CARDIOMYOCYTE MATURATION: ADVANCES AND IMPLICATIONS FOR REGENERATIVE MEDECINE

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Background. Ischemic heart disease remains a leading cause of mortality worldwide. The application of heart transplantation is limited by donor shortage and risk of rejection. Therefore, cardiac tissue engineering has emerged as a promising regenerative approach to restore myocardial function. However, most engineered constructs exhibit immature, fetal-like cardiomyocyte phenotypes characterized by reduced conduction velocity, weak contractile force, altered gene expression, and unstable resting membrane potential.
Objective of the Study. To analyze and systematize current strategies for promoting maturation of stem cell-derived cardiomyocytes, including long-term culture, biophysical stimulation, metabolic interventions, and in-vivo studies.
Material and Methods. The study presented here is based on specialized literature extracted from databases such as PubMed, HINARI, and ScienceDirect. The search covered 18 publications from 2020 to 2025.
Results. Cardiomyocyte maturation encompasses several key processes, including cell size increase, myofibril maturation, metabolic transition from glycolysis to fatty acid oxidation, formation of a mature action potential, T-tubule development, mitochondrial expansion, and polyploidization. Biophysical stimulation, such as electrical pacing, cyclic mechanical stretch, substrate stiffness (8-11 kPa), and nanotopography, plays a central role in maturation. In contrast, the absence of mechanical stress leads to sarcomere disassembly and reduced contractility. Long-term culture improves cell morphology and function, but has proven insufficient for T-tubule formation. Co-culture with endothelial cells, epicardial cells, and cardiac fibroblasts enhances vascularization, graft size, and structural organization. The optimal fibroblast content in the seed (30%) promotes cardiomyocyte proliferation by secreting extracellular matrix factors, while adult fibroblasts secrete growth cytokines. Metabolic modulation promotes fatty acid oxidation and mitochondrial biogenesis by using T3, glucocorticoids, angiotensin II, and endothelial-derived microRNAs. In vivo transplantation appears to be the most effective method, as numerous experiments have demonstrated the transition of cardiomyocytes to mature isoforms. This demonstrates that the cells have the potential for maturation, but in vitro conditions are inadequate.
Conclusion. Overall, even with these modern natural engineering techniques, stem cell-derived cardiomyocytes in artificial cardiac tissue remain primarily in the early and late fetal stages of cardiomyocyte maturity. Although it possesses regenerative potential, incomplete maturation remains a significant barrier to clinical translation.

Keywords
regenerative cardiology; cardiomyocyte maturation; engineered heart tissue; metabolic remodeling.

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