Abstract

Improvements in the care of patients with cardiovascular disease have led to improved survival but also a burgeoning population of patients with advanced heart disease. Cardiac stem cells (CSC) continue to promise opportunities to repair damaged cardiac tissue. However, precisely how stem cells accomplish cardiac repair, especially after ischemic damage, remains controversial. It has been postulated that the clinical benefit of adult stem cells for cardiovascular disease results from the release of cytokines and growth factors by the transplanted cells, stimulation of new blood vessel growth, enhancing tissue perfusion, and via preservation or even regeneration of myocardial tissue, leading to improvements in cardiac performance after myocardial infarction and in patients with advanced heart failure, reducing inflammation, and scar formation, as well as protecting cardiomyocytes from apoptosis. In addition, reducing fibrosis these factors might also stimulate endogenous repair by activating cardiac stem cells. Interestingly, stem cells discovered to be resident in the heart appear to be functionally superior to extra-cardiac adult stem cells when transplanted for cardiac repair and regeneration. Stem cells are the seeds of tissue repair and regeneration and a promising source for novel therapies. However, apart from hematopoietic stem cell (HSC) transplantation, all other stem cell treatments yet remain experimental. Mounting hopes have encouraged numerous clinical trials, but it has been difficult to obtain unequivocal evidence for robust clinical benefit. This review provides a historic framework and an abridgment of how the theories of CSC origin and potential evolved from early times to the present day. The development of more effective cardiac therapies may thus require targeting this important cell population. Here, we summarize and offer some thoughts on the state of the field of cell therapy for ischemic heart diseases and the therapeutic potential of cardiac stem cells.

Keywords: Cardiovascular disease; Hematopoietic stem cell; Clinical trials; Cardiac therapies

Introduction

Cardiovascular diseases (CVD) is the leading cause of morbidity and mortality world wide and it accounts over 17 million people die per year, a number that is expected to grow to over 23.6 million by 2030 [1]. In the past fifty years, contrary to the advanced therapeutics, better managements, state of the art surgical interventions and organ transplantations, more than half of patients with heart failure die within five years of initial diagnosis [2,3]. Recent reports demonstrated CSC still accounted for 31.3% of all deaths, or 1 of every 3 deaths in the USA. It has also been reported that 7.6 million cases of myocardial infarction (MI) and 5.7 million of heart failure patients in USA. Moreover, during 2000 to 2010, the cardiovascular operations and procedures has increased by 28%, which is a huge burden to the healthcare system. For 2011 alone, the direct and indirect estimated costs of CVD and stroke were $320.1 billion verses $216.6 billion for all cancer in the USA [3,4]. Alarming, the estimated global expenditure of CVD is $863 billion, and it would rise to $1044 billion by 2030 [5].

The limitation of the current available (drugs, intervention or operation) therapies is unable to compensate the irreversible loss of functional cardiomyocytes [6,7]. On the other hand, it has been reported that the adult heart possesses a stem cell compartment that can regenerate cardiomyocytes and coronary vessels [8-10]. It has immense potential to rejuvenate lost myocardium and to repopulate the hypertrophic decompensated heart with functional cardiomyocytes, which improves vascular contractility, ventricular function and wall thickness [9].

Accordingly, thus the current challenges of cardiovascular therapies are to examine extensively for robust and novel concepts of cell based therapy, tissue engineering or reprogramming of adult stem cells (ASCs) [8-11]. Over the decades, researchers have been investigating in order to identify stem cells capable of differentiating into cell lineages different from the organ of origin to be employed for the regeneration of the damaged heart [12-14]. The most studied and characterized stem cells are embryonic stem cells (ESCs) and bone marrow-derived cells (BMCs). However, a remarkable progress has been made in the clinical application of BMCs and many other ASCs in heart failure of ischemic and non-ischemic origin [15-18].

