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Perspective

Perspectives: Cardiomyocytes from Skeletal Muscle Stem Cells for Cardiac Repair

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Heart failure is a major contributor to mortality in the United States. Many cardiomyocytes (CM) die following myocardial insult, and the post-natal mammalian heart has very limited regenerative capacity. Heart organ transplantation is a final therapeutic option to prevent patient death when heart failure is imminent. However, donor organ availability cannot completely meet current demands, and long-term prognosis remains unsatisfactory. Cellular cardiomyoplasty has emerged as one potential option to reverse maladaptive remodeling and restore contractile function. It involves the transplantation of cells into the heart to repair damaged myocardium. Choosing the right cell type remains a subject of debate. Using fetal CMs or embryonic stem (ES) cells would be undesirable from an ethical standpoint because they require the destruction of embryos and fetuses. While induced pluripotent stem cells (iPSc) can generate CMs with high purity, and direct CM induction from fibroblasts can produce CMs without reprogramming to pluripotency, their phenotype remains immature. Genome modification also poses a risk of oncogenic transformation in vivo [1,2]. Use of autologous adult stem cells overcomes the risks of tumor formation and other safety factors involved in iPSc generation or direct CM induction from fibroblasts. Various types of adult stem/progenitor cells have been tested for cardiac repair including skeletal myoblasts, bone marrow derived stem cells (BMSC), adipose stem cells (ASC), and more recently, cardiac stem cells (CSC). While many of these stem cell types have shown functional improvements in animal and clinical models, these benefits were thought to be primarily due to paracrine mechanisms that stimulate angiogenesis and attenuate fibrosis [3]. Few BMSCs and ASCs differentiate into CMs. CSCs are promising, but their isolation remains a challenge, and CSC pools are often depleted after myocardial injury [4]. In human trials, only high-dose skeletal myoblast transplantation has been shown to produce contractile tissue in vivo with functional improvement in some human patients. However, high incidence of ventricular arrhythmias is a major issue for the use of skeletal myoblasts for cardiac repair. The cause of ventricular arrhythmia following skeletal myoblast transplantation is lack of electrical coupling between donor myoblasts and surrounding myocardium [5]. Despite this early limitation, skeletal myoblasts remain one of the few widely investigated cell types which can generate contractile force to support a failing heart.

Adult skeletal muscle contains various stem/progenitor cell populations aside from skeletal myoblasts (satellite cells). Skeletal muscle stem cells (skmSC) are multipotent cells that retain their myogenic heritage but have greater multilineage potential, being able to generate other tissue types including, bone, cartilage, and fat [6]. They are isolated from muscle biopsies by a modified pre-plate method. Since cardiac and skeletal muscle both arise from mesoderm, and cardiac and skeletal muscle share major transcription factor and sarcomere proteins during development [7], it has been theorized that skmSCs can differentiate into CM-like cells, which would overcome the limitations of skeletal myoblast transplantation. Our research has focused on determining the methods by which skmSCs can differentiate into CMs. We first reported that rat skmSCs cultured in a 3D environment with collagen and matrix factors differentiated into functional CM-like cells that beat spontaneously, generated contractile force, expressed cardiac-specific genes/proteins including connexin-43 gap junctions, displayed cardiac-like intracellular calcium transients, and responded to isoproterenol [8]. Recently, we reported that human skmSCs cultured as a 3D engineered tissue also beat spontaneously, generated force, expressed cardiac-specific genes/proteins, displayed cardiac-like intracellular calcium transients, and responded to isoproterenol [9]. However, they retained properties of skeletal muscle including expression of MyoD, myogenin, and fast skeletal MHC. In addition, their electrical coupling remained immature. Interestingly, iPSc derived CMs also expressed these skeletal muscle genes/proteins, supporting the idea of an overlapping biochemical signature between immature cardiac and skeletal muscle [9].

Based on these findings, we hypothesize that generating more functionally CM-like cells depends on finding factors/methods that (1) promote cardiomyocyte differentiation and (2) suppress skeletal muscle differentiation. This idea is supported by a study by Crippa et al. They found that a specific microRNA, miR-669, regulated the switch between cardiac and skeletal muscle lineages in CSCs by post-transcriptionally targeting MyoD [10]. Recently, we found that using a combination of appropriately-timed small molecules and growth factors increased cardiac gene expression, improved contractile performance, and potentiated electrical coupling of human skmSC derived engineered tissue

(unpublished data). However, these cells still retain some skeletal muscle properties.

In light of our previous findings and recent work, multiple factors are likely required to promote advanced functional differentiation of skmSCs towards CMs. The external microenvironment and internal molecular switches are likely both important in promoting CM differentiation. Cardiac specific ECM has been shown to promote cardiomyocyte differentiation of embryonic stem cells [11]. Post-transcriptional modifications such as acetylation and methylation have also been implicated in CM differentiation [12]. As previously mentioned, cardiac and skeletal muscle share considerable similarities during development, but these similarities are lost when these tissues become terminally differentiated after birth. How this terminal switch takes place remains poorly understood. Studying developing cardiac and skeletal muscle using new high-throughput genomics tools such as RNA sequencing may reveal new transcription factors or post-transcriptional regulators which were previously not known to be important in muscle differentiation. These new factors can be applied to skmSCs to promote CM differentiation.

While previous cell transplantation studies showed functional improvements following cell transplantation, few cells have demonstrated long-term engraftment. Many cells die when they are exposed to the harsh environment of the post-infarcted heart. Tissue engineering may offer some advantages over traditional delivery methods. Using a scaffold improves the retention and engraftment of transplanted cells by shielding cells from the harsh environment and providing an anchorage matrix.

Tackling a problem as large as heart disease requires an equally large commitment of time, effort, and resources. It will also require novel, interdisciplinary thinking. From an engineering perspective, the heart is a complex structure. From a developmental biology perspective, it is dynamic, while systems biology views this dynamism in a broader context. Studying striated muscle developmental biology using transcriptomics and systems biology can fill in some of the knowledge gaps related to terminal muscle differentiation. Regenerative medicine and cellular engineering can apply these new findings to optimize skmSCs for cardiac repair. Finally, tissue engineering can provide a means to best integrate these engineered cells with an existing system (the heart).

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