal myoblasts or pluripotent stem cells) that lead to exogenous grafts within the heart, with the degree of coupling and the extent of inhomogeneity being critical determinants of the net effect.

KEYWORDS Cardiac stem cells; Cardiospheres; Cardiac regeneration

ABBREVIATIONS **BMMNC** = bone marrow mononuclear cell; **CADUCEUS** = Cardiosphere-Derived Cells for Heart Regeneration after Myocardial Infarction; **CDC** = cardiosphere-derived cell; **CSp** = cardiosphere; **EP** = electrophysiological; **MI** = myocardial infarction; **MRI** = magnetic resonance imaging; **MSC** = mesenchymal stem cell; **SkMB** = skeletal myoblast

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A. Introduction

Heart disease, encompassing acute coronary syndromes, heart failure, and sudden cardiac death, constitutes the number 1 killer in the United States.[1] Present therapies are focused on early revascularization in acute coronary syndromes,[2] pharmacological therapies that modulate neurohormonal changes in heart failure,[3] and devices or ablation to treat arrhythmias.[4,5] Cardiac regenerative therapies seek, instead, to regrow healthy myocardial tissue by cell transplantation into the injured heart. As shown in Table 1, ideal cells should be derived from easily obtained tissue, readily grown in large numbers, available "off the shelf" for acute indications, nonimmunogenic, nonarrhythmogenic, and able to regenerate healthy myocardium. The effects of cell therapy on arrhythmogenesis are potentially salutary, given that improving pump function and increasing viable myocardium might suppress ventricular arrhythmias. On the other hand, new strands of viable tissue might create inhomogeneities of conduction and thereby potentiate arrhythmogenesis.

Different cell types and delivery modalities have been studied in both preclinical models and clinical trials, most often in the setting of recent myocardial infarction (MI).[6] The effects on arrhythmogenesis range from exacerbation to apparent suppression. Direct and indirect effects of cell transplantation can affect not only the extent but also the characteristics of the host tissue, with important consequences for the electrophysiological (EP) properties of the infarct border zone and remote myocardium. Given the significance of early ventricular arrhythmias after acute MI, particularly in those patients with ventricular dysfunction, arrhythmogenesis is a critical factor to consider in selecting the most appropriate cell therapy strategy. After more than a decade of stuttering progress,[6] we now have reasons to believe that therapeutic regeneration can be safely achieved in human beings by using cardiosphere (CSp)-derived cells (CDCs; in the Cardiosphere-Derived Cells for Heart Regeneration after Myocardial Infarction [CADUCEUS] trial[7]).

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Table 1 Desirable features of cells that are used to treat heart disease

- Derived from easily obtained tissue source
- Readily grown in large numbers by using standardized techniques
- "Off-the-shelf" availability for acute indications
- Nonimmunogenic
- Nonarrhythmogenic
- Regenerative capacity

But the path has been tortuous and instructive. Let us first consider the lessons learned from the use of noncardiac cell types in patients with heart disease. The first product in the clinic was the skeletal myoblast (SkMB).[8] The motivation for using SkMBs was logical and straightforward: the failing heart lacks contractile units, so why not supplement the number of contractile units by transplanting autologous skeletal muscle cells into the myocardium? Cells derived from the bone marrow were next into the clinic,[9] with a less solid pathophysiological basis for translation, based on the since-discredited[10,11] premise that bone marrow cells can easily transdifferentiate into cardiomyocytes and blood vessels after transplantation into the heart.[12]

B. Cell therapy and arrhythmias: Lessons learned from noncardiac cell types

As summarized in Figure 1, EP changes induced by cell therapy can affect basic cellular arrhythmogenic mechanisms (reentry, abnormal automaticity, and triggered activity) both directly and indirectly. Newly formed tissue strands within the heart, derived from cells with distinct EP phenotypes, can potentially increase tissue heterogeneity. These tissue strands (formed from phenotypically different and/or noncoupled cells) can promote a proarrhythmic substrate by creating barriers to conduction and/or ectopic foci.

