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The winding road to regenerating the human heart

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ABSTRACT

Regenerating the human heart is a challenge that has engaged researchers and clinicians around the globe for nearly a century. From the repair of the first septal defect in 1953, followed by the first successful heart transplant in 1967, and later to the first infusion of bone marrow-derived cells to the human myocardium in 2002, significant progress has been made in heart repair. However, chronic heart failure remains a leading pathological burden worldwide. Why has regenerating the human heart been such a challenge, and how close are we to achieving clinically relevant regeneration? Exciting progress has been made to establish cell transplantation techniques in recent years, and new preclinical studies in large animal models have shed light on the promises and challenges that lie ahead. In this review, we will discuss the history of cell therapy approaches and provide an overview of clinical trials using cell transplantation for heart regeneration. Focusing on the delivery of human stem cell-derived cardiomyocytes, current experimental strategies in the field will be discussed as well as their clinical translation potential. Although the human heart has not been regenerated yet, decades of experimental progress have guided us onto a promising path.

Summary: Previous work in clinical cell therapy for heart repair using bone marrow mononuclear cells, mesenchymal stem cells, and cardiac-derived cells have overall demonstrated safety and modest efficacy. Recent advancements using human stem cell-derived cardiomyocytes have established them as a next generation cell type for moving forward, however certain challenges must be overcome for this technique to be successful in the clinics.

1. Introduction

A myocardial infarction (MI) transforms healthy and contractile myocardium into an akinetic, fibrotic tissue, resulting in a heart that cannot pump blood at full capacity. As the heart is one of the least regenerative organs in the body, this often leads to the development of chronic heart failure — a disease with a 50% survival rate over 5 years [1]. Current treatment options are limited and consist primarily of palliative drugs, organ replacement by heart transplant (available to <0.1% of heart failure patients), or mechanical assist devices (with complications related to infection, thrombosis, and power supply). While these available treatments have greatly impacted the trajectory of patient health after an MI, ischemic heart disease remains the number one cause of death and disability worldwide [2].

In recent years, the field of heart regeneration has emerged from a far-fetched notion to the forefront of cardiac research. Heart regeneration is an interdisciplinary field with the goal of restoring functional myocardium after cardiac injury [3]. Approaches to repair the injured heart have been widespread and include cell transplantation, gene therapy, stimulating innate repair pathways, direct cellular reprogramming, cardiac tissue engineering, and biomaterial delivery. The most established strategy for heart repair has been the delivery of exogenous cells. Nearly every cell type imaginable has been transplanted into the damaged myocardium, from skeletal myoblasts to pluripotent stem cells and their derivatives. It is an exciting but challenging time for physicians, scientists, and engineers in the field — we now have over a decade of experience in clinical trials contributing to heart regeneration research, and there are several promising preclinical strategies emerging as contenders to our current clinical approaches.

In this review, we provide an overview of the clinical trial progression using cell therapy to regenerate the heart after ischemic injury and discuss strengths and limitations of these trials. We will then discuss current experimental strategies designed to improve upon what we have learned in these clinical trials, focusing on the advancements in stem cell-derived cardiomyocyte transplantation and the clinical translatability of this approach for heart repair.

2. Cell therapy clinical trials for heart repair

Approximately 1 billion cardiomyocytes are lost during an MI [3]. As the adult human heart has an extremely limited regenerative capacity, this damaged myocardial tissue is replaced by fibrotic scar. There is increasing evidence of the slow cardiomyocyte turnover rate during normal organ growth and development (reviewed in Ref. [4]), and following myocardial injury [5], however, this turnover accounts for a

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low percentage of cells. Up to 3% of preexisting cardiomyocytes near the injury region undergo cell division while most DNA replication occurs without cytokinesis as a hypertrophic response, and there is minimal contribution from progenitor cells [5]. As a result, the innate generation of de novo cardiomyocytes post-MI falls orders of magnitude short of meaningful regeneration.

