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Epigenetics, Ethnicity, Bioinformatics and Nanotechnology Opening Frontiers in Cardiac Medicine

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Abstract

Stem cell based therapy directed towards improving the long-term therapeutic outcome of heart disease in many regards remains in its infancy. Although strategies with bone marrow derived stem cells have been prevalent in clinical trials, other stem cell resources are less explored. The ability to use reprogrammed somatic cells for patient-optimized therapies, either from direct reprogramming to cardiac lineage or reprogramming first to pluripotent stem cells, requires expanding our understanding of how the epigenetic landscape affects downstream differentiation into cardiomyocytes or other specialized cardiac cells. Helping to fill this information gap are advances in whole genome analysis and bioinformatics, coupled with in vitro differentiation protocols further optimized through the use of nanotechnology to aid in biomimetic representation of the cardiogenic niche. Nanotechnology is also providing new functional assays for comparative quantitative assessment of derived cells. The interdisciplinary juggernaut being applied to understanding cardiac development, regulatory pathways and transitions, roles of ethnicity, and disease pathways is expected to propel the field within the next decade with new promise for therapeutic potential to address the devastating morbid diseases associated with cardiovascular diseases.

Keywords

iPSC, ESC, Cardiovascular, Cardiomyocytes, Differentiation, Reprogramming, SNP

Short Review

The impact of heart disease on long-term survival has remained largely unchanged for over two decades, even described to have poorer life expectancy than many cancers [1]. Globally cardiovascular disease (CVD) remains the number one cause of death according the World Health Organization (WHO), representing 17.5 million people or 31 percent of all global deaths. The 2015 update by the American Heart Association (AHA) in conjunction with the Center for Disease Control (CDC), National Institutes of Health (NIH) and other agencies emphasizes the immense global health and economic burdens of cardiovascular disease (CVD) with stroke, congenital heart disease, heart failure, and rhythm disorders being among major clinical disease conditions. In 2011, 1 in 9 deaths mentioned heart failure (HF) similar to levels in 1995. Coronary heart disease alone resulted in 1 in 7 deaths in the US in 2011, or 375,295 reported deaths, including myocardial infarctions. In the US a coronary event occurs every 34 seconds, resulting in death every 84 seconds. Despite longer initial survival the poor overall long-term prognosis is concerning. Although natural repair and regeneration mechanisms exist for the heart, these are still being explored but decrease with increasing age [2,3]. Significant hope lies in stem cell efforts to bring treatment solutions, initially in terms of cardiomyoplasty and other cell therapies for myocardial infarctions [4], but beyond this to expand on fundamental concepts of heart development and disease.

In cardiac ischemic injury, the loss of cardiomyocytes through apoptosis, along with activation of inflammatory and repair responses that include remodeling of the injured area with myofibroblast tissue play critical roles in heart failure. To restore electromechanical action of ventricular muscle and pumping activity lost in myocardial infarctions requires replacing myofibroblast scar tissue with new cardiomyocytes [5]. The successful derivation of mammalian cardiomyocytes from stem cells *in vitro* has been explored from adult cardiac stem cells, pluripotent embryonic and induced pluripotent stem cells [6-8] and induced cardiac direct reprogramming [9,10] approaches. Clinical trials have relied primarily on bone marrow derived stem cells and have seen minimal or no effect [11], bringing into question whether bone marrow represents the best source of stem cells for cardiac therapies [12]. Clinical trials that use alternate stem cell sources, such as endogenous CSCs to address ischemic cardiomyopathy [13-15] have produced encouraging results with reduced infarct size and improved left ventricle function suggesting therapeutic regeneration without side effects. In addition the first world hESC clinical trial for cardiac repair is underway, initiated in 2014, to address left ventricular systolic dysfunction with contraction reduced at or below 35% [16]. A challenge in comparing effectiveness of non-endogenous stem cell sources in clinical trials, is that not all stem cell derived cardiomyocyte sources are characterized at the transcriptome or epigenome level of detail which is expected to include relevant information to predict interactions with other cells *in vivo* that may influence integration success.

