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Innovations in stem cells, gene editing, and tissue engineering in cardiovascular regenerative medicine

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ABSTRACT

Cardiovascular regenerative medicine represents a rapidly advancing frontier aimed at repairing or replacing damaged myocardial tissue and restoring cardiovascular function. With heart disease remaining the leading cause of morbidity and mortality worldwide, traditional interventions often fall short of reversing tissue loss or functional impairment. Recent breakthroughs in stem cell biology, tissue engineering, gene editing, and biomaterials have catalyzed the development of novel therapeutic strategies. Among these, induced pluripotent stem cells (iPSCs), cardiac organoids, and extracellular vesicle-based therapies have shown substantial promise in both preclinical and early-phase clinical studies. The integration of CRISPR/Cas9 gene editing and bio-printing technologies has further enhanced the precision and customization of regenerative approaches. Additionally, advancements in single-cell sequencing and spatial transcriptomics have improved our understanding of cardiac cellular heterogeneity and pathophysiology, guiding the refinement of therapeutic targets. Despite significant progress, challenges such as low cell engraftment, immune rejection, and scalability continue to impede clinical translation. This review explores current research trends and innovations within cardiovascular regenerative medicine, highlighting transformative techniques and their translational potential while underscoring the need for continued interdisciplinary collaboration to overcome remaining obstacles.

KEYWORDS

Cardiovascular regenerative medicine; Induced pluripotent stem cells (iPSCs); Gene editing (CRISPR/Cas9); Tissue engineering; Cardiac organoids

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Introduction

Cardiovascular diseases (CVDs) remain a dominant health burden globally, accounting for an estimated 17.9 million deaths each year. The human heart possesses minimal regenerative capacity, rendering it particularly vulnerable to irreversible damage following ischemic injury such as myocardial infarction [1]. Traditional therapies, including pharmacological interventions and mechanical devices, are primarily palliative and fail to address the underlying loss of functional myocardial tissue. In response, regenerative medicine has emerged as a transformative paradigm, offering the potential to restore cardiac structure and function through biological means [2]. Leveraging advances in stem cell biology, bioengineering, and molecular genetics, cardiovascular regenerative medicine seeks to not only repair damaged tissues but also to re-establish the physiological homeostasis of the cardiovascular system [3].

This field is underpinned by a multidisciplinary approach, integrating insights from developmental biology, materials science, and immunology to devise therapeutic solutions that are both effective and sustainable.

Stem Cell-Based Therapies

The use of stem cells in heart regeneration has attracted great interest, especially following the discovery of induced pluripotent stem cells (iPSCs) [4]. Reprogrammed cells, which are isolated from adult somatic cells, have been shown to differentiate into cardiomyocytes, endothelial cells, and smooth muscle cells. Studies have increasingly centered on promoting the maturation and functional integration of cardiomyocytes derived from iPSCs into host myocardium [5]. Some of the notable developments are the application of three-dimensional cardiac patches and tissue constructs that replicate the native myocardial environment. Further, research has shown that preconditioning stem cells with hypoxic or biochemical stimuli can enhance their survival and regenerative effectiveness after transplantation. Even with these developments, issues remain regarding arrhythmogenicity, tumorigenicity, and immune compatibility, requiring ongoing refinement of cell sourcing, differentiation protocols, and delivery techniques.

Cardiac Organoids and Tissue Engineering

Cardiac organoids, or mini-hearts, are three-dimensional, self-organizing structures derived from stem cells that can recapitulate the development and function of human heart tissue. Cardiac organoids have now emerged as highly valuable tools for the modeling of cardiovascular disease, drug discovery, and regenerative intervention testing. Research has been focused on incorporating vascularization and innervation into organoid models to make them more physiologically relevant. Concurrent efforts in tissue engineering have given rise to bioengineered scaffolds that are seeded with cardiomyocytes and other supportive cells. Such constructs seek to mimic the mechanical and electrical characteristics of native myocardium, and some utilize decellularized

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extracellular matrices or synthetic polymers optimized for best biomechanical performance. The synergy between engineered tissues and organoid technology is opening the door to scalable, transplantable constructs that may be able to replace damaged heart tissue [6].

Gene Editing and Molecular Approaches

The use of gene editing tools, especially CRISPR/Cas9, has created new possibilities for the repair of genetic defects underlying cardiomyopathies and other congenital cardiovascular diseases. In addition to monogenic conditions, CRISPR-powered tools are being explored to manipulate expression of genes in adult cardiac tissue to facilitate regeneration and functional restoration. Recent research has shown successful in vivo editing of fibrosis, hypertrophy, and inflammatory genes, thus preventing pathological remodeling after myocardial infarction [7]. In complement to gene editing, the application of non-coding RNAs, including microRNAs and long non-coding RNAs, is increasing for their roles in cardiac regeneration. Delivery vectors, such as lipid nanoparticles and viral vectors, are also being engineered to achieve targeted and sustained therapeutic effects, further augmenting the viability of the molecular interventions [8].

Extracellular Vesicles and Paracrine Signaling

New evidence indicates that the regenerative effects of stem cell therapies are potentially mediated to a large extent by paracrine mechanisms, specifically through extracellular vesicles (EVs) like exosomes. EVs carry bioactive molecules such as proteins, lipids, and RNAs that alter the local microenvironment and induce tissue repair. Studies are currently aimed at isolating and engineering EVs to increase their therapeutic payload and targeting specificity [9]. EV-based therapies have a number of benefits over cell-based therapies, such as reduced immunogenicity, simpler storage, and lower tumorigenesis risk. EVs derived from iPSCs or mesenchymal stem cells have been demonstrated in preclinical models to enhance cardiac function, decrease fibrosis, and induce angiogenesis in heart failure and myocardial infarction models [10].

Advanced Imaging and Omics Technologies

To optimize regenerative approaches, it is crucial to decipher the intricate cellular and molecular environment of the damaged heart. Enhanced single-cell RNA sequencing, spatial transcriptomics, and proteomics allow for high-resolution cardiac cell-type mapping and dynamic responses to injury and treatment [11]. These technologies are revealing new biomarkers and therapeutic targets, in addition to offering important mechanistic insights into regeneration. At the same time, advances in cardiac imaging, including molecular MRI and PET, are enabling real-time tissue integration, viability, and functional recovery post-treatment [12]. The combination of omics information with imaging results is enabling the creation of predictive models to inform personalized regenerative therapy.

Conclusions

Cardiovascular regenerative medicine is being revolutionized by synergy between stem cell biology, tissue engineering, gene editing, and molecular diagnostics. Although the therapeutic translation of these treatments continues to be plagued by concerns about safety, scalability, and regulation, the field is moving toward efficacious solutions that have the potential to redefine heart disease treatment. Interdisciplinary teamwork, strong preclinical validation, and well-conducted clinical trials will be critical to close the gap between experimental promise and therapeutic reality. With ongoing innovation and strategic investment, regenerative medicine has the potential to transform cardiovascular care and greatly enhance patient outcomes in the decades ahead.

Disclosure Statement

The authors declare that they have no competing interests.

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