Stem Cells

Stem cells are the mother of all cells. The hallmark of stem cell is the ability to self-renew, proliferate, or differentiate into specialized cell types [19,20]. They retain the potency to divide indefinitely and give rise to new cells to replace cells that die or are lost [18-23]. Importantly, therefore, stem cells are the progenitor cells of the blood, heart, brain, bones, skin, muscles, etc [24,25]. There are different sources of stem cells but all types of stem cells have the same capacity to develop into any types of cells (Figure 1).

In 1997, for the first time researchers were demonstrated that cellular and regenerative therapies hold great promise and showed bone marrow-derived CD34+ cells can give rise to endothelial-like cells and improve neovascularization after ischemia [26]. Latter on multiple experimental and several clinical studies evidenced that a wide variety of cell types such as skeletal myoblasts, cardiac stem cells, and...
mesenchymal stem cells showed their ability to mend the heart [27-30]. Subsequent clinical trials showed some benefit but also raised safety concerns with respect to arrhythmic events induced by non-integrated skeletal muscle cells [22]. However, cultured bone marrow-derived, cardiac stem cells, embryonic stem cells, or induced pluripotent stem cells are the important sources for producing cardiomyocytes.

**Types of stem cells**

There are two most common sources of stem cells based on their origin:

1. Embryos (embryonic stem cells) and
2. Adult tissue (adult stem cells).

**Embryos (embryonic stem cells):** The origin of embryonic stem cells (ESCs) is embryo of blastocyst stage. In humans, mice and other primates, the embryo, at this stage is a ball of approximately 100 cells. Human embryonic stem cells (hESCs) are obtained from supernumerary human IVF (in vitro fertilization) embryos by submitting ethical norms that cannot be used for the couple’s infertility treatment. The derivation of mouse ES cells was first reported in 1981 [31,32]. Their regenerative property distinguishes them from all other organ-specific stem cells identified so far.

1. It can be maintained and propagated indefinitely as homogeneous population of undifferentiated cells in culture, and they can retain normal karyotypes following extensive passages in culture.
2. They are pluripotent cells, with high potential to produce every cell type in the body. The pluripotent property of mouse ESCs was demonstrated by their ability to contribute to all tissues of adult mice including the cardiac progenitor cells [31,33,34].

The unique property of the ESCs paves the way for in vitro model of embryonic development for studying the fundamental mechanisms of the early development of cell lineage induction and specification. Additionally, the ESCs differentiation system is viewed by many as a novel and unlimited source of cells and tissues for transplantation for the treatment of all sorts of diseases. Subsequently, in 1998 human embryonic stem cells (hESCs) was isolated which significantly elevated the interest in the embryonic stem cell therapy and also put forth the concept of regenerative medicine remarkably closer to reality [35,36]. Because of their pluripotent nature and potency to differentiate to all cell types in the body, they have been considered as a paramount source for regenerative medicine [37,38]. In view of the fact that ground breaking discovery of hESCs, extensive studies have been performed regarding factors regulating pluripotency and differentiation to specialized functional cell types [39-41]. In particular, these properties made ESCs interesting for cardiac regeneration [42], but still long road to go for perfection.

**Adult (somatic) stem cells:** Adult stem cells (ASCs) are undifferentiated cells found throughout the body that divide to replace dying cells and regenerate injured tissues. ASCs can be isolated from several sources for example from body amniotic fluid, and other ASCs (Table 1).

Among them bone marrow is the rich source of stem cells that can be used to treat several chronic diseases including heart diseases. For years, scientists are working to uncover the potential use of stem cells to treat ischemic heart diseases and repair injured tissues of the
Pro-angiogenic factors play a vital role in promoting the most important part of cardioreparative functions of transplanted cardiac stem cells (Table 2).

Cell survival: Several cytoprotective factors along with anti-apoptotic factors also play an integral role to protect cardiomyocytes. Cytoprotective factors, VEGF, HGF, IGF, SDF-1, act alone or in the combination with several other factors to execute their actions. Anti-apoptotic factors work by decreasing the expression of transcripts specific to cell death such as Bax, caspase-3 and Fas are pParacrine produced by CSCs are known to exert potent cytoprotective effects in cardiovascular cell types (53,18) microRNAs in CSC derived exosome have also shown promising cytoprotective effect by improving tubule formation of endothelial cells and decreased pro-fibrotic gene expression of fibroblasts [54].

