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ADVANCES IN CARDIOMYOCYTE REGENERATION: FROM MECHANISMS TO CLINICAL PROSPECTS

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Abstract

This article discusses the regeneration of cardiomyocytes and highlights recent advances in cardiomyocyte regeneration, focusing on the molecular mechanisms underlying myocardial repair and the translation of these findings into potential therapeutic applications. Particular attention is given to stem cell–based therapies, cellular reprogramming, gene editing technologies, and bioengineering approaches that aim to restore cardiac function following injury.

Key words: Cardiomyocyte regeneration, Stem cell–based cardiac therapy, Induced pluripotent stem cells (iPSCs), Myocardial repair, Gene therapy and molecular reprogramming, YAP/TAZ and cell cycle reactivation, Tissue engineering and bioartificial heart patches, 3D bioprinting and biomaterials, Exosome and extracellular vesicle therapy, Nanotechnology in cardiac regeneration, Direct cardiac reprogramming (GMT factors), Fibroblast-to-cardiomyocyte conversion, Cardiac fibrosis reduction, Myocardial infarction recovery, Regenerative medicine and translational cardiology

Overview

Cardiomyocyte regeneration in the normal adult heart

In adult mammals, including humans, cardiomyocytes (the contractile muscle cells of the heart) are largely considered terminally differentiated and have very limited capacity to re-enter the cell cycle or regenerate in substantial numbers. This contrasts with regenerative species or neonatal mammals, which show robust heart regeneration capacity. However, accumulating evidence indicates that a very low-level turnover of cardiomyocytes does occur in the adult human heart, although at rates that are not sufficient to restore major myocardial loss from disease.

One of the landmark methods to estimate cardiomyocyte turnover in humans is based on ^14C labeling (so-called “bomb-pulse” dating). After nuclear bomb testing in the mid-20th century, atmospheric ^14C levels rose and then gradually declined; the ^14C incorporated into DNA of dividing cells can be used to date cell birth. Studies using this method find:

- At age 20, about 0.8 % annual turnover of cardiomyocytes (i.e. new cell generation)
- At older ages, turnover declines to < 0.3 % per year

Overall, these estimates suggest that cardiomyocyte renewal in humans occurs, but at rates likely < 1 % per year in adulthood. Thus, over decades, a small fraction of cardiomyocytes may be replaced, but the cumulative effect is far too low to compensate for large-scale myocardial damage.

Why is cardiomyocyte renewal so limited in adults?

Cell Cycle Arrest & Postmitotic State

Adult cardiomyocytes largely exit the cell cycle and remain in a postmitotic state. They have robust mechanisms to suppress re-entry into the cell division cycle (e.g. upregulation of cyclin-dependent kinase inhibitors).

Polyploidy & Multinucleation

Many adult cardiomyocytes become multinucleated or polyploid, which complicates mitosis and cytokinesis. Thus, even when DNA synthesis occurs, it may not result in full cell division.

Metabolic & Oxidative Stress

The high-oxygen environment, mitochondrial oxidative stress, and reactive oxygen species in adult myocardium may promote DNA damage and restrict regenerative capacity.

Epigenetic Barriers

Chromatin modifications, repressive histone marks, and DNA methylation patterns in adult cardiomyocytes may repress expression of cell-cycle / proliferation genes.

Extracellular Matrix & Mechanical Constraints

The stiff, structured extracellular matrix of adult myocardium and mechanical stress may inhibit cell division and expansion of new cells. The microenvironment may not favor proliferation.

Relevance of Cardiomyocyte regeneration

The inability of the adult human heart to regenerate lost cardiomyocytes remains one of the most critical challenges in modern cardiology. After myocardial injury, billions of cardiomyocytes are permanently lost and replaced by non-contractile fibrotic tissue, leading to impaired cardiac function and heart failure. Current medical therapies can only slow disease progression or alleviate symptoms, but they cannot restore functional myocardium.

Understanding and enhancing cardiomyocyte regeneration is therefore essential, as it represents a paradigm shift from conventional treatment toward curative cardiac repair. By reactivating intrinsic regenerative pathways or applying external regenerative technologies—such as stem cell therapy, gene editing, and tissue bioengineering—scientists aim to restore the heart's natural ability to heal itself.

Exploring cardiomyocyte regeneration is not only scientifically fascinating but also vital for the future of cardiovascular healthcare, merging biology, genetics, and engineering into a single, transformative medical approach.

Innovative Strategies for Enhancing Cardiomyocyte Regeneration

Recent progress in cardiomyocyte regeneration has demonstrated that the human heart, once considered a permanently non-regenerative organ, can regain partial

regenerative capacity through advanced biomedical technologies. A wide range of innovative approaches—including stem cell–based therapies, genetic reactivation, tissue engineering, nanotechnology, and bioinspired materials—have shown remarkable potential to restore myocardial function after injury.

