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Cardiomyocyte Division and Cardiac Regeneration

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Abstract. For decades, it has been believed that the heart loses its regenerative capacity shortly after birth. However, recent research has shown that the adult heart has some ability to regenerate, though the degree of new cardiomyocyte formation can vary. This ongoing debate has not only advanced our knowledge of heart growth and repair but has also sparked confusion about the potential for cardiac regeneration. This review explores various factors influencing cardiomyocyte proliferation and cardiac regeneration, such as the body's metabolic state, the key regulatory roles of growth factors, epigenetic regulation, and gaseous signaling molecules. The aim is to reconsider cardiac regeneration as a potential therapeutic target for heart-related diseases, providing new insights and strategies to address the challenges in treating human heart diseases.

Keywords: cardiomyocyte, cardiac regeneration, repair, heart-related diseases

1. Introduction

The heart is a hollow organ composed of muscle tissue, with a complex internal structure primarily consisting of chambers and four sets of valves [1]. Through regular expansion and contraction, the heart pumps venous blood into the pulmonary artery for gas exchange, which then enters the left atrium [2]. This process helps eliminate metabolic waste such as carbon dioxide and continuously supplies oxygen and nutrients to tissues and organs throughout the body [3]. Cardiovascular diseases refer to conditions that affect the structure and function of the heart, typically including coronary artery disease, heart failure, arrhythmias, and heart valve diseases. These conditions can hinder the heart's ability to pump effectively, disrupting normal blood flow and impacting other organs and systems throughout the body [4]. Cardiovascular diseases rank among the top causes of death globally [5]. According to data from the World Health Organization (WHO), cardiovascular diseases cause approximately 17.5 million deaths annually, accounting for about 31% of global deaths. The incidence of these diseases is influenced by various factors, including age, gender, lifestyle, and genetic factors. With the aging population and changes in lifestyle, the incidence of cardiovascular diseases is on the rise globally [6].

The systolic and diastolic functions of the heart depend on the heart muscle, and cardiomyocytes (CMs) are the main cells that make up the heart. Cardiac regeneration depends on the proliferative capacity of cardiomyocytes. However, previous studies have shown that due to factors such as changes in cardiomyocyte energy metabolism, alterations in cell cycle-related factors [7], structural changes in cardiomyocytes, and modifications in the oxygen-rich microenvironment of

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cardiomyocytes, the proliferative ability of mature cardiomyocytes is very limited. As a result, the heart cannot repair itself after injury through cardiomyocyte division [8]. Instead, fibroblasts secrete collagen to form scar tissue, ultimately affecting heart function [9]. Therefore, for decades, the prevailing belief has been that the adult heart cannot regenerate the lost myocardium after injury.

Due to the changes in the proliferative capacity of CMs during the injury process, it is of significant importance for achieving functional and structural regeneration of the myocardium, and for the treatment of heart diseases such as myocardial infarction [10]. This review summarizes factors affecting cardiomyocyte proliferation and cardiac regeneration, providing references for heart disease treatment.

2. Metabolic state and cellular environment

The relationship between oxygen levels and cardiomyocyte regeneration has been explored in several studies, highlighting the impact of oxygen on postnatal heart development [11]. However, this ability to proliferate diminishes soon after birth, as cardiomyocytes adapt to a normoxic environment and shift their energy metabolism to oxidative phosphorylation to support their growing energy needs [12]. These findings indicate that oxygen levels could be crucial in regulating the regenerative capacity of cardiomyocytes, likely through their influence on cellular metabolism and signaling pathways.

Studies indicate that changes in mitochondrial function, are closely related to cardiomyocyte regenerative capacity [13].

Experimental models have demonstrated that altering oxygen levels can indeed affect cardiomyocyte proliferation. Exposure of neonatal mice to a hyperoxic environment (100% O2) leads to increased oxidative DNA damage and a reduction in cardiomyocyte proliferation, whereas mild hypoxia (15% O2) promotes cardiomyocyte division. These results suggest that elevated oxygen levels may inhibit cardiomyocyte regeneration, whereas hypoxia appears to facilitate cardiomyocyte regeneration by reducing DNA damage and promoting mitosis.

