International Journal of
Surgery Research and Practice

Wang, Int J Surg Res Pract 2014, 1:1
ISSN: 2378-3397

Editorial: Open Access

Induced Pluripotent Stem Cells and Heart Failure Therapy

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Heart failure is a major public health concern worldwide, and coronary artery disease in particular is the leading cause of death in developed countries [1]. Percutaneous coronary interventions can effectively treat coronary artery disease, but the management of ventricular remodeling and chronic ischemic cardiomyopathy after Myocardial Infarction (MI) remains a challenge. The human heart has very limited regenerative capacity, which is insufficient to replace the cells lost after MI. Stem cell therapy is a promising new approach to restoring cardiac function and preventing ventricular remodeling after acute MI.

Although cardiac stem cells that can differentiate into all types of cardiac cells are present in the adult myocardium, their relevance in regeneration is still controversial. Incomplete Cardiomyocyte (CM) regeneration, particularly after injury, was originally attributed to stem cell differentiation that was insufficient to completely repair or replace the damaged tissue [2]; and Mesenchymal stem cells (MSCs), which could improve infarcted myocardium function, but would not survive in the heart for a long term [3]. Both undifferentiated Embryonic stem cells (ESCs) and ESC-derived CMs could survive, but they are not recommended for clinical applications because of ethical concerns arising from the cells' embryonic origin, and allograft rejection. Hence, MSCs and ESCs are not good candidates for regenerative medicine.

One of the most significant achievements in stem cell research is the successful generation of induced pluripotent stem cells (iPSCs). In 2006, the Yamanaka group discovered that somatic cells could be reprogrammed into iPSCs by ectopically expressing four key factors: Oct3/4, Sox2, c-Myc, and Klf4 [4]. The reprogrammed cells were called induced pluripotent stem cells because they resembled ESCs in morphology, gene expression, and developmental potential. For this research, S. Yamanaka were awarded the Nobel Prize in 2012. This discovery has given rise to great excitement and interest in cardiovascular regenerative medicine researchers because iPSCs are a promising alterative for clinical applications. iPSCs can be easily derived from adult patients' own cells, and therefore bypass ethical and immunogenic concerns.

Although cardiomyogenic differentiation of iPSCs has already shown promises a therapy for heart failure, the procedure carries a serious implication. Transplantation of undifferentiated iPSCs into cardiac tissue has revealed the cells' tumorigenic potential, which originates in their embryonic nature [5,6]. On the other hand, transplantation of iPSC-derived cardiomyocytes (iPSC-CMs) can avoid this serious limitation: grafts remain within the infarcted heart and improve cardiac function after ischemic damage. Transplantation of iPSC-CMs into infarcted ventricles has resulted in formation of gap junction proteins between iPSC-CMs and host CMs, suggesting transplanted cardiac myocytes are integrated into the native myocardium [7]. Nevertheless, the maturation state of iPSC-CMs remains a challenge for therapeutic applications.

Another safety concern is the integration of viral encoded transcription factor insertions into the host genome. Research in this area has resulted in the development of numerous safe methods to avoid genomic integration. Non-viral or non-integrating methods involve transient expression of reprogramming factors without genomic integration. For example, iPSCs can be generated with Sendai virus (an RNA virus cannot be integrated into the genome), removable transposon systems, and direct delivery of recombinant proteins, synthetic mRNA, and even small-molecule compounds [8]. These results provided strong evidence that viral integration methodologies are not required for in vitro reprogramming. This was an important step toward making the technology safer for clinical applications.

We are still on the road to cardiac applications of iPSCs, but it remains largely an unmapped route, open to exploration. How can we effectively improve the efficiency of iPSC differentiation into cardiac lineages? Will different iPSC lines show distinct differentiation profiles? Which profiles would be advantageous (or disadvantageous) to treat heart failure? Is the original cell source related to the cardiac commitment of iPS cells? What human iPSC technologies will be optimal for treating heart failure? Research to answer these questions is underway.

Acknowledgement

The authors would like to thank Ana María Rodríguez, PhD, a member of the Baylor College of Medicine Michael E. DeBakey Department of Surgery Research Core Team, for her editorial assistance during the preparation of this manuscript.

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Citation: Wang H (2014) Induced Pluripotent Stem Cells and Heart Failure Therapy. Int J Surg Res Pract 1:001e

Received: August 17, 2014: **Accepted:** August 20, 2014: **Published:** August 23, 2014

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