Remodeling of extracellular matrix: Remodelling of extracellular matrix (ECM) by CSC is carried out by various promoters such as metalloproteinases (MMPs), adrenomedulin and thymosin-β. assist CSC migration into the scarred tissue, an effect that was potentiated when CSCs were treated with HGF and IGF-1. These molecules suppress MMP-2 and MMP-9 protein expression, an also assist migration of CSC into scarred tissue [53].

Activation of endogenous stem cells and re-entry of cardiomyocyte cell cycle: Transplanted CSC also activate endogenous original stem cells. Several secreted proteins are interlinked to carry out this function. The proteins which contribute to the activation of endogenous CSCs for cardiac repair are adrenomedulin, connective tissue growth factor, atrial natriuretic factor and interleukin-1 receptor-like-1, IL-1 receptor-like-1 [53]. Factors released by CSC which help in activation of endogenous stem cells and migration of CSC are c-Ki+T, Nkx2.5+, GRO-α/CXCL-1, ENA-78/CXCL-5, MIF and HGF Follistatin like-1 (FSTL-1) protein has also been studied in mice and pigs as a key factor responsible for the activation of endogenous stem cells [55].

Conclusions

Stem cell therapy for various kind of heart diseases has recently been emerged as a promising therapy which can lead to improvement in the care of patients and better survival benefit. However, precisely how stem cells act to repair the damaged cardiomyocytes, especially

Table 1: Sources of adult stem cells.

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<tr>
<th>Source of stem cells</th>
<th>Description</th>
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<tr>
<td>From body</td>
<td>Almost all tissues and organs contain a tiny number of ASCs that helps in maintaining them, live dormant for years. They divide and produce new cells only when they are activated by tissue injury, disease or anything else that makes the body need more cells. Examples are bone marrow, blood vessels, heart, skeletal muscle, skin, brain, gut, liver, etc.</td>
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<td>From amniotic fluid</td>
<td>Amniotic fluid contains fetal cells including mesenchymal stem cells, which are able to make a variety of cells and tissues.</td>
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<td>From pluripotent stem cells</td>
<td>Any types of ASCs can be isolated from pluripotent stem cells. These ASCs are the in-vitro model for testing different compounds and mechanical factors. Since, these cells match genetically so it eliminates the problem of tissue rejection and toxic therapies to suppress the immune system.</td>
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<tr>
<td>From other adult stem cells</td>
<td>ASCs can trans differentiate into apparently unrelated cell types (such as brain stem cells that differentiate into blood cells or blood-forming cells that differentiate into cardiac muscle cells). Indeed, it is unclear whether trans differentiation may occur in human cells, or whether it could be made to happen reliably in the lab.</td>
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Table 2: Potency of the stem cells.

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<th>Stem cell potency</th>
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<td>Stem cells further classified in different types based on their potency (Table 2).</td>
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Cardioreparative functions of transplanted cardiac stem cells

Induction of neovascularization: Pro-angiogenic factors play a vital role in promoting the most important part of cardioreparative function, neovascularization. Several pro-angiogenic and anti-apoptotic factors factors interlink with each other to carry out repair mechanism which include transcription factor Gata-4, neovascular endothelial growth factor (VEGF), angiogenin, angiopoietin, basic fibroblast growth factor (bFGF), hepatocyte growth factor (HGF), insulin-like growth factor 1 (IGF-1), interleukin-1β (IL-1β), and tumor necrosis factor-α (TNF-α) and transforming growth factor-β (TGF-β) [53].
after ischemic damage, are still not very well studied. Large clinical trials are still needed to bring the clarity to this dynamic field of cardiac stem cell therapy.

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