Further investigations involving ROS scavengers such as N-acetylcysteine (NAC) demonstrated that clearing ROS after birth can extend the regenerative potential of mammalian hearts. Studies confirm ROS critically arrest postnatal CMs; ROS mod. boosts heart regen. by promoting division & suppressing DDR.

The reprogramming of glucose metabolism is also crucial in regulating cardiomyocyte regeneration. Adult cardiomyocytes have high metabolic activity and significant energy needs, which are mainly fulfilled through oxidative phosphorylation and the promotion of mitochondrial biogenesis [14]. The ATP produced via oxidative phosphorylation is approximately 20 times greater than that generated by glycolysis; however, this process also results in the generation of elevated levels of ROS [15]. The harmful effects of ROS on adult cardiomyocytes include oxidative DNA damage, activation of DNA damage response (DDR) pathways, and subsequent cell cycle arrest, all of which lead to cellular senescence and the senescent phenotype [16]. These processes lead to a significant decline in the regenerative capacity of cardiomyocytes. These findings suggest that mitochondrial respiration and subsequent ROS generation regulate the proliferation of cardiomyocytes.

3. Growth factors and cytokines

Current research indicates that growth factors are essential in stimulating cardiomyocyte proliferation and facilitating cardiac regeneration and repair [17].

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To date, 23 members of the FGF family have been identified, playing a role in processes such as embryogenesis, angiogenesis, growth, and cell survival, with much of the research concentrating on FGF-1 and FGF-2 [18]. FGF-1/2 released by CMs during myocardial ischemia bind FGFR1. Their established angio properties underpin therapeutic potential for chronic IHD. In 1992, Yanagisawa-Miwa et al. demonstrated the acute cardioprotective effects of FGF-2 in canine hearts, mainly due to its angiogenic properties. So far, the clinical use of FGF has mainly centered on its strong ability to stimulate myocardial angiogenesis and arteriogenesis. However, due to FGF's notable hypotensive effects, it is essential to determine a safe and effective dose that enhances cardiomyocyte regeneration without causing a drop in blood pressure.

Vascular endothelial growth factor (VEGF), a 45 kDa polypeptide, plays a crucial role in regulating angiogenesis in the heart and has been investigated in clinical trials for therapeutic angiogenesis in chronic ischemic heart disease [19]. VEGF is generated in response to myocardial ischemia and binds to the high-affinity tyrosine kinase receptors, flt-1 and KDR, which are mainly found on vascular endothelial cells but also present on cardiomyocytes [20]. It has various pleiotropic effects, including an acute cardioprotective effect, as shown in experimental studies. VEGF mRNA production in cardiomyocytes is induced by hypoxia or mitochondrial inhibition, mediated by hypoxia-inducible factors [21]. Research has indicated that VEGF pre-treatment enhances functional recovery and decreases cardiac enzyme release following ischemia-reperfusion injury, although its cardioprotective effect was initially linked to vascular effects. VEGFRs on CMs indicate direct VEGF effects. VEGF activates MEK1/2-Erk1/2 (CMs) and PI3K-Akt (ECs), enabling cytoptx. IPC upregulates VEGF via PKCε. VEGFR-KO mice exhibit exacerbated I/R injury, confirming VEGF's cardioprotective role. Despite these findings, further pre-clinical studies are needed to confirm VEGF’s direct cardioprotective effect at the cardiomyocyte level [22].

For instance, IL-6 plays a crucial role in the inflammatory response following cardiac injury, promoting cardiomyocyte proliferation and repair, particularly after acute myocardial injury. IL-6 supports cardiac repair by modulating the immune response [23]. IFN-γ primarily enhances immune responses and participates in the inflammatory reaction in the heart, regulating cardiomyocyte apoptosis and proliferation, thereby influencing cardiac repair and regeneration [24]. GFs and Cytks synergize in CM regeneration: GFs directly promote CM proliferation/survival, while Cytks regulate inflammation, immunity, and ECM remodeling. They collectively coordinate proliferation, fibrosis, and inflammation during cardiac repair, enabling functional recovery.