The ability of stem cell studies to inform on signaling pathways underlying mesoderm and cardiac mesoderm differentiation [17] as well as heart morphogenetic development and heart disease models that impact cardiac therapy [18] reflect key aspects of a field that is clearly untapped in potential. The application of bioinformatics

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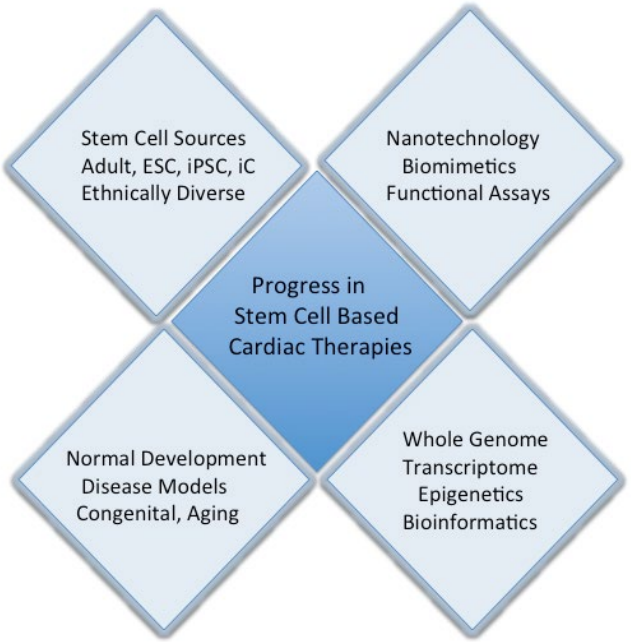

Figure 1: An interdisciplinary approach to stem cell therapies in cardiac health.

to cardiogenesis continues to be critical to identify numerous contributing pathways that underlie precise temporal transitions operating in heart development. In addition to gene signatures and transcription factor cascades [19], small nucleotide polymorphisms (SNPs) have been shown to impact cardiac therapies [20], including ethnic risk factors [21] and are important in optimizing personalized medical intervention. The availability of new resources of ethnically diverse stem cell lines [22] will allow opportunities to expand our knowledge of contributing genes and pathways relevant to ethnic populations. To what extent embryonic developmental pathways and cell fate decisions are recapitulated by *in vitro* manipulation of stem cells is still being explored [23]. In part these questions are being addressed through whole genome analysis and bioinformatics, including added regulatory detail in transcriptome and epigenetics during cardiac developmental transitions [18]. Cross-disciplinary nanotechnology applications include design of custom microwell scaffolds for generating uniformly sized 3D cardiospheres and differentiation intermediates, such as embryoid bodies [22,24], new methods for visually quantifying beating *in vitro* [25] and opportunities for micro electromechanical systems (MEMS), drug screening platforms, scaffolds and cell delivery [26-28].

In the developing embryo the heart is the first organ to become functional and cardiac precursor cells are present even before gastrulation and tri-lineage germ layer formation into mesoderm, ectoderm and endoderm [29]. Cardiomyocytes that derive from the mesoderm are preceded by several developmental morphogenic stages that include formation of the primitive streak, the epithelial-mesenchymal transition and formation of mesendoderm before lineage separation into endoderm and mesoderm. In addition to specialized cardiomyocytes, multiple cell types develop from mesoderm including bone and cartilage, adipose tissue, striated and smooth muscle, blood and lymph vessels and cells, and specialized cells for kidney, spleen and gonad function as well as serous membrane epithelium [30,31]. The ability of cells during development to naturally integrate into specific tissue, organ and systemic domains suggests that we should be able to control these events in myocardial repair, given the appropriate niche and temporal gene expression information, analogous to the use of the early embryonic environment and pathways to inform on reprogramming control genes in iPSC technology [32,33].