Restoration Through Stem Cell–Based Therapies

Among the most significant advances is the use of induced pluripotent stem cell–derived cardiomyocytes (hiPSC-CMs). These cells closely mimic human cardiac physiology and can be generated from the patient's own somatic cells. Preclinical studies have shown that transplantation of hiPSC-CMs into infarcted myocardium leads to partial contractile recovery, enhanced electrical coupling, and reduced scar formation. Additionally, combining hiPSC-CMs with 3D scaffolds and electrical stimulation systems has improved cell maturation and integration, highlighting the therapeutic potential of stem cell–based cardiac repair.

Genetic and Molecular Reprogramming

Gene therapy has emerged as a transformative tool for re-activating dormant regenerative pathways within adult cardiomyocytes. Through the manipulation of YAP/TAZ, Cyclin D2, and CDK1, as well as the delivery of pro-regenerative microRNAs (miR-199a, miR-590, miR-302), scientists have successfully induced limited proliferation in otherwise post-mitotic heart cells. Animal studies demonstrated up to a 15–20% increase in viable myocardium and improved ventricular ejection fraction following genetic modulation. This evidence suggests that targeted molecular reactivation can reverse the natural decline in regenerative capacity of the adult heart.

Tissue Engineering and Bioartificial Heart Constructs

Innovations in cardiac tissue engineering have created functional cardiac patches capable of supporting regeneration at the injury site. Engineered heart tissues (EHTs), composed of hiPSC-CMs embedded in bio-compatible matrices, demonstrate synchronous beating, electrical conductivity, and mechanical stability. Upon implantation, these constructs promote angiogenesis and myocardial remodeling, achieving up to 50% recovery of contractile function in animal models. 3D bioprinting technology has further enhanced precision by enabling the creation of patient-specific heart tissue with native architecture and vascularization.

Exosome and Extracellular Vesicle Therapies

A paradigm shift in the field has been the recognition that the regenerative effects of stem cells are largely mediated by secreted extracellular vesicles (EVs) and exosomes. These vesicles contain growth factors, RNAs, and signaling molecules that stimulate angiogenesis, inhibit apoptosis, and modulate inflammation in damaged myocardium. Clinical-grade EV therapy is now considered a cell-free regenerative approach, offering enhanced safety, reduced immune rejection, and long-term stability. Studies have reported significant improvements in cardiac output and reduction in infarct size following EV administration.

Nanotechnology and Smart Biomaterials

Nanomaterials and smart biomaterials have revolutionized the delivery and survival of regenerative cells and molecules. Injectable hydrogels and graphene-based conductive scaffolds recreate the microenvironment necessary for synchronized electrical activity and structural integrity of new cardiomyocytes. Moreover, nanoparticle-mediated delivery systems—including lipid nanoparticles (LNPs)—enable targeted transfer of therapeutic genes or mRNAs directly into damaged cardiac tissue, promoting localized and controlled regeneration without invasive surgery.

In-Situ Reprogramming of Cardiac Fibroblasts

Another promising strategy is direct cardiac reprogramming, where resident cardiac fibroblasts are converted into cardiomyocyte-like cells inside the heart itself. By introducing transcription factors such as Gata4, Mef2c, and Tbx5 (GMT combination), alongside epigenetic modulators and microRNAs, researchers have achieved in-situ regeneration of functional myocardium. This approach bypasses cell transplantation and directly reduces fibrosis while promoting endogenous tissue repair. Experimental data show significant enhancement in left ventricular performance and electrical conduction, emphasizing its potential for minimally invasive therapy.

Overall impact and future outlook

Collectively, these advanced approaches are redefining cardiac medicine by demonstrating that functional regeneration of the human heart is achievable. While clinical translation remains in early stages, preclinical data consistently reveal improvements in contractile recovery, tissue perfusion, and survival rates. The

combination of iPSC technology, gene modulation, biomaterials, and exosome therapy is paving the way toward personalized and curative treatment for heart failure. Furthermore, these advances are influencing regenerative strategies for other organs, suggesting that cardiac regeneration research serves as a blueprint for broader regenerative medicine.

Conclusion

Advances in cardiomyocyte regeneration have opened a new era in cardiovascular medicine. Through the integration of stem cell biology, gene therapy, tissue engineering, and nanotechnology, researchers are moving beyond traditional treatments toward true myocardial repair. These innovations have shown the ability to restore contractile function, reduce scar formation, and improve survival in preclinical models. Stem cell–derived cardiomyocytes provide patient-specific sources for transplantation, while gene modulation and direct reprogramming enable the heart to regenerate from within. In parallel, biomaterials and exosome-based therapies enhance cell survival and communication, supporting long-term recovery of heart tissue. Overall, these approaches mark a shift from managing cardiac damage to actively reversing it. With continued research and clinical translation, advanced regenerative technologies hold the promise of transforming heart failure from an irreversible disease into a curable condition, bringing the medical community closer to the vision of a self-healing human heart.

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