4. Gaseous signaling molecules

The connection between carbon monoxide (CO) and the heart has been widely explored in both clinical and preclinical studies, with considerable attention given to its potential adverse effects on the heart [25]. However, numerous studies suggest that CO can be used safely and provides strong cardioprotective effects in both small and large animal models relevant to clinical applications. In the past two decades, extensive research has focused on exploring the therapeutic potential of low-dose, exogenous CO in the myocardium [26]. CO research dates back to 1949, when several studies showed that CO can be produced endogenously, especially during increased red blood cell breakdown. Notably, the upregulation of heme oxygenase-1 (HO-1) following ischemia-reperfusion injury in the myocardium has been identified as a key factor in mediating cardioprotection [27]. The mechanisms of its action may include not only the generation of CO but also the metabolism of cytotoxic heme. Exogenous CO can replicate the effects of HO-1 induction, reducing myocardial infarct size in rats, lowering apoptosis, and improving myocardial contractility [28]. Moreover, the

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impact of HO-1/CO on mitochondria is essential for the differentiation of cardiac stem cells into cardiomyocytes.

H_2S and NO, gaseous mediators, promote CM regeneration and cardiac repair post-ischemic injury. NO is endogenously produced via NOS and non-enzymatic pathways, exerting vasodilatory and angiogenic effects via cGMP induction [29].. NO donor compounds, like nitroglycerin, have been used for over a century in treating and preventing ischemic heart disease, including angina, through sublingual and parenteral administration. Furthermore, NO is acknowledged as a key mediator in preconditioning and postconditioning strategies, where short episodes of ischemia and reperfusion are induced before or after ischemia to reduce ischemia-reperfusion injury [30].

As a crucial molecule in maintaining cellular and tissue homeostasis, Hydrogen sulfide (H2S) is widely recognized for its protective properties in many organs, especially in cardiac injury [31,32]. Many studies have shown that H2S can promote cardiomyocyte regeneration to improve cardiovascular-related diseases, such as diabetic cardiomyopathy. Gong WW et al established a mouse model of diabetic cardiomyopathy through a continuous high-glucose diet and found that plasma H2S levels were significantly decreased, along with a notable downregulation in the expression of genes associated with myocardial H2S production [33]. Researchers inhibited H_2S production using dl-propargylglycine (PAG), resulting in significant impairment of cardiac function and regeneration. This impairment manifested as reduced left ventricular ejection fraction (LVEF), increased fibrosis, and decreased diastolic thickness of the left ventricular anterior wall (LVAWd). These findings indicate H_2S protects cardiomyocytes against diabetic cardiomyopathy (DCM) by suppressing necrotic apoptosis. Conversely, the H_2S donor sodium hydrosulfide (NaHS) promoted cardiac regeneration and cardiomyocyte proliferation [34].. Mice treated with NaHS following myocardial infarction showed better left ventricular function, less scar tissue, and increased cardiomyocyte proliferation, as indicated by higher levels of mitotic marker expression [35]. These findings indicate that H2S not only facilitates cardiomyocyte division but also promotes tissue repair following myocardial injury by reducing fibrosis and improving cardiac function.

Moreover, H2S, as an antioxidant, exerts protective effects in various diseases by scavenging ROS generated during pathological processes [36]. Inhibition of H2S synthesis using PAG was shown to halt cardiac regeneration and cardiomyocyte (CM) proliferation following myocardial infarction or apical resection in 2-day-old mice, accompanied by increased ROS accumulation. In contrast, NaHS administration enhanced cardiac regeneration in 7d-old mice after myocardial infarction, stimulated cardiomyocyte proliferation, and improved ROS clearance. By eliminating ROS, H2S alleviated oxidative DNA damage in cardiomyocytes [37].

