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Editorial

Cardiovascular Surgery Contributing to Regenerative Medicine

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Editorial

Cardiovascular disease remains the leading cause of death worldwide. Regenerative medicine is now emerging as a new therapeutic approach for severe cardiac diseases resistant to conventional therapies [1]. Numerous valuable outcomes over more than decades of basic research are now on the horizon of translation to clinical application ("from bench to clinic"). In the field of translational research, there is a phrase "The valley of death", which indicates the situation that patients could not survive without having excellent therapies brought from basic researches because of the lack of personnel who transport the knowledge to suffering patients [2]. The results of basic research must be validated by preclinical experiments in animal disease models that mimic human diseases before the techniques can be applied clinically. In this regard, cardiovascular surgeons, as experts in human surgical treatments, are the personnel best-suited to make practical contributions to advance regenerative medical research and to bridge the gap between basic research and clinical arena with their surgical skill and clinical point of view [3].

Acute ischemic injury and chronic cardiomyopathies lead to permanent loss of cardiac tissue and, consequently, heart failure. Cell transplantation is thought to be an ideal therapeutic method for replacing lost myocardium. Of the available cell sources, stem cells are now widely preferred for research or clinical trials concerning cardiac cell therapy [1]. The discovery of various stem cell populations possessing cardiogenic potential and the subsequent development of methods to isolate and expand these cells have begun to shape the notion of restorative therapy. In spite of the great deal of knowledge gained through numerous basic research studies, significant barriers to a true cardiac regeneration remain, and the field still lacks results sufficiently conclusive to support full-scale implementation of such therapies. Many clinical studies have conducted using these somatic stem cells so far: TOPCARE-AMI, BOOST, REPAIR-AMI, LateTime (Bone marrow hematopoietic stem cells), REGENT (endothelial progenitor cells), POSEIDON (mesenchymal stem cells), MAGIC, CAuSMIC (skeletal myoblasts), CADUCEUS, SCIPIO (cardiac stem/progenitor cells) and so on [4]. However, most of these clinical studies have shown relatively limited clinical benefits in general. These marginal results indicate that more efficient approaches for stem cell therapy are needed to realize full-scale stem cell-based therapy.

It is commonly believed that the low rates of grafted cell survival and engraftment diminish their potential and are serious technical limitations of stem cell therapy. Over 70% of injected cells have been reported to die progressively during the first 48 hours after needle injection due to the hypoxic, inflammatory, and/or fibrotic environment. Therefore, new strategies such as combining the cells with bioengineering techniques have been developed and shown improvement of the efficiency of stem cell therapies. Starting with initial experiments performed by combining the cell injection with injectable biomaterials (collagen, fibrin, gelatin or Matrigel), brand-new techniques such as the creation of microtissues (cell sheets, patches or engineered cardiac tissue) are now being developed in order to enhance both cell survival and the homogeneous and organized distribution of the cells. We have utilized a scaffold-free cell sheet technology using culture dishes covalently grafted with the temperature-responsive polymer poly (N-isopropylacrylamide) (PIPAAm), which enables the preparation of cell sheets without enzymatic digestion [5]. We showed that mouse embryonic stem cell (ESC)-derived cell sheet transplantation to a rat myocardial infarction model improved cardiac function through indirect paracrine mechanisms such as tissue neovascularization. The direct mechanical support of the transplanted cell sheets would be desirable for more effective cardiac regeneration. However, no evidence of the reinforcement of contraction by the physical integration of the cell sheet and host myocardium was reported to date. To realize that, more increased survival of cell sheets would be essential, and supplemental strategies together with current cell sheet transplantation, such as vascularization of cell sheet, might be promising.

Obtaining sufficient volume of cardiac cells which can survive after transplantation and creating patches/organs that mimic the structure and function of the heart remain challenging. In this regard, induced pluripotent stem cells (iPSCs) possess great potential for cardiac regeneration as they can be expanded geometrically and repeatedly *in vitro*, can give rise to multiple cardiac cell lineage cells once allowed to differentiate, and lack the ethical and immunogenic issues associated with the use of ESCs [6]. The advantages of these properties of iPSC are especially significant for the heart as opposed to other organs, such as endocrine or sensory organs, as the heart functions as an assembly of many types of cells, including cardiomyocytes and others, and as numerous ($>10^8$) heart-composing cells might be required to fully repair a damaged human heart. This approach to repairing cardiac tissue has been tested in preclinical studies with encouraging results including our result [5]. However, no human trials of the use of ESCs or iPSCs for cardiac repair have been attempted so far. Challenges for

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safer treatment using hiPSCs such as generation of human iPS cell lines without genomic integration by using episomal vectors which may reduce tumorigenesis due to mutations after transplantation should be further explored for clinical application of iPSCs [7].

