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Commentary: The far-out prospect of cardiac regeneration after myocardial infarction

Sumner E. Kilmarx, AB,[a] and Leora B. Balsam, MD[b]

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CENTRAL MESSAGE

A promising technology that uses induced pluripotent stem cells for cardiac regeneration after myocardial infarction faces many barriers before it can be implemented clinically.

Heart disease continues to be the leading cause of death for all Americans, and coronary artery disease is the most common form of heart disease.[1] Worldwide, ischemic heart disease (IHD) accounts for nearly 9 million deaths annually.[2] Not surprisingly, there is great interest in developing methods to reduce the disease burden and mortality surrounding IHD, and the limited regenerative ability of the human heart makes it a uniquely attractive target for stem cell therapy. In a recent article, Osada and colleagues[3] describe their success with transplanting human induced pluripotent stem cell–derived cardiac tissue grafts into a postmyocardial infarction rat model. While previous attempts at transplanting allogenic cardiomyocytes have been promising,[4] the current paper highlights both the success of the human induced pluripotent stem cell–derived cardiac tissue technology, as well as its functional utility as a strategy for postmyocardial infarction cardiac regeneration.

The authors have been developing their stem cell–derived cardiomyocyte graft for many years. They have previously described their differentiation of clinical-grade human pluripotent stem cells into high-yield cardiomyocytes and vascular endothelial cells using transcription factor signaling, as well as their creation of a transplantable graft composed of stackable cardiomyocyte sheets using gelatin hydrogel microspheres (GHMs) between each sheet. The crucial addition of GHMs mitigates against diffusion-mediated hypoxic graft necrosis and allows the stacking of up to 15 cell sheets, increasing the thickness (and theoretically, function) of the transplantable graft.[5] In the present study, these tissue grafts of contractile myocytes were implanted onto the anterior ventricular wall of rats with recent myocardial infarction caused by surgical ligation of the left anterior descending artery. These treated rats were then observed for 4 weeks and compared with control rats (sham operations) and rats with "inferior" grafts (no GHM used in graft construction). The authors demonstrated that the GHM-grafted rats experienced significantly greater cardiac recovery based on echocardiographic parameters, as well as impressive histologic findings of increased neovascularization, reduced scar size, and increased sarcomere maturation. On the surface, the authors have compiled exciting evidence to support further research into the use of stem cells to regenerate cardiac tissue and prevent adverse ventricular remodeling after infarct.

Nevertheless, a cautious approach to a new technology is always wise. This fledgling technology has several major limitations stymieing widespread implementation. Implanting foreign biological tissue raises grave concerns about tumorigenicity and—specifically within the heart—arrhythmogenicity.[6,7] The authors did not find any evidence of neoplasm in their rats, but they were limited by a relatively short timescale and small number of subjects. They also did not evaluate for arrhythmias in their subjects. Furthermore, the current model is only applicable in the acute postmyocardial infarction period and has not been studied in chronic IHD. In fact, the rat model at hand is of

From the [a]University of Massachusetts Chan Medical School; and [b]Division of Cardiac Surgery, UMass Memorial Medical Center, Worcester, Mass.

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Address for reprints: Leora B. Balsam, MD, Division of Cardiac Surgery, UMass Memorial Medical Center, University Campus, 55 Lake Ave North, Worcester, MA 01655 (E-mail: leora.balsam@umassmemorial.org).

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uncertain relevance, as the infarction is surgically induced in animals with otherwise-healthy coronary arteries, as opposed to those with progressive atherosclerotic disease. Applying this technology to humans would also require a significant increase in scale, as well as a surgical procedure. The authors have created an elegant and successful tissue graft. Without undermining their fascinating results, much more work needs to be done before cardiac regeneration can be considered a viable treatment option in clinical IHD.

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