Exogenous cell transplantation aims to repair damaged myocardial tissue either by delivering cells that act via paracrine-mediated effects or by providing de novo cardiomyocytes that directly contribute to force production. Toward this goal, numerous clinical trials have been conducted using cell types including skeletal myoblasts, bone marrow-derived hematopoietic cells, mesenchymal stem cells (MSCs, also known as marrow stromal cells), adipose-derived cells, endothelial progenitor cells, and cardiac-derived cells (CDCs) (reviewed in Refs. [6–9]). A schematic overview of the derivation, delivery mode, and proposed mechanism of action for the major groups of cell therapies is provided in Fig. 1. An ideal cell type for replacing damaged myocardial tissue would have contractile and electrophysiological properties, the ability to survive and integrate into an ischemic area, proliferation potential, and the ability to elicit a paracrine effect to stimulate endogenous regeneration (e.g., vascularization; discussed in detail in Refs. [9] and [10]). Despite the plethora of cell types tested in clinical trials to date, none has met all of these expectations. The type of cell used for transplantation inherently places restrictions on important variables that may affect the success of cell therapy, making it difficult to directly compare results across trials. These include the delivery mode (intracoronary catheter, transendocardial catheter, or epicardial catheter delivery compared to epicardial delivery in tissue patches), the availability of autologous or allogenic cells, and the timing of cell delivery dependent on the need for in vitro cell expansion (i.e., MSCs require extensive in vitro expansion, while unfractionated bone marrow cells may be delivered the same day of isolation).

The field has made tremendous progress in terms of establishing clinical trial design, delivery techniques, and demonstrating safety; however, the clinical benefits have been modest at best. This indicates that there is room for improvement on our cell source. The two major cell sources used in the clinics thus far have been bone marrow-derived cells and cardiac explant-derived cells, which are discussed below.

2.1. Bone marrow-derived cells

Following closely behind the first major wave of clinical trials in the field using skeletal myoblasts [11], bone marrow-derived cells paved the way for intracoronary cell therapy in the heart, transitioning quickly into the clinic despite the scarcity of published evidence supporting their role in heart regeneration at the time [12,13].

2.1.1. Bone marrow-derived mononuclear cell derivatives

Most bone marrow-derived cell transplantation trials in the heart have used an unfractionated subpopulation called bone marrow mononuclear cells (BMMNCs) (reviewed in Ref. [14]). Referring to BMMNCs as a stem cell preparation is a misnomer because true stem cells comprise well below 0.1% of the total mononuclear cell population. Unfractionated BMMNCs principally consist of a heterogeneous population of hematopoietic cells including monocytes, committed myeloid progenitor cells and lymphocytes, and a small population of hematopoietic and mesenchymal stem cells [9,15].

Intracoronary transplantation of BMMNCs into patients with acute MI was first reported in 2002 [13], and while this trial has been discredited for ethics violations, it was followed by a flurry of more rigorously performed studies. Most of these early BMMNC studies enrolled acute MI patients with ST-segment elevation and a baseline ejection fraction of 40–50%, and they reported functional improvement after treatment. One such study was the BOOST trial [16] in which autologous BMMNCs (characterized as $<1\%$ $CD34^+$) were isolated from patients and delivered by intracoronary infusion to the infarct-related artery the same day. No serious adverse events were reported in either group, and cardiac magnetic resonance imaging (MRI) at 6 months indicated a significant increase in left ventricular (LV) ejection fraction after cell treatment (compared to placebo control), providing evidence that intracoronary infusion of BMMNCs improves systolic function in acute MI patients. In longer-term follow-up studies, however, the control group showed a "catch-up" period of recovery, such that benefits of BMMNCs could no longer be demonstrated [17]. Results from the REPAIR-AMI trial [18] further supported efficacy for BMMNCs, reporting a 5.5% increase in LV ejection fraction at 4 months after intracoronary infusion of BMMNCs compared to a 3.0% improvement in controls. While the results of this study were hindered by the use of quantitative LV angiography to assess function as opposed to cardiac MRI, the enrollment of over 200 patients made this the largest BMMNC trial at the time and set the standard for expected systolic improvement, albeit a modest increase, after cell therapy. The same group reported that functional improvement persists up to 5 years posttreatment in a subset of patients who were enrolled in the TOP-CARE-AMI trial [19–21], which compared the benefits of BMMNCs to those of autologous circulating progenitor cells isolated from venous blood.

Despite these and other studies reporting functional improvement after BMMNC treatment (reviewed in Ref. [22]), larger trials employing greater degrees of randomization, placebo controls, and blinding conducted in the years following have not replicated these results. The Cardiovascular Cell Therapy Research Network (CCTRN) was designed to facilitate cell-based therapies in the United States [23] and sponsored the FOCUS-CCTRN trial [24], which was one of the first trials to target patients with chronic LV dysfunction who had not qualified for revascularization therapy post-MI. Enrolled patients had a mean baseline ejection fraction of 30–32% and New York Heart Association (NYHA) class of 2 or 3, and while there was no improvement in the primary endpoints of LV end systolic volume or maximