**Cardiac Anisotropy, Regeneration, and Rhythm**

With great interest, we read the commentary of Anderson et al. on the recent publication of Chong et al about the large-scale use of human embryonic stem cell–derived cardiomyocytes to regenerate infarcted, nonhuman primate myocardium. In their commentary, they focus on the development of ventricular tachyarrhythmias after injection of large numbers of human embryonic stem cell–derived cardiomyocytes, as reported by Chong et al. We like to extend the discussion about the origin of these arrhythmias. In our opinion, a crucial aspect of cell injection in infarcted myocardium remains unnoticed in both the article of Chong et al and the commentary of Anderson et al, being the anisotropic nature of myocardial tissue requiring proper spatial integration (ie, alignment) of the implanted cells.

In the adult heart, rod-shaped cardiomyocytes are aligned in specific directions and coupled mainly at the polar ends, resulting in anisotropic electric propagation (ie, velocity depends on direction), which contributes to optimal cardiac function. Significant disruption of this highly organized tissue architecture, for example after myocardial infarction, could disturb coordinated impulse propagation and contraction. Importantly, these are the same processes that, together with the extracellular matrix, normally seem to guide and maintain the alignment of cardiomyocytes.

In an attempt to restore electric and contractile function after myocardial infarction, Chong et al injected around 1 billion immature human embryonic stem cell–derived cardiomyocytes in damaged myocardium, which most likely does no longer provide the cues for proper alignment. As a result, the engrafted cardiac cells may align randomly, or suboptimally at best, resulting in increased electric heterogeneity, thereby providing a possible, additional explanation for the rhythm disturbances found by Chong et al.

Malalignment of implanted cardiomyocytes could also explain the lack of improvement in contractile function because generation of significant contractile force by myocardial tissue requires proper alignment of cardiomyocytes. Unfortunately, cell alignment was not assessed. This would have been of interest because one can appreciate that with an increase in cellular graft size, proper donor cell alignment becomes more important. Of note, among the numerous reports on cell transplantation into damaged myocardium, only few describe a transplant-related increase in proarrhythmic risk. This seems, however, not surprising considering that virtually all studies report relatively low engraftment rates of mostly nonexcitable cells. In contrast, Chong et al achieved much higher engraftment rates of cells virtually all expressing sarcomeric α-actinin, suggesting a cardiomyocyte-like phenotype. This is important because the impact of donor cell alignment on impulse propagation after cardiac cell therapy is even more pronounced for excitable cells like cardiomyocytes.

Nevertheless, how total heart size (and therefore heart rate), infarct size, engraftment rate of (non)excitable cells, and their alignment are related to each other in terms of proarrhythmic risk is incompletely understood. This certainly warrants further investigation given the serious nature of ventricular tachyarrhythmias, including studies on how to guide cell alignment in damaged myocardium.

In conclusion, the role of donor cell alignment should be considered in the ongoing discussions about the therapeutic potential of cardiac cell therapy, including transplantation of human embryonic stem cell–derived cardiomyocytes. By guiding the alignment of implanted stem cell–derived cardiomyocytes to match the native 3-dimensional tissue architecture, a graft-associated increase in proarrhythmic risk is probably prevented while the contractile performance of the heart is improved. Although challenging in many aspects, the unique features of cardiac regenerative medicine are worth the efforts of our scientific community.

**Disclosures**

None.

**References**


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