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Commentary: I fix what's broken—including the heart

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Myocardial infarction causes irreversible heart tissue damage, leading to scar formation and inevitably ischemic heart failure (IHF). It affects roughly 6 million Americans, one half of whom will die within the first 5 years of diagnosis.¹ Despite the advantages of percutaneous coronary intervention, time (90-minute door-to-balloon) remains still a limitation to avoid scarring and fibrosis.²

Hence, ischemic heart failure has still a great impact on both hospital admission and economic burden. Either transplantation or left ventricular assistance are considered the gold standard for the treatment of end-stage IHF, but both are limited by donor shortage and complication rates, respectively.^{3,4}

For many years, heart tissue was considered not repairable, since after ischemic damage, cardiomyocytes were unable to regenerate cardiac tissue and therefore a fibrotic scar forms in place of it.⁵ However, in recent decades, stem cells started to be considered for the treatment of IHF, leading to their injection in different types of exogenous cells. In 2007, Smith and colleagues⁶ described the isolation procedure of cardiosphere-derived cells (CDCs) by means of a percutaneous endomyocardial biopsy. Since then, different attempts have been made to improve the potentiality of CDCs to differentiate, replacing scar with new myocardium.⁷⁻⁹ Hosoyama and colleagues⁷ demonstrated the role of hypoxia to prime CDCs implanted into the ischemic heart. In that condition, vascular endothelial

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CENTRAL MESSAGE

The power of myocardial repair by cardiosphere-derived cells can be enhanced using transcriptional activators, acting on selected cardio-specific genes.

growth factor production increased, and fibrosis was reduced. Takehara and colleagues⁸ investigated the priming role of pretreatment of CDCs with basic fibroblast growth factor. The isolation of CDCs from patients taking beta-blockers was shown to provide greater extraction of CDCs. Moreover, these CDCs showed a reduced expression of fibrosis-associated micro-RNAs, whereas there was a greater expression of cardiac regeneration-associated micro-RNAs.⁹

While we await phase 2 trial (ALLSTAR [ALLogeneic Heart Stem Cells to Achieve Myocardial Regeneration], DYNAMIC [Dilated cardiomyopathy iNtervention With Allogeneic Myocardially regenerative Cells]) results,^{10,11} the paper from Sano and colleagues¹² strengthens interest in CDCs, showing how to handle synthetic transcriptional activators derived from the clustered regularly interspaced short palindromic repeat (CRISPR)-Cas9 system to prime endogenous expression of genes. The authors selected some cardio-specific target genes (Gata4, Mef2c, Nkx2-5, Hand2, and Tnnt2) to verify whether dCas9-based transcriptional activators could regulate endogenous gene expression in CDCs using single and multiple sgRNAs, demonstrating significantly greater expression of differentiation factors such as Gata4, Hand2, and Tnnt2. The clinical epiphenomenon was a significant increase of left ventricular systolic function with respect to either CDCs without transcriptional activation or control group. Finally, CDCs with transcriptional activation showed a significant reduction of scar area.¹²

In 1966, Bernard Malamud, the Pulitzer Prize winner, wrote *The Fixer*,¹³ where he stated “I fix what’s

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broken—except in the heart.” Nowadays, we are closer and closer to saying “I fix what’s broken—including the heart.”

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