One future direction of regenerative medicine supported by cardiovascular surgery is the combination of stem cell therapy and conventional surgical procedures. Concomitant coronary artery bypass grafting (CABG) and stem cell administration has been studied in patients with chronic myocardial ischemia, but the results were too marginal to justify full-scale therapeutic implementation. The combination of cell therapy and various surgical procedures other than CABG, such as left ventricular assist device implantation, left ventricular reconstruction or mitral repair for ischemic mitral insufficiency, might be a promising strategy in the future and could provide hope for many patients, especially those with severe chronic heart failure who are ineligible for heart transplantation. Another direction of future research is the further elucidation of the mechanisms of cardiac repair through cell therapy. Previous studies of somatic stem cell therapy relied on injections of heterogeneous cell populations, which limited the insights they could provide into the cellular and molecular behaviors and mechanisms of action of transplanted cells. An understanding of the roles of each cell population as well as the various complex intercellular interactions in the heterogeneous populations transplanted would be a breakthrough in the improvement of cardiac cell therapy. Utilizing the mouse ESC differentiation system to obtain defined cardiovascular populations, we recently found a major cellular mechanism, that is, cardiomyocytes are essential for sufficient cardiac restoration after sub-acute myocardial infarction mainly through angiogenesis [5]. This approach to the elucidation of the regenerative mechanisms could be especially important in the context of chronic heart diseases.

There are many promising approaches to cardiac regeneration besides cell therapies discussed above. The generation of human hearts from other animals by using interspecific chimera technology with blastocyst complementation is one such approach [8]. Another avenue of regenerative medicine is gene therapy, which is emerging as a potential treatment option in patients suffering from a wide spectrum of cardiovascular diseases, including coronary artery disease, peripheral vascular disease, vein graft failure, and in-stent restenosis. MicroRNAs (miRNAs), which are small, non-coding RNAs that regulate gene expression in a sequence-dependent manner, are also being investigated as a new modality of gene therapy for ischemic heart disease or vascular diseases. In 2010, Ieda et al. reported that a combination of three developmental transcription factors (Gata4, Mef2c, and Tbx5) directly reprogrammed postnatal cardiac or dermal fibroblasts into differentiated cardiomyocyte-like cells in vitro (direct reprogramming) [9]. This technology was recently applied to an *in-vivo* mouse MI model in which the three genes were delivered by a retroviral vector, resulting in the direct reprogramming of cardiac fibroblasts within the infarction site into cardiomyocyte-like cells and the amelioration of cardiac dysfunction. Therefore, despite concerns over the ethics and safety of gene therapy, it is a promising segment of the broad field of cardiovascular disease research.

Here we introduced the current status and future directions of stem cell therapy for treatment of cardiac disease and other approaches to cardiac regenerative research. We emphasize that we should not discuss which of these therapeutic modalities is to be preferred but rather consider them as components of an integrated medicine that would, as the summation of the new therapies introduced in this review and others that were not discussed, constitute a step towards the realization of cardiac regenerative therapy as a realistic option. In this context, the potential of cardiovascular surgery as the integrator of basic research and clinical practice is virtually immeasurable. Cardiac regenerative medicine, in combination with current treatment modalities, may help to further reduce the mortality and improve the quality of life of patients with severe cardiovascular disease.

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References

1. Chien KR. Regenerative medicine and human models of human disease. Nature. 2008; 453: 302-305.
2. Butler D. Translational research: crossing the valley of death. Nature. 2008; 453: 840-842.
3. Masumoto H, Sakata R. Cardiovascular surgery for realization of regenerative medicine. Gen Thorac Cardiovasc Surg. 2012; 60: 744-755.
4. Masumoto H, Yamashita J K. In Pluripotent Stem Cells. Deepa Bhartiya, Nibedita Lenka, editors. 2013; 459-476.
5. Masumoto H, Matsuo T, Yamamizu K, Uosaki H, Narazaki G, Katayama S, et al. Pluripotent stem cell-engineered cell sheets reassembled with defined cardiovascular populations ameliorate reduction in infarct heart function through cardiomyocyte-mediated neovascularization. Stem Cells. 2012; 30: 1196-1205.
6. Kastenberg ZJ, Odorico JS. Alternative sources of pluripotency: science, ethics, and stem cells. Transplant Rev (Orlando). 2008; 22: 215-222.
7. Okita K, Matsumura Y, Sato Y, Okada A, Morizane A, Okamoto S, et al. A more efficient method to generate integration-free human iPS cells. Nat Methods. 2011; 8: 409-412.
8. Kobayashi T, Yamaguchi T, Hamanaka S, Kato-Itoh M, Yamazaki Y, Ibata M, et al. Generation of rat pancreas in mouse by interspecific blastocyst injection of pluripotent stem cells. Cell. 2010; 142: 787-799.
9. Ieda M, Fu JD, Delgado-Olguin P, Vedantham V, Hayashi Y, Bruneau BG, et al. Direct reprogramming of fibroblasts into functional cardiomyocytes by defined factors. Cell. 2010; 142: 375-386.

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