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Editorial

Cardiac Regeneration: Challenges and Clinical Applications

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Myocardial Infarction (MI) also known as heart attack is a major cause of death every year worldwide. Even in developed countries, heart failures/diseases remain a leading cause of morbidity and mortality affecting approximately 500,000 individuals per year. In a healthy individual, myocardial cellular repair mechanisms maintain heart's standard operating function and homeostasis.Imbalance in these repair mechanisms sets off a heart attack. Currently, heart transplantation and mechanical circulatory support serve as reliable sources of treatment for MI and as means to improve post-infarct ventricular function. Scientists have been working from more than 25 years to find ways for cardiac regeneration after an immediate heart attack. Although these procedures and other medications have been developed to provide improvements in heart function, there are no absolute significant means to replenish cardiomyocytes and regenerate damaged cardiac muscle till date. Stem-cell therapy, in vivo & in vitro cellular reprogramming, gene & cell therapy, biological-device combination products are some of the areas which have been in spotlight for the past few years from a research perspective.

The concept of reprogramming somatic cell type to a differentiated cell fate without first becoming a stem/progenitor cell was thoroughly studied by many groups across the world as it can be a very powerful tool in regenerative medicine. In 2010, a major breakthrough came in the field when Ieda et al.,showed that three crucial developmental transcription factors (Gata4, Mef2c, Tbx5) were able to successfully reprogram cardiac fibroblasts directly into cardiomyocyte-like cells (iCMs) [1]. Direct cellular reprogramming, also known as "transdifferentiation" can be a potential strategy for reprogramming resident fibroblasts in the heart to differentiated cardiomyocyte-like cells by inducing cardiac transdifferentiation through "cardiac-differentiating factors" bypassing a progenitor stage. The reprogrammed iCMs were similar to cardiomyocytes in their epigenetic state and also global gene expression. A significant focus has been on improving the reprogramming efficiency through various approaches as the transdifferentiation rate of fibroblasts to iCMs is relatively inefficient.

Our lab in 2012,(Mathison et al.,)has shown that pre-treating infarcted myocardium with gene transfer of angiogenic VEGF enhances the GMT-mediated cellular reprogramming efficacy in reducing the scarring of myocardium i.e., fibrosis and substantial improvement in myocardial function post MI [2]. This significant study advanced the field by assimilating a clinically relevant strategy of pre-treating infarcted myocardium with angiogenic VEGF to improve the function of postinfarct myocardium. Another important study from Mathison et al., showed the use of a polycistronic "triplet" vector encoding all 3 transgenes(GMT), which enhanced the postinfarct ventricular function in comparison to "singlet" vectors [3].

From a clinical perspective, non-integrating expression vectors (Adenovirus) are more preferable as they have numerous advantages when compared to retro and lentiviral delivery systems. To test this hypothesis, efficacy of Adenovirus vs. lentivirus vectors encoding Gata4, Mef2c and Tbx5 to transdifferentiate cardiac fibroblasts to iCMs was assessed. Contrary to the belief that Ad-infected cells are prone to immune-mediated cytolysis, the data obtained in this study [4] demonstrates that adenoviral vector encoding GMT is able to significantly improve cardiac function after MI in the rat heart. These findings have potential useful applications that can be translated to treat patients with heart failure.

Additional factors such as epigenetic regulators, microRNAs, were explored in order to improve the efficiency and robustness of reprogramming fibroblasts to iCMs. MicroRNAs are shown to be key players which target signaling pathways, epigenetic regulation of key transcription factors. Jayawardane et al., used a combination of miRNAs (miR-1, miR-133, miR-208 and miR-499) into neonatal cardiac fibroblasts and succeeded in obtaining functional iCMs [5]. Cardiac reprogramming mediated through miRNA might be a secure application in clinic given its advantages of not being incorporated into the host genome. Consequently, multiple groups published the use of a cocktail containing- key transcription factors, small molecules, signaling inhibitors to promote cardiac reprogramming. Most of the studies were performed in mouse and rat myocardial infarction models while some focused on converting human fibroblasts to functional cardiomyocytes through

various approaches.Recently, we demonstrated that in porcine and human cells, conventional GMT was insufficient for reprogramming. But, by the addition of key transdifferentiating factors Hand2, Myocardin or microRNA (miR)-590 alone, in combination with GMT was able to successfully reprogram cardiac fibroblasts to iCMs [6]. This study reveals a novel mechanism where miR-590 upregulated key gene signatures associated with a matured cardiomyocyte phenotype and suppressed other fibroblast-associated genes by directly inhibiting expression of the zinc-finger protein, Sp1 (specificity protein1) showing that Sp1 is a direct target of miR-590. Sp1 was previously reported to play an essential regulatory role in gene expression (col1a1, TGF) relevant to fibrosis. Collectively, the findings from this study suggest novel pathways applicable to human cardiac reprogramming.

Stem-cell based regenerative therapy with induced pluripotent stem (iPS) cells has its limitations like- efficient transplantation and integration within the area of injured myocardium, tumorigenicity and immunogenicity risks. With all these drawbacks, direct cardiac cellular reprogramming holds promise to treat heart failures. It has attracted considerableattention although being a relatively new field. It sustains great potential for cardiovascular disease research and treatment both from a clinical and biological standpoint. An interesting aspect in studying the mechanisms involved in cardiac reprogramming is the complex interplay amongst transcriptional regulators, epigenetic modifiers and miRNAs.Further studies, including improving the reprogramming efficiency of human cardiac fibroblasts, safe delivery of iCMs, therapeutic efficacy and suitable larger animal models, are needed. New regenerative therapies are constantly in demand and the need to develop, improve the current approach is required to advance the field. In summary, this report is a brief review highlighting the most recent improvements and challenges in cardiac regeneration with an emphasis on our crucial contributions to the field.

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