Journal of Stem Cells & Regenerative Medicine
ISSN 0973 - 7154

EDITORIAL

JSRM Code: 014010100001

Germline Stem Cells in Myocardial Regeneration – A new hope worth a delve

The heart is the first organ to be fully formed and become functional in the developing human embryo at a mere 22-23 days of intra-uterine life. Cell division in cardiac myocytes is blocked in the adult[1], wherein they repair more by enlargement (hypertrophy) rather than proliferation while responding to injury. Therefore, in regenerative cell therapies for the myocardium, the cells *in vitro* cultured and injected, how far they make the native cardiomyocytes to enter the cell cycle again and/or proliferate or fuse with the native cardiac myocytes remain a major question. In most cardiac regenerative cell-based therapies using adult somatic and stem cells[2], both intra and extra-cardiac derived, modes of action have been reported to be more of a paracrine nature instead of integration with the host cardiac tissue via cellular contacts[3]. Regeneration of the myocardial tissue is made even more complex than other tissues such as the spinal cord, as in addition to regeneration of the muscle components, re-establishment of a functional syncytium or integration of the regenerated cells/tissue with the pre-existing syncytium by establishment of the integrated conducting system is required[4] without which cells transplanted in aiding a regeneration may complicate the outcome by becoming foci of ectopic electrical activity leading to severe arrhythmias needing the implantation of cardioverter defibrillators[3].Therefore, it is wise to postulate that than adult cells like BMMNC, HSC, MSC, EPCs etc which might be safer in terms of risk of teratogenicity and carcinogenicity, their plasticity being limited, pluripotent stem cells such as embryonic cells (ESC) and induced pluripotent stem (iPS) cells may be better candidates for cell-based therapies owing to their increased plasticity compared to adult derived intra-cardiac and extra-cardiac cells. Pluripotent stem cells having more potential for cardiac cell differentiation, nevertheless have associated issues such as teratoma formation, genetic instability, ethical issues (embryonic and fetal stem cells) and accumulation of mitochondrial DNA mutations in iPSCs[5].

Mahapatra *et al*[6] in this issue report the potential of germline pluripotent stem cells (hgPSCs) obtained from testes, which become pluripotent from their native unipotent nature when removed from their niche and can be induced to form paracrine effector-yielding cardiac cells. The advantages of this pluripotent cell population has been suggested that they do not have risk of teratoma formation *in vivo* as the pluripotency genes are down-regulated once differentiation starts. Also, these cells do not have the ethical issues associated with embryonic and fetal stem cells. They further note that while cardiac cells derived from human ES and human iPS cells consistently show rhythmic beating; hgPSC-derived cardiac cells did not. According to the authors, this is perhaps advantageous as it will prevent the development of arrhythmias after *in vivo* transplantation, albeit expression and secretion of key paracrine factors known to be pro-growth and pro-differentiation retaining the regenerative potential through expression and secretion of key paracrine factors which promote cellular growth and differentiation[6]. This study brings into focus the inability of the cardiac cells induced from testes derived germline stem cells to beat spontaneously as an advantage but it is essential that cell-based therapies must aim at regeneration of a functional cardiac syncytium by optimal integration of the transplanted cells with the host tissue. Germline stem cells have been derived from the ovary too[7]. These cells from ovary might be considered more functional compared to testes derived germline stem cells for two reasons, (i) the ovum itself having the ability to be activated by chemical stimulation to form nonembryonic blastocysts giving rise to parthenogenetic stem cells (PSCs)[8] and (ii) PSC-derived cardiomyocytes have been proven to have seamless electrical integration into recipient myocardium[9]. Developing a novel solution to unmet needs has to balance between efficacy and risks from both safety and ethical aspects. With Pluripotent stem cells (embryonic stem cells and iPS cells) having greater potency but higher risk on one end while adult stem cells with proven safety but limited efficacy on the other end, the germline stem cells with the recent data evolving on their potency and safety[10] balancing between the above two types of cells could be a safe bet, which however, needs to be proven with extensive research.

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