References

1. Cao N, Huang Y, Zheng J, Spencer CI, Zhang Y, Fu J, et al. Conversion of human fibroblasts into functional cardiomyocytes by small molecules. *Science*. 2016;352:1213-20.
2. Ieda M, Fu JD, Delgado-Olguin P, Vedantham V, Hayashi Y, Bruneau BG, et al. Direct reprogramming of fibroblasts into functional cardiomyocytes by defined factors. *Cell*. 2010;3:375-86.
3. Mathison M, Gersch RP, Nasser A, Lilo S, Korman M, Fourman M, et al. In vivo cardiac cellular reprogramming efficacy is enhanced by angiogenic preconditioning of the infarcted myocardium with vascular endothelial growth factor. *J Am Heart Assoc*. 2012;1:e005652.
4. Sadahiro T, Yamanaka S, Ieda M. Direct cardiac reprogramming: progress and challenges in basic biology and clinical applications. *Circ Res*. 2015;116:1378-91.
5. He WJ, Hou Q, Han QW, Han WD, Fu XB. Pluripotent reprogramming and lineage reprogramming: promises and challenges in cardiovascular regeneration. *Tissue Eng Part B Rev*. 2013;20:304-13.

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EDITORIAL COMMENTARY

Transdifferentiation: A new frontier in cardiovascular cell therapy

Michael Ibrahim, MD, PhD, and Pavan Atluri, MD

From the Division of Cardiovascular Surgery, Department of Surgery, University of Pennsylvania, Philadelphia, Pa. Disclosures: Authors have nothing to disclose with regard to commercial support.

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Address for reprints: Pavan Atluri, MD, Division of Cardiovascular Surgery, Department of Surgery, University of Pennsylvania, Silverstein 6, 3400 Spruce St, Philadelphia, PA 19104 (E-mail: pavan.atluri@uphs.upenn.edu).

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Heart failure, the final common pathway of cardiac pathologic remodeling, represents the clinical manifestation of loss of cardiomyocyte number and function in a well-described downward spiral, where increasing mechanical overload leads to pathologic hypertrophy and progressive cell death.¹ The holy grail of stem cell therapy has been to replace those cardiomyocytes lost or damaged in the pathogenesis of heart failure. This requires (1) the development of de novo mature contractile cardiomyocytes that are not immunogenic, (2) the engraftment and survival of these cells such that they can make a meaningful contribution to contraction, and (3) electrical coupling of these cells for concerted action. These have proved elusive goals, and an ideal stem cell population has not been identified. The prospect of using transdifferentiation to manipulate native cell populations into viable contractile myocardium represents a potential breakthrough to these problems, as Kota and colleagues discuss in this issue of the *Journal*.²

A decade ago, Takahashi and Yamanaka³ showed that it was possible to use a cocktail of cellular reprogramming factors to revert terminally differentiated cells to a state of pluripotency, so-called induced pluripotent stem cells.

Pavan Atluri, MD (left), and Michael Ibrahim, MD, PhD (right).

Central Message

Transdifferentiation of in situ fibroblasts to functional cardiomyocytes by means of gene- or small factor-based therapies represents a potentially significant advance in stem cell therapy for heart failure.

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These cells may be subsequently directed into cardiomyocyte cell fates, but their use is plagued by many issues, not least by the hurdle of achieving cell engraftment. This problem stimulated the development of direct cellular reprogramming, the use of signaling factors to convert one terminally differentiated cell type into another, without the pluripotent stage.

Fibroblasts, the most numerous cells in the mammalian heart, are a sophisticated population of pleiotropic cells that play a role in scaffolding contracting cardiomyocytes, intercellular signaling, and contraction.^{4,5} Ieda and

colleagues⁶ showed that it was possible to use gene transfer to reprogram cardiac fibroblasts directly into induced cardiomyocytes. Rosengart's group⁷ have shown that this strategy can substantially augment function in animal models. Recently, Cao and associates⁸ have shown that transdifferentiation can be achieved with small molecules, avoiding the need for gene transfer and its associated problems, generating so-called chemically induced cardiomyocytes, if at a lower rate than that in gene therapy studies. It remains to be seen whether this approach can produce improvements in cardiac function that could be clinically significant.

The development of a therapeutically efficacious method of using small molecules to induce transdifferentiation without the potential hurdles of pluripotency and cell delivery and engraftment would represent a substantial step forward toward the holy grail of stem cell therapy. A number of experimental steps are required to achieve this goal, not least in optimizing the environment for these cells in a scarred, ischemic myocardium. the use of prevascularization factors to enhance the conditions for these new, metabolically active cells is one approach,⁶ and it may be used in combination with established technologies such as a

left ventricular assist device platform, which reduces workload and wall strain and enhances coronary perfusion.⁹

References

1. Jessup M, Brozena S. Heart failure. *N Engl J Med*. 2003;348:2007-18.
2. Kota PS, Naguib MR, Patel V, Rosengart TK. Less may be more: using small molecules to reprogram human cells into functional cardiomyocytes. *J Thorac Cardiovasc Surg*. 2017;153:128-30.
3. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell*. 2006;126:663-76.
4. Cartledge JE, Kane C, Dias P, Tesfom M, Clarke L, McKee B, et al. Functional crosstalk between cardiac fibroblasts and adult cardiomyocytes by soluble mediators. *Cardiovasc Res*. 2015;105:260-70.
5. Souders CA, Bowers SL, Baudino TA. Cardiac fibroblast: the renaissance cell. *Circ Res*. 2009;105:1164-76.
6. Ieda M, Fu JD, Delgado-Olguin P, Vedantham V, Hayashi Y, Bruneau BG, et al. Direct reprogramming of fibroblasts into functional cardiomyocytes by defined factors. *Cell*. 2010;142:375-86.
7. Mathison M, Gersch RP, Nasser A, Lilo S, Korman M, Fourman M, et al. In vivo cardiac cellular reprogramming efficacy is enhanced by angiogenic preconditioning of the infarcted myocardium with vascular endothelial growth factor. *J Am Heart Assoc*. 2012;1:e005652.
8. Cao N, Huang Y, Zheng J, Spencer CI, Zhang Y, Fu JD, et al. Conversion of human fibroblasts into functional cardiomyocytes by small molecules. *Science*. 2016;352:1216-20.
9. Ibrahim M, Rao C, Athanasiou T, Yacoub MH, Terracciano CM. Mechanical unloading and cell therapy have a synergistic role in the recovery and regeneration of the failing heart. *Eur J Cardiothorac Surg*. 2012;42:312-8.