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STUDY OF THE POSSIBILITIES OF RESTORING THE CONDUCTION OF WAVE EXCITATION IN FIBROUS AREAS OF THE MYOCARDIUM USING REPROGRAMMING OF NON-EXCITABLE CARDIOMYOCYTE CELLS

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Abstract

Electrical waves are transmitted in cardiac tissue by excitable cells — cardiomyocytes. Excessive fibroblast content can interfere with the propagation of electrical signals. The presented work is devoted to the development of a minimized chemical cocktail that reprograms fibroblasts into functional cardiomyocytes with sufficient efficiency. This work represents a new potential application of regenerative medicine in the field of cardiovascular disease.

The disruption of normal electromechanical excitation wave propagation in cardiac tissue can lead to cardiac arrhythmias, asynchronous myocardial contractions, and even cardiac arrest. Electromechanical excitation waves are transmitted by excitable cardiac cells — cardiomyocytes. Following ischemia or other pathological conditions, these conducting cells may be replaced by non-conductive fibroblasts. Excessive fibroblast content in cardiac tissue interferes with proper excitation wave propagation throughout the myocardium.

The presented work is devoted to the development of a minimized four-component chemical cocktail (CHIR99021, BMP4, Activin A, IWP2) that efficiently reprograms fibroblasts into functional cardiomyocytes without pluripotent stage. Importantly, the minimal component design enhances clinical translatability by simplifying manufacturing and reducing potential immunogenicity compared to complex multi-factor cocktails. This strategy represents a promising path toward clinical application, offering a safe and effective solution for restoring cardiac function post-MI through endogenous tissue reprogramming. The minimized cocktail design provides an optimal balance between functional efficacy and practical therapeutic implementation. Quantitative analyzes in this study included calcium imaging (Fluo-4), patch clamp electrophysiology, immunocytochemistry of the cardiac marker α-actinin, and conduction velocity measurements using an optical mapping and potential-dependent dye (Di-8-ANEPPS).

Our results demonstrate 56–83 % conversion efficiency to α-actinin-positive cells across rat and human fibroblast models, with the derived cells exhibiting characteristic calcium transients. In vivo studies in rat models of myocardial infarction (MI) confirmed systemically delivered cocktail safety, showing no hematological toxicity, while optical mapping revealed 84 % conductive area in treated infarcts (vs. 71 % controls). Crucially, partial reprogramming sufficed to establish conduction pathways exceeding the percolation threshold (20–30 %), enabling electrical propagation. This work represents a new potential application of regenerative medicine in the field of cardiovascular disease.