Creation of "3D thick cardiac tissue" for the treatment of heart failure

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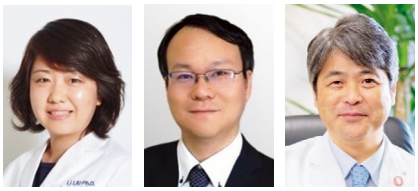

Abstract

Human-induced pluripotent stem cell (hiPSC)-derived cardiac patches show great potential for treating myocardial infarction but are limited by their thickness. In this study, we developed a 3D multilayer fibrous scaffold with dynamic perfusion, enabling the seeding of approximately 20 million hiPSC-derived cardiomyocytes in a single step. The resulting 1 mm-thick cardiac tissue demonstrated well-organized structure, high viability, enhanced contractile properties, and increased cytokine secretion. When transplanted, this 3D tissue exhibited improved operability compared to scaffold-free patches and significantly enhanced functional recovery while reducing fibrosis in a myocardial infarction rat model. This multilayer fiber-based cardiac tissue holds strong potential for future clinical trials in patients with heart disease. Additionally, the 3D scaffold could be applied to other areas of wound repair, such as the intestines, nerves, liver, and more.

Background & Results

For patients with severe heart failure, when the limitations of pharmacological therapy are exceeded, the only available treatment options are replacement therapies, such as heart transplantation or artificial heart implantation. However, these replacement strategies are associated with significant challenges, including donor shortages and complications. Consequently, the transplantation of human pluripotent stem cell-derived cardiomyocytes (hiPS-CMs) has emerged as a promising regenerative approach for restoring cardiac function and has garnered global attention. In 2020, a first-in-human trial utilizing hiPS-CM sheets for ischemic cardiomyopathy (ICM) patients was successfully conducted, followed by investigator-initiated clinical trials, with eight patients having undergone transplantation to date. Nevertheless, to further enhance the therapeutic efficacy of regenerative treatments and develop strategies applicable to all cases of severe heart failure, including those eligible for replacement therapies, several challenges remain. These challenges include: (1) insufficient number of transplanted cells, (2) the high immunogenicity of cardiomyocytes, which impedes long-term engraftment, (3) the immaturity of the transplanted cells, resulting in suboptimal contractile force, and (4) the limitations of a 2D structure in generating adequate myocardial contraction force. To overcome these obstacles, it is essential to employ biomedical engineering approaches to construct 3D myocardial tissue capable of providing mechanical support and enhancing immunosuppressive effects by administering a larger quantity of cells.

In this study, we developed a method for constructing thick, iPS-derived cardiomyocyte tissue using tissue engineering techniques, allowing for a substantial number of transplanted cells to mechanically contribute to host myocardial contraction. We further optimized a culture protocol to successfully achieve, for the first time, the construction of tissue with a thickness exceeding 1 mm, while maintaining a high cell survival rate. In vitro experiments demonstrated that this thick myocardial tissue exhibited superior mechanical, electrophysiological, and molecular properties compared to conventional thin myocardial sheets. Additionally, transplantation into myocardial infarction model animals revealed that, compared to conventional thin myocardial sheets, a significantly larger number of cardiomyocytes remained at the transplant site in the thick myocardial tissue group, resulting in marked improvements in cardiac function and a significant suppression of fibrosis.

Significance of the research and Future perspective

Currently, clinical trials using iPSC-derived myocardial tissue for the treatment of heart failure are underway worldwide. The thick myocardial tissue we have developed is considered an effective regenerative medicine approach for all cases of severe heart failure, including those suitable for replacement therapy. Furthermore, this 3D scaffold is expected to be applicable to the repair of other organs, such as the skin, skeletal muscle, and liver.

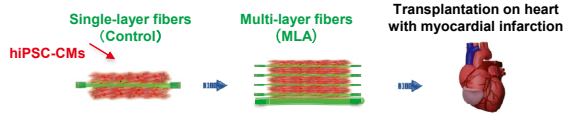

Figure 1 Schematics of Construction and Transplantation of Cardiac Tissue with Multilayer Fiber Sheet

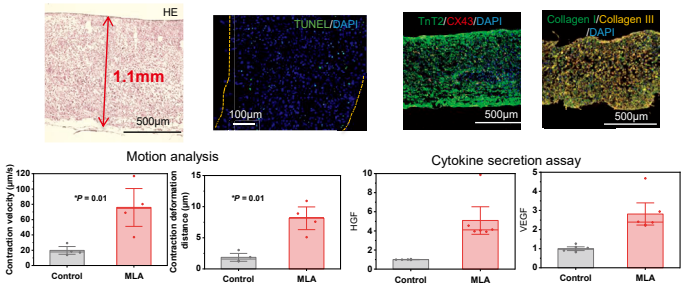

Figure 2 Construction and Functional Evaluation of 3D Thick Cardiac Tissue

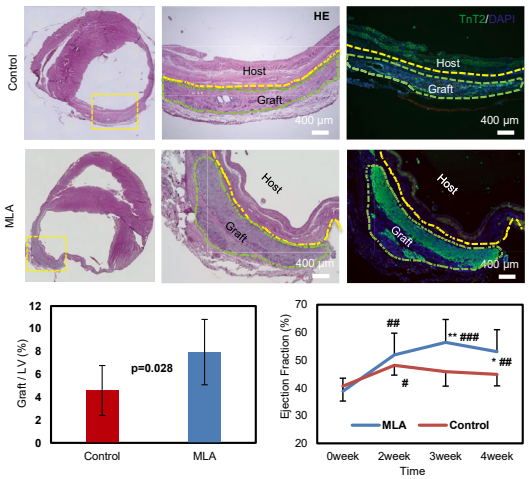

Figure 3 Efficacy Evaluation for the Treatment of Myocardial Infarction

Patent	Japanese Patent Application No. 2022-208940, No. PCT/JP2015/079364
Treatise	Li, Junjun; Qu, Xiang; Liu, Li et al. Developing thick cardiac tissue with a multilayer fiber sheet for treating myocardial infarction. Advanced Fiber Materials. 2023, 5(6), 1905–1918. doi: 10.1007/s42765-023-00313-4 Qu, Xiang; Li, Junjun; Liu, Li et al. ONO-1301 enhances post-transplantation survival of human induced pluripotent stem cell-derived cardiac tissue sheet by promoting angiogenesis. The Journal of Heart and Lung Transplantation. 2023, 42(6), 716-729. doi: 10.1016/j.healun.2023.01.018 Li, Junjun; Minami, Itsunari; Shiozaki, Motoko et al. Human pluripotent stem cell-derived cardiac tissue-like constructs for repairing the infarcted myocardium. Stem Cell Reports. 2017, 9(5), 1546-1559. doi: 10.1016/j.stemcr.2017.09.007
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Keyword	tissue engineering, pluripotent stem cell, cardiomyocyte, myocardial infarction, regenerative therapy