Mammalian Cardiomyocyte Development and Differentiation

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Notoriously, the adult mammalian heart has a very limited ability to regenerate its functional cardiac cells, cardiomyocytes, after injury. However, the neonatal mammalian heart has a window of regeneration that allows for the repair and renewal of cardiomyocytes after injury. This specific timeline has been of interest in the field of cardiovascular and regenerative biology as a potential target for adult cardiomyocyte repair.

cardiac regeneration neonatal cardiomyocytes epigenetics

1. Introduction

Heart failure has been the leading cause of death worldwide for many years, making it a major public health and clinical concern globally [1]. Because of the detrimental and devastating effect heart failure induces on our population, it is crucial to understand the pathology and progression of the disease to find improved treatments and clinical approaches.

Current clinical approaches have been modest at best. Most treatments, including hypertensive medications, diuretics, and lifestyle changes, have helped decrease the risk factors of cardiovascular disease and heart failure [2], but there is currently no cure for heart failure [3]. To truly cure heart failure, the use of heart transplants and stem cells has been the major focus of most research [4][5]. More dire and aggressive measures are needed for heart failure treatment because the adult heart has a limited ability to regenerate after injury [6]. Specifically, the adult cardiomyocytes or muscle cells in the heart do not grow and divide frequently, leading to a loss of functional cells in the heart after an injury that is often replaced by scarring [7][8][9]. The use of stem cells was originally hypothesized as an option for cardiac cell replacement because of the ability of some stem cells to differentiate into cardiomyocyte-like cells and replaced any lost cardiomyocytes after injury. This is a major area of research currently, but engraftment issues, immune responses, and actual clinical approaches have still caused barriers to stem cell use in patients [10]. Thus, unfortunately, heart transplants are rare and stem cells have been less than promising. This has led to new cardiac-based therapeutics, including cardiac regeneration and epigenetic regulation of cardiac cells, specifically of cardiomyocytes [11].

Cardiac regeneration has been of interest because of the important timeline of cardiomyocyte development. The embryonic and neonatal mammalian heart has the ability to grow and repair after injury, but the adult mammalian heart has a subsequent inability to regenerate cardiomyocytes [12]. The embryonic mammalian heart can regenerate and grow cardiomyocytes in cycles of proliferation. Often, these new cardiomyocytes are derived from

progenitor cells utilized during embryonic development [12][13]. The neonatal mammalian heart does have the ability to regenerate after injury. It is usually summarized that within the first week of life, neonatal murine cardiomyocytes can proliferate. More recent studies have narrowed this down to within the first two days of life, stating that neonatal mice can fully recover only after an aggressive injury that is received within the first two days after birth [14][15]. For other animals and models, this window of regeneration can vary [16][17]. However, for all mammals, once into adulthood, the ability of the heart to regenerate cardiomyocytes is lost, especially after severe injury [18]. Unlike mammals, the *Danio rerio* (zebrafish) is an exception to this ability. Zebrafish have cardiomyocytes that can regenerate into adulthood. Zebrafish can fully repair an adult heart after injury, making them a model organism to study cardiac regeneration [19].

Because there is such a distinct window of regeneration in most mammalian organisms, cardiomyocyte regeneration regulation has been a major area of focus in mouse, rat, and zebrafish models. Often, neonatal heart injury can be induced via apical resection, and a neonatal mouse heart can regenerate and heal to become fully functioning [20]. The ability is then lost into adulthood. Due to the regenerative potential of neonatal hearts, targeting neonatal regenerative genes and signaling has been considered for adult heart mechanisms, specifically after injury [21][22]. Current research has found that some developmental genes could be a major target [23][24][25], but the standout of these findings has narrowed major changes to epigenetic modifications [25][26].

Epigenetic modifications are chemical modifications that occur on top of the DNA, outside of the normal genetic coding [27]. Often, epigenetic regulation dictates chromatin structure and accessibility [28]. Epigenetic modifications and their subsequent chromatic regulation play a major role in compacting the DNA that is wrapped around histones within the nucleus of the cell, which can affect gene expression and DNA binding proteins [29]. These epigenetic modifiers often fall into three main roles: writers, readers, or erasers [30].

2. Mammalian Cardiomyocyte Development and Differentiation

Cardiomyocytes are the main functional cells in the heart. They are responsible for the contraction and relaxation within the heart muscle [31], which has directly correlated these cells to heart function via echocardiography and histological measurements [32][33]. Often, with the loss of functional cardiomyocytes after injury, there is a decrease in heart function as measured by ejection fraction, fractional shortening, and cardiac output [33]. Because mammalian cardiomyocytes have a very specific ability to regenerate in the early stages of development, it is vital to understand the epigenetic differences and changes that occur in adult cardiomyocytes. Embryonically, cardiomyocytes are derived from the mesoderm during gastrulation. Specifically, these cardiac precursor cells form a cardiac crescent, which is often where committed cardiovascular cells are found during development [34]. The commitment to the cardiac lineage is often associated with transcription factors, such as Nkx2.5 and Gata4 [34]. Interestingly, more recently, this has also been connected to epigenetic changes, including increased histone modifications, DNA methylation, and chromatin remodeling, directly regulating cardiomyocyte differentiation genes and pathways [9]. In a neonatal heart, the cardiomyocytes have a unique ability to regenerate during the first few days after birth [20]. It has been found that earlier in the neonatal stages, the cardiomyocytes have increased ability

to repair after injury, respond to immunological challenges, and even divide regularly often due to changes in chromatin accessibility and epigenetic regulation [25].

The neonatal mammalian cardiomyocytes eventually become terminally differentiated [35]. These are deemed the mature adult cardiomyocytes, which are known for the contractile function in the adult heart muscle. Once the cardiomyocytes become terminally differentiated, they can no longer regenerate. Importantly, this means they do not go through the cell cycle regularly [36]. Thus, neonatal cardiomyocytes are often categorized by genes that are associated with this dedifferentiated state or ability to transition through the cell cycle [37], while adult cardiomyocytes are often labeled and characterized by genes that are associated with this terminally differentiated state [38]. Additionally, adult cardiomyocytes are often characterized by their mitochondrial function, which can provide a detailed understanding of the adult cell metabolism [39]. The maturation of adult cardiomyocytes is associated with the cell's terminal structure, metabolism, and function of differentiated cardiomyocytes [23]. Normally, the need for new mature cardiomyocytes is not necessary in the adult heart. However, after injury or stress, the heart loses adult cardiomyocytes and can no longer grow and replace the lost cells [40]. This results in the cells being replaced by proliferative pathological fibroblasts, which increase scarring and decreases heart function. Overall, this cellular replacement can have long-lasting negative effects on health and heart function [41]. Because of these monumental changes, targeting the differences between the differentiated adult cardiomyocytes and their neonatal counterparts have been of interest, with the overall goal of reprogramming adult cardiomyocyte to be like their neonatal counterparts [42]. One of the most substantial methods for this theory has been through epigenetic regulation in neonatal versus adult mammalian cardiomyocytes.

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