A growing body of work supports cell-based therapeutics as a promising strategy for treating cardiovascular disease. Patients who receive stem cells, previously isolated from the bone marrow (eg, mesenchymal stem cells [MSCs]) or the heart (cardiac stem cells [CSCs]), experience improved cardiac anatomy, increased functional capacity, and quality of life. With regard to MSCs and CSCs, scar tissue is reduced and replaced by contractile myocardium, accompanied by increased tissue perfusion, due most likely to neovascularization and improved endothelial function, globally and locally.

Previous studies hypothesized that the therapeutic capacity of transplanted cells is derived from their ability to differentiate into cardiomyocytes. However, this concept has not yet been meaningfully achieved. In a recent study by Chong et al, nonhuman primates were administered 10^9 human embryonic stem cells–derived cardiomyocytes after myocardial infarction. In this study, they achieved engraftment but no functional recovery. Similar findings were recently reported by others. Thus, engraftment and differentiation are not sufficient for cardiac repair.

In contrast, transplantation of cells with lower capacity to form new myocytes does significantly enhance repair. This seemingly paradoxical effect coupled with important new mechanistic insights underlying cardiac biology raises the idea that the heart possesses regenerative capacity that may be a therapeutically targeted. Notably, after the landmark discovery by Beltrami et al, a series of studies showed that human myocyte turnover occurs during life, a phenomenon upregulated by injury. Notably, Bergmann et al estimated that under physiological conditions, 39% of healthy myocytes by age 75 develop postnatally.

Cell therapy promotes repair by enhancing endogenous cardiomyocyte turnover. For example, although few MSCs directly transdifferentiate into cardiomyocytes after transplantation, the majority of them establish cell–cell interactions with host myocardium and stimulate endogenous cardiomyocyte turnover and differentiation of CSCs. Similarly, although CSC transplantation was thought to promote repair via direct remuscularization, it was later shown also to stimulate endogenous myocyte turnover and progenitor cell recruitment.

Importantly, while some reports suggest that CSCs hold minimal endogenous regenerative activity, we and others have shown this is a modifiable process which, for example, is substantially enhanced after cell–cell contact with MSCs, These cell–cell interactions closely resemble interactions within stem cell niches and prompted the idea of combining both cell types into a single-cell therapeutic (Combo). Compared with monocellular therapeutic schemes, Combo demonstrated superior capacity to induce and sustain myocardial repair. Engraftment, heart function, and scar size reduction were enhanced, whereas the rate of cardiomyocyte turnover and endothelial function were significantly increased. From a mechanistic standpoint, the interactions of MSCs with CSCs are thought to involve production and exchange of growth factors, micro-RNAs, microvesicles, and mitochondria with the host myocardium or each other.

In this issue, Quijada et al have advanced the concept of cell combination therapy and suggest that Combo may promote repair through mechanisms involving fusion between MSCs and CSCs. The resulting hybrid cells (dubbed CardioChimeras [CCs]) exhibit enhanced regenerative capacity, compared with each cell type alone.

Although it is unknown whether CCs exist naturally in humans, Quijada et al used ex vivo bioengineering to test this idea in mice. Compared with the parent cells, CCs exhibited enhanced cardiovascular lineage commitment. When cocultured with cardiomyocytes, CCs prevented maladaptive hypertrophy and apoptosis, at a level similar to Combo or each cell type alone, although only one of the CC clones enhanced cardiac gene transcription to a level comparable with Combo. When transplanted in mice with myocardial infarction, CCs were equally effective to Combo, although the degree of recovery varied between different CC preparations.

From a translational standpoint, CCs represent an interesting modality. It introduces cell fusion, previously associated with an increased risk for arrhythmias, as a potentially useful strategy for myocardial regeneration.

In parallel, it raises many concerns. For example, stochastic fusion of CSCs and MSCs will likely result in significant variability in generating therapeutically competent CCs. To this end, further optimization of the methodology will be required before it becomes clinically relevant (ie, prospective identification and selection of CSC and MSC founder clones). Similarly, it is unclear whether CCs retain the immunotolerant MSC phenotype that would make them an attractive

**Cell Therapy: Targeting Endogenous Repair Versus Remuscularization**

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alternative to Combo. Finally, it will be important to understand how the elimination of MSC–CSC interactions, which are an essential stem cell niche property and which we have found to play an important role for regeneration, may affect the therapeutic outcome in the clinical setting.

In summary, the findings by Quijada et al further support the finding that combination cell therapy provides the most promising cell-based strategy for enhancing cardiac repair. The concept of cell–cell fusion as an additional mechanism of action is exciting, and its potential applicability into the clinical setting warrants further investigation.

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References


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