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REVIEW

New Developments in Cardiac Regeneration

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Numerous pharmacological and device therapies have improved adverse cardiac remodelling and mortality in heart failure. However, none are able to regenerate damaged cardiac tissue. Stem cell based therapies using multipotent (adult) stem cells and pluripotent stem cells are new approaches that could potentially achieve the elusive goal of true cardiac regeneration. Over the past two decades, various stem cell based approaches have been shown to improve left ventricular function in pre-clinical animal models. Promising results rapidly led to clinical trials, initially using bone marrow-derived mononuclear cells, then mesenchymal stromal cell populations and, more recently, progenitor cells from the adult heart itself. These have been shown to be safe and have advanced our understanding of potential suitable recipients, cell delivery routes, and possible mechanisms of action. However, efficacy in these trials has been inconsistent. Human pluripotent stem cells (hPSCs) are another potential source of stem cells for cardiac regeneration. They could theoretically provide an unlimited source of cardiomyocytes or cardiac progenitors. Pre-clinical studies in both small and large animal models have shown robust engraftment and improvements in cardiac function. The first clinical trial using hPSC-derived cardiac derivatives has now commenced and others are imminent. In this brief review article, we summarise recent developments in stem cell therapies aimed at cardiac regeneration, including discussion of types of cell and non-cell-based strategies being explored.

Keywords Heart failure • Myocardial infarction • Regeneration • Adult stem cells • Pluripotent stem cells • Cell transplantation • Non-cell strategies

Introduction

It is estimated that myocardial infarction (MI) occurs every nine minutes in Australia [1]. With access to primary percutaneous coronary intervention and improved symptom-to-reperfusion times, the mortality of acute coronary syndromes has significantly decreased over the past decade [2]. This, combined with our ageing population, means that more people are living with resultant chronic heart failure (HF) [3,4]. There has been slow but steady progress with HF treatments and these are summarised in Figure 1. Angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta blockers, aldosterone antagonists, cardiac devices and, recently, angiotensin-receptor-neprilysin inhibitors have shown efficacy in reversing pathological ventricular remodelling and improving outcomes for HF [5–13]. Despite this, the overall mortality rate for patients with chronic HF remains high at about 20% over two years

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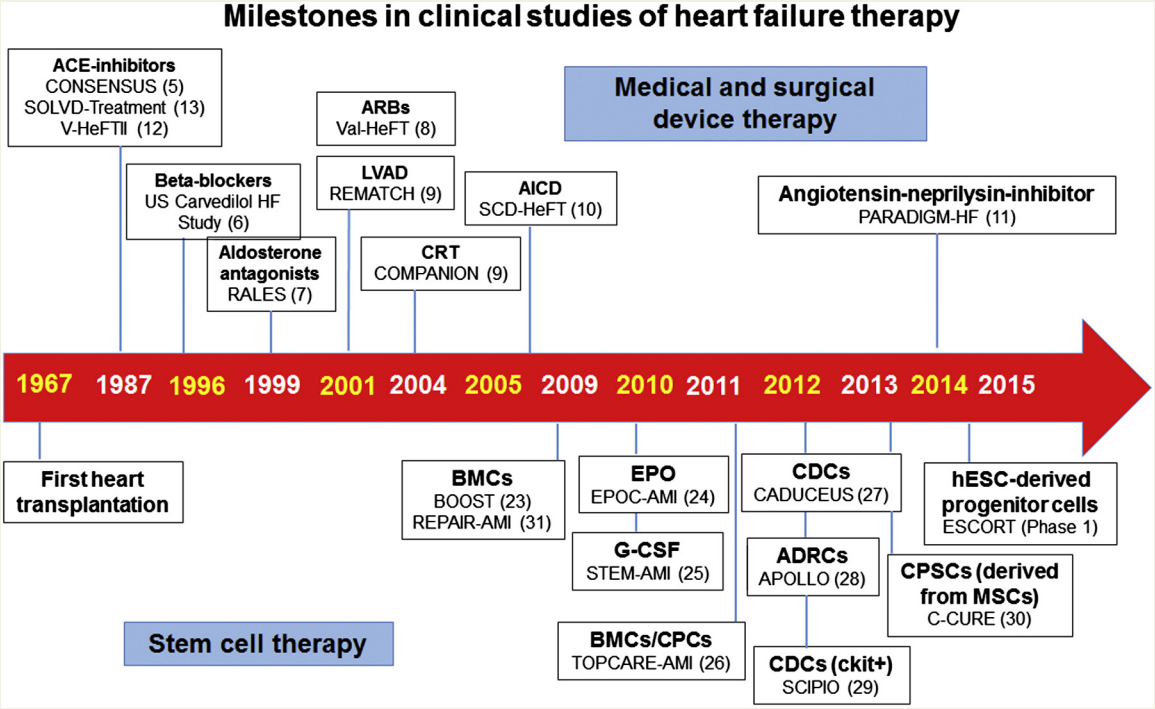

Figure 1 Milestones in clinical studies of heart failure therapy.
Abbreviations
ACE angiotensin-converting enzyme; ADRC adipose tissue-derived regenerative cell; AICD automated implantable cardioverter defibrillator; ARB angiotensin receptor blocker; BMC bone marrow-derived stem cell; CDC cardiosphere-derived cell; CPC circulating progenitor cell; CPSC cardiopoietic stem cell; CRT cardiac resynchronisation therapy; EPO erythropoietin; G-CSF granulocyte stimulating factor; hESC human embryonic stem cell; LVAD left ventricular assist device; MSC mesenchymal stem cells.

[11]. This has fuelled interest in stem cell therapies that could lead to regeneration of damaged cardiac tissue. This short review will evaluate controversies within the cardiac regenerative field and discuss barriers to successful clinical translation of the myriad potential therapeutics.

Adult Stem Cells and Pluripotent Stem Cells: What is the Difference?

It has now been almost two decades since early attempts were made in cardiac cell therapy. Many stem cell types have undergone extensive investigation and can be broadly categorised into adult stem cells (ASCs) or pluripotent stem cells (PSCs). The research trajectories in these two cell groups have been very different.

Adult stem cells are multipotent cells that have been identified in many fully developed organs. These include populations from extra-cardiac sources (skeletal myoblasts, bone marrow-derived mononuclear cells, bone marrow-derived mesenchymal stem cells, adipose-derived mesenchymal stem cells and endothelial progenitor cells). Adult stem cells also include resident cardiac progenitor cell (CPC) populations, including c-Kit+, Sca1+, Isl1+, cardiac colony-forming unit fibroblasts, cardiosphere-derived cells and epicardium-derived cells [14]. Adult stem cells are considered multipotent and have some limited ability to form various differentiated cell types. The benefits and limitations associated with transplantation of ASCs for cardiac regeneration are outlined in Figure 2.

In vitro, ASCs can differentiate into multiple cell types, including cardiomyocytes (CMs). There is also modest evidence to support similar differentiation after transplantation in various animal models of cardiac injury. However, ASCs appear to have little intrinsic cardiomyogenic ability and are unable to produce robustly contractile CM syncytia. Furthermore, inadequate cell survival, retention and ''homing'' (cell migration from site of delivery to site of injury) remain challenges in all transplantation strategies [15–17].

Overall, the use of ASCs for repair of the injured heart has shown encouraging (although inconsistent) results in improving cardiac function [18]. Various studies suggest that most of the beneficial effects of ASCs are mediated through paracrine actions (from secreted exosomes, anti-apoptotic, immunomodulatory or proangiogenic factors) [19–21], and modulation of extracellular matrix [22], rather than being from true cardiomyogenic potential.

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