How the initial epigenetic landscape impacts potential for cardiogenesis and cardiomyocyte formation has not yet been well explored along with additional patient factors of age, ethnicity and gender due to a gap in resources. A study underway in my laboratory is exploring transcriptome and epigenome profiles of ethnic replicate iPSC lines generated in house [19] from self-declared Hispanic-Latino, African American and Asian ethnicities. Of interest is the ability to predict efficiency of cardiomyocyte formation while also monitoring formation of other mesodermal-derived cells as well as cells of endoderm and ectoderm origin. We observed that the stochastic nature of reprogramming which generates differences in gene expression even amongst replicate lines derived from a single somatic cell source, can either have little impact or generate differences in differentiation to beating cardiomyocytes while not affecting other cell types. Advancing the success of stem cell derived cardiomyocytes in clinical trials, may well rely on a better understanding of the transcriptomes and epigenomes of the cells we classify roughly as identical. By co-evaluating transcriptome, epigenetic and patient specific differences of ethnicity, age and gender as well as disease history we can identify relevant cross-pathway signaling cascades in cardiomyocyte formation with the goal to overcome integration and remodeling barriers that bear on heart disease and personalized biomedical therapies.

The combined interdisciplinary understanding of cardiogenesis that is being obtained through stem cell studies that bring into consideration epigenetic landscapes, ethnicity, optimized nanotechnology, and bioinformatics profiling (Figure 1) will set a comprehensive standard for broader stem cell based therapies. The next decade is expected to bring a significant leap in our understanding of normal cardiogenesis and disease in a patient diverse population and bolster the hope for improved therapeutic outcomes.

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References

1. Joffe SW, Webster K, McManus DD, Kiernan MS, Lessard D, et al. (2013) Improved survival after heart failure: a community-based perspective. J Am Heart Assoc 2: e000053.
2. Rota M, Goichberg P, Anversa P, Leri A (2015) Aging Effects on Cardiac Progenitor Cell Physiology. Compr Physiol 5: 1775-1814.
3. Gnecchi M, Pisano F, Bariani R (2015) microRNA and Cardiac Regeneration. Adv Exp Med Biol 887: 119-141.
4. Madonna R, Ferdinandy P, De Caterina R, Willerson JT, Marian AJ2 (2014) Recent developments in cardiovascular stem cells. Circ Res 115: e71-78.
5. Boudoulas KD and Hatxopoulos AK (2009) Cardiac repair and regeneration: the Rubik's cube of cell therapy for heart disease. Disease Models and Mechanisms 2: 344-358.
6. Beltrami AP, Barlucchi L, Torella D, Baker M, Limana F, et al. (2003) Adult cardiac stem cells are multipotent and support myocardial regeneration. Cell 114: 763-776.
7. Boheler KR, Czyz J, Tweedie D, Yang HT, Anisimov SV, et al. (2002) Differentiation of pluripotent embryonic stem cells into cardiomyocytes. Circ Res 91: 189-201.
8. Karakikes I, Ameen M, Termglinchan V, Wu JC (2015) Human induced pluripotent stem cell-derived cardiomyocytes: insights into molecular, cellular, and functional phenotypes. Circ Res 117: 80-88.
9. Ieda M, Fu JD, Delgado-Olguin P, Vedantham V, Hayashi Y, et al. (2010) Direct reprogramming of fibroblasts into functional cardiomyocytes by defined factors. Cell 142: 375-386.
10. Chen O, Qian L (2015) Direct Cardiac Reprogramming: Advances in Cardiac Regeneration. Biomed Res Int 2015: 580406.
11. Abbott A (2014) Doubts over heart stem-cell therapy. Nature 509: 15-16.
12. Leri A, Kajstura J, Anversa P, Frishman WH (2008) Myocardial regeneration and stem cell repair. Curr Probl Cardiol 33: 91-153.
13. Takehara N, Ogata T, Nakata M, Kami D, Nakamura T, et al. (2012) The ALCADIA (Autologous Human Cardiac-Derived Stem Cell to Treat Ischemic Cardiomyopathy) Trial. Circulation. 126: 2776-2799.
14. Makkar RR, Smith RR, Cheng K, Malliaras K, Thomson LEJ, Berman D et al. (2012) Intracoronary cardiosphere-derived cells for heart regeneration after myocardial infarction (CADUCEUS): a prosepective, randomized phase 1 trial. Lancet 379: 895-904.

