



Novel Cell Replacement Strategies for Heart Failure Treatment

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Heart Failure Treatment

Myocardial infarction (MI), or heart attack, is caused by the blockage of blood flow in the heart, which reduces oxygen levels, damages tissues (ischemia) and kills close to one billion cardiomyocytes (infarction) [1]. Fibroblasts then migrate into the infarcted area where they proliferate to create a cardiomyocyte-depleted scar that cannot contribute to the electrophysiologically-driven contractions of the heart. This often causes HF leading to fatigue, peripheral edema, or even death. To find more effective therapies for HF, we need to improve our understanding of its pathophysiology and develop new approaches to treating it.

Cell-replacement therapy has emerged as a novel approach to treat HF. This approach relies on the theory that after MI or in HF, lost cardiomyocytes can be replaced by adding either new cardiomyocytes or a potential source of cardiomyocytes such as stem cells. To find the most effective approach, researchers have tested several types of stem cells including skeletal myoblasts [2], cardiac progenitor cells [3], and mesenchymal stem cells from bone marrow [4]. However, they have only been modestly successful because the beneficial effects are mainly mediated by indirect paracrine mechanisms: stem cells do not transdifferentiate into cardiomyocytes *in-vivo* and the number of stem cells retained in the heart after delivery is disappointingly low [5]. Fortunately, cell-replacement therapy for HF using pluripotent stem-cell-derived cardiomyocytes showed more promising results in rodents and non-human primates because they integrate and electrically couple with the healthy myocardium [6-8]. However, technologies involving stem-cell-derived cardiomyocytes must be further optimized before they can effectively treat HF. Specifically, we need to find methods that improve the efficiency and consistency of cardiomyocyte differentiation in large scale, their survival in disease conditions, their integration into cardiac tissue, and their resistance to autoimmune rejection.

Recently, Srivastava laboratory and others demonstrated an alternative approach-transdifferentiation of resident cardiac fibroblasts (CFs) into cardiomyocytes, called direct cardiac reprogramming. They initially illustrated that CFs transdifferentiate into a more cardiac-like state both *in-vitro* and *in-vivo* when treated with a combination of three transcription factors associated with cardiogenesis-Gata4, Mef2c, and Tbx5 (GMT) [9]. Building on this technology, subsequent reports have shown that various combinations of transcription factors, and microRNAs and other combinations [10-13]. However, the efficiency of reprogramming and extent of cardiac-specific gene expression and morphology, such as sarcomere organization, have been consistently better *in-vivo* than *in-vitro* [14,15].

In fact, reprogramming CFs *in-vivo* improved cardiac function after injury (e.g., ejection fraction, cardiac output, and stroke volume) [14, 15]. While reprogramming the pool of endogenous cardiac fibroblasts

into cardiomyocyte-like cells is a promising approach for cardiac regeneration, the methods must be refined to enhance the efficiency and quality of their reprogramming. Thus, we must understand the mechanism by which the reprogramming factors fundamentally alter the cell state. This work is currently conducted by various groups around the world to identify the barriers for cell transdifferentiation.

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