SkMBs can be easily grown in vitro and are relatively resistant to hypoxic and ischemic conditions.[2,13] These features accelerated early studies with these cells as potential candidates for cardiomyoplasty.[8] Early animal studies demonstrated that SkMB-derived muscle grafts remained functionally isolated from the surrounding myocardium but did not reveal an increased frequency in ventricular tachycardia or fibrillation.[14] SkMBs grow and differentiate, forming elongated structures called myotubes, which are contractile but lack connexin 43 (the predominant gap junction of the ventricular myocardium).[15] In vitro, SkMBs cocultured with neonatal cardiomyocytes were found to slow conduction velocity and promote reentry-induced arrhythmias in cellular monolayers studied with high-resolution optical mapping.[15] Interestingly, the proarrhythmic effect was reduced when cells were engineered to overexpress connexin 43,[15] a finding translated afterward to an animal model.[16] The deficiency in connexin 43, with the consequent inability to electrically couple to the surrounding myocardium, results in areas of slow conduction and a substrate for reentrant arrhythmias. In concordance with the results from experimental models, clinical studies delivering SkMBs to patients with ischemic cardiomyopathy for cardiac regener-

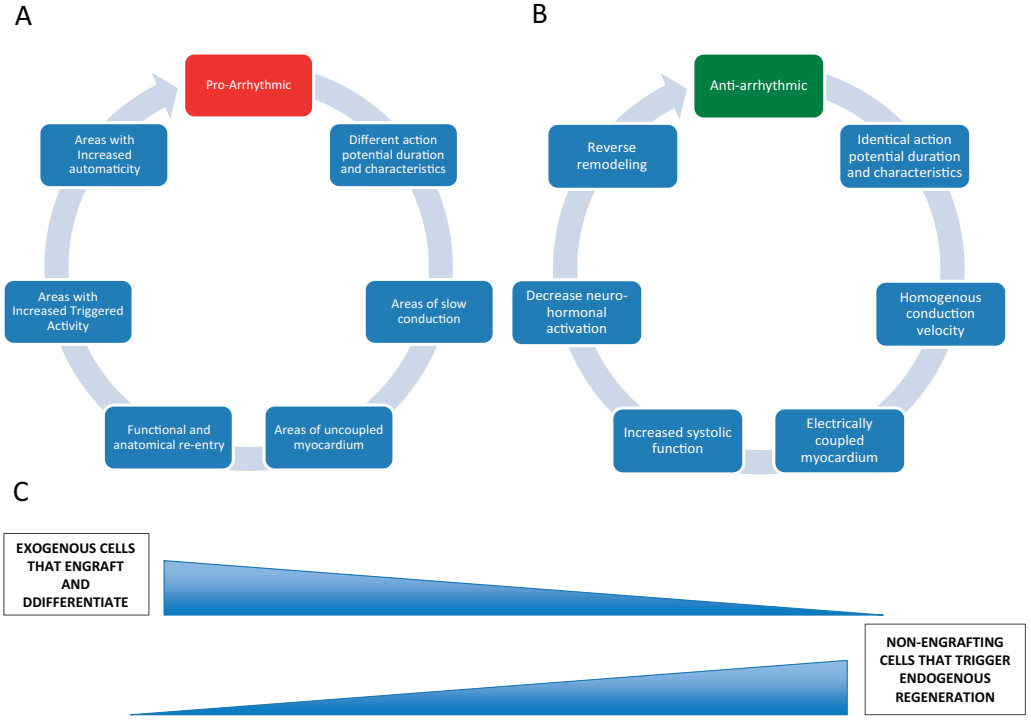

Figure 1 Potential proarrhythmic **(A)** and antiarrhythmic **(B)** mechanisms of cardiac cell therapy. While some of the antiarrhythmic mechanisms **(B)** can be observed with exogenous regeneration, these effects could potentially be blunted by proarrhythmic mechanisms **(A)**. More "homogeneous" tissue and fewer arrhythmias could be expected from cell types that act indirectly to trigger endogenous repair **(C)**.