15. Bolli R, Chugh AR, D'Amario D, Loughran JH, Stoddard MF et al. (2011) Effect of Cardiac Stem Cells in Patients with Ischemic Cardiomyopathy: Initial Results of the SCIPIO Trial. Lancet 378: 1847–1857.

16. Ilic D, Devito L, Miere C, Codognotto S3 (2015) Human embryonic and induced pluripotent stem cells in clinical trials. Br Med Bull 116: 19-27.

17. Chin CJ, Cooper AR, Lill GR, Evseenko D, Zhu Y, et al. (2016) Genetic tagging during human mesoderm differentiation reveals tripotent lateral plate mesodermal progenitors. Stem Cells 2351.

18. Wamstad JA, Alexander JM, Truty RM, Shrikumar A, Li F, et al. (2012) Dynamic and coordinated epigenetic regulation of developmental transitions in the cardiac lineage. Cell 151: 206-220.

19. Doss MX, Gaspar JA, Winkler J, Hescheler J, Schulz H, et al. (2012) Specific gene signatures and pathways in mesodermal cells and their derivatives derived from embryonic stem cells. Stem Cell Rev 8: 43-54.

20. Aleong RG, Sauer WH, Robertson AD, Liggett SB, Bristow MR (2013) Adrenergic receptor polymorphisms and prevention of ventricular arrhythmias with bucindolol in patients with chronic heart failure. Circ Arrhythm Electrophysiol 6: 137-143.

21. Lettre G, Palmer CD, Young T, Ejebe KG, Allayee H, et al. (2011) Genome-wide association study of coronary heart disease and its risk factors in 8,090 African Americans: the NHLBI CARe Project. PLoS Genet 7: e1001300.

22. Chang EA, Tomov ML, Suhr ST, Luo J, Olmsted ZT, et al. (2015) Derivation of Ethnically Diverse Human Induced Pluripotent Stem Cell Lines. Sci Rep 5: 15234.

23. Van Vliet P, Wu SM, Zaffran S, Pucéat M (2012) Early cardiac development: a view from stem cells to embryos. Cardiovasc Res 96: 352-362.

24. Tomov ML, Tsompana M, Olmsted Z, Buck M, Paluh, JL (2016) Human embryoid body transcriptomes reveal maturation differences influenced by size and formation in custom microarrays. J Nanosci and Nanotech. In press.

25. Zhao Y and Zhang X (2006) Cellular mechanics study in cardiac myocytes using PDMS pillars array. Sensors and Actuators A 125: 398-404.

26. Paluh JL, Dai G, Chrisey DB (2011) In search of the holy grail: engineering the stem cell niche. European Pharmaceutical Review 16: 28-33.

27. Cassidy JW (2014) Nanotechnology in the Regeneration of Complex Tissues. Bone Tissue Regen Insights 5: 25-35.

28. Li X, Tamama K, Xie X, Guan J4 (2016) Improving Cell Engraftment in Cardiac Stem Cell Therapy. Stem Cells Int 2016: 7168797.

29. Brand T (2003) Heart development: molecular insights into cardiac specification and early morphogenesis. Dev Biol 258: 1-19.

30. Pansky B (1982) Review of medical embryology.In germ layers and their derivatives. New York Macmillan 25.

31. Murry CE, Keller G (2008) Differentiation of embryonic stem cells to clinically relevant populations: lessons from embryonic development. Cell 132: 661-680.

32. Takahashi K, Yamanaka S (2006) Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell 126: 663-676.

33. Stadtfeld M, Hochedlinger K (2010) Induced pluripotency: history, mechanisms, and applications. Genes Dev 24: 2239-2263.