5. Epigenetic and transcriptional regulation

Recent studies have increasingly shown that epigenetic modifications contribute to heart health and the prevention of heart disease. Exercise and other lifestyle factors can induce epigenetic changes, such as DNA/RNA methylation, histone modifications, and non-coding RNAs, which may enhance repair following cardiac injury [38].

Environmental factors, such as diet, exercise and smoking can induce epigenetic modifications that may either positively or negatively impact heart disease. These factors can affect cardiovascular risk factors like aging, dyslipidemia, obesity, and diabetes, or directly disrupt cardiac homeostasis [39]. Age-related changes in epigenetic patterns include a global decrease in DNA methylation, reduced acetylation of histone H3 at lysine 9, decreased trimethylation of histone H3 at lysine 9 and lysine 27, and dysregulation of miR-29 and miR-146 expression [40]. These age-induced epigenetic

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changes lead to cardiac dysfunction by disrupting hematopoietic stem cell self-renewal and reducing angiogenesis potential. Epigenetic alterations also directly affect cardiac function [41].

RNA methylation, especially m6A, has been linked to heart disease. For instance, changes in m6A modification during cardiac hypertrophy and heart failure can alter protein levels, contributing to the progression of heart failure [42]. FTO, a key regulator of m6A, is decreased in failing hearts from humans, pigs, and mice, as well as in mouse cardiomyocytes under hypoxic conditions. Increasing FTO expression helps mitigate ischemia-induced cardiac remodeling and enhances cardiac contractility. Nguyen et al. found that the heart-specific loss of Telomeric silencing factor 1-like, a histone methyltransferase responsible for H3K79 methylation in mammals, led to a dilated cardiomyopathy (DCM)-like phenotype in mice, impairing cardiomyocyte regeneration. Additionally, specific deletion of Dicer, an enzyme involved in miRNA biogenesis, has been shown to accelerate the progression of heart failure and hinder regeneration after cardiac injury. In summary, epigenetic regulation of gene expression greatly influences cardiac function and is essential for the repair and regeneration of cardiomyocytes after cardiac injury.

6. Conclusion and future directions

This review highlights various critical factors influencing cardiomyocyte proliferation and heart regeneration, including the metabolic state, growth factors, cytokines, gaseous signaling molecules, and epigenetic regulation. The relationship between oxygen levels and cardiac regeneration is crucial, with studies showing that hypoxia can promote cardiomyocyte division, while elevated oxygen levels inhibit it, primarily due to oxidative damage. Additionally, growth factors such as FGF and VEGF play pivotal roles in angiogenesis and myocardial repair, although their application in promoting heart regeneration must be carefully regulated to avoid potential adverse effects like hypotension or excessive fibrosis. Furthermore, gaseous molecules such as CO, NO, and H_2S have shown significant promise in promoting cardiomyocyte regeneration and protecting the heart from ischemic injury. Epigenetic modifications, such as DNA/RNA methylation and histone modifications, also influence the regenerative potential of the heart, with lifestyle factors like exercise and diet playing a crucial role in modulating these pathways. Together, these factors contribute to the complex and dynamic process of cardiac regeneration and repair.

While the factors discussed in this review offer a promising basis for heart regeneration, further research is needed to fully comprehend their mechanisms and maximize their therapeutic potential. Future studies should focus on fine-tuning the use of growth factors and cytokines to maximize their regenerative effects while minimizing unwanted side effects, such as vascular instability or inflammation. Additionally, exploring the precise regulation of oxygen levels and mitochondrial function could uncover new strategies to enhance cardiomyocyte proliferation and improve heart function post-injury. The development of targeted delivery systems for gaseous signaling molecules and the exploration of epigenetic therapies hold significant potential in improving cardiac repair. Furthermore, a deeper investigation into the roles of protein tyrosine phosphatases (PTPs) in cardiac regeneration could lead to novel therapeutic approaches, particularly in the context of metabolic diseases that influence heart health. Ultimately, combining these insights with emerging technologies, such as gene editing and stem cell therapy, may offer transformative strategies for treating cardiovascular diseases and promoting long-term cardiac regeneration.

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