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Commentary: Cardiac cellular "time travel" to when it was bouncing

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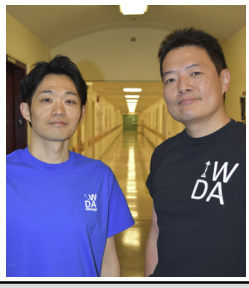

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CENTRAL MESSAGE

Cardiac cellular reprogramming therapy is a rising technology to cope with heart failure. It still needs a breakthrough to expand clinical applications.

We congratulate Ryan and colleagues[1] on their expert opinion regarding clinical potential of angiogenic therapy and cellular reprogramming. This article provides a current status and a future possibility of angiogenic therapy and cardiac cellular reprogramming to treat ischemic heart diseases.

Despite recent advancements in medicine and technology, ischemic heart disease is still one of the leading causes of death worldwide. The gold standard treatment strategies for severe ischemic heart disease are percutaneous catheter intervention or coronary artery bypass grafting on top of guideline-directed medical therapy.[2] While these therapies have been proven to improve survival rates and quality of life in those patient populations, there are still limitations. In general, myocardial revascularization therapy helps to preserve the viable myocardium but does not contribute to restoring nonviable myocardium (ie, infarction). Infarcted myocardial tissues are eventually replaced with unfunctional fibrotic tissues, so-called maladaptive remodeling. Once ischemic heart diseases progress to the phase of maladaptive remodeling, the conventional revascularization with percutaneous catheter intervention/coronary artery bypass grafting is no longer helpful, since there is no target vasculature to revascularize. Transmyocardial revascularization was once expected as a promising technology to treat "nonviable" lesions; however, its efficacy was limited.[3] A breakthrough in this field is needed.

Regenerative medicine has emerged in the last decade as a rising therapy for many fields. In this article, the authors describe the clinical potential of angiogenic therapy and cellular reprogramming for myocardial regeneration. Currently, there are 2 major approaches for myocardium regeneration. One is to use myocardial cells derived from induced pluripotent stem cell in vitro.[4] This approach, however, raises some concerns, including poor engraftment rates, cost effectiveness, and the potential risk of tumorigenesis. The other approach is cellular reprogramming therapy.[5] Damaged cardiomyocytes degenerate to fibroblast cells, which do not have any contractile function. By applying the transduction of cardiac-specific transcription factors into the fibroblast cells, those cells are converted to induced cardiomyocyte-like cells. The reprogramming technique uses intrinsic host cells to restore myocardium rather than allogeneic/xenogeneic transplantation, which could reduce a possible rejection reaction. It is also reported that there might be a synergic effect when the cardiac reprogramming technique is combined with angiogenic therapy.[6] It could be a breakthrough and might facilitate clinical applications of cardiac cellular reprogramming technology.

It is true that there are a lot of challenges to overcome and further studies are warranted before generalized clinical use of these therapeutic technologies. However, we are hoping the technology broadens therapeutic options for patients suffering from severe ischemic heart disease. We appreciate for the authors giving us updated knowledge and deep

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insight about the current use of cardiac cellular reprogramming therapy.

References

1. Ryan CT, Patel V, Rosengart TK. Clinical potential of angiogenic therapy and cellular reprogramming. *J Thorac Cardiovasc Surg Open*. 2021;6:108-15.
2. Fihn SD, Blankenship JC, Alexander KP, Bittl JA, Byrne JG, Fletcher BJ, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association task force on practice guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *Circulation*. 2014;130:1749-67.
3. Shah N, Hajouli S. Transmyocardial laser extravascular angiogenesis. In: StatPearls [Internet]. Treasure Island, FL: StatPearls Publishing; 2020.
4. Yoshida Y, Yamanaka S. Induced pluripotent stem cells 10 years later: for cardiac applications. *Circ Res*. 2017;120:1958-68.
5. Sadahiro T, Yamanaka S, Ieda M. Direct cardiac reprogramming: progress and challenges in basic biology and clinical applications. *Circ Res*. 2015;116:1378-91.
6. Mathison M, Gersch RP, Nasser A, Lilo S, Korman M, Fourman M, et al. In vivo cardiac cellular reprogramming efficacy is enhanced by angiogenic preconditioning of the infarcted myocardium with vascular endothelial growth factor. *J Am Heart Assoc*. 2012;1:e005652.