

PROCEEDINGS

Biofabrication of Human Engineered Heart Constructs for Myocardial Infarction Modeling

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ABSTRACT

Myocardial infarction (MI) is a major cardiovascular disease that endangers human health globally. Human engineered heart constructs (hEHCs), developed based on advanced biomaterials and innovative biofabrication technologies, represent a promising, transformative approach for elucidating MI pathological mechanisms and developing novel regenerative therapies. However, two critical limitations severely restrict the translational application of current hEHCs: the substantial structural and functional discrepancies between hEHCs and adult myocardium; and the insufficient biomimetic fidelity of MI models derived from hEHCs in recapitulating pathological remodeling processes and core phenotypes post-MI. To address these challenges, we first established a human myocardial system based on human induced pluripotent stem cell (hiPSC)-derived cardiac lineage cells and fibrin hydrogel. Coupled with the dynamic flow field mechanical training strategy, this system enabled hEHCs to acquire core structural and functional characteristics of adult myocardium, including a sarcomere length of 2.1 μm , regularly aligned T-tubules, an average calcium signal conduction velocity of 0.2 m/s, and an average contractile force of 45 mN/mm². Based on this biomimetic hEHC platform, we developed a humanized myocardial injury and repair model via controlled regional cryoinjury, which faithfully mimic the hypoxic stress, fibrotic remodeling, and electrophysiological dysfunction post-MI. Using this model, we screened and verified the significant effect of a sequential dosing regimen of TGF- β inhibitor SB431542, Rho kinase inhibitor Y27632, and WNT activator CHIR99021 in promoting functional regeneration of infarcted myocardium. To further overcome the macrostructural biomimicry limitation of existing models, we propose a biofabrication strategy integrating rigid-skeleton-assisted vascular formation and dynamically triggered enzymolysis-driven myocardial remodeling. With this strategy, we biofabricated a functionalized ventricular chamber with perfusable vascular network, and ultimately obtained a human myocardial research platform with both biomimetic architecture and physiological functionality. This platform offers a novel tool for basic cardiovascular disease research, development of innovative therapeutic regimens, and preclinical translational validation.

KEYWORDS

Myocardial infarction; biofabrication; engineered heart constructs; disease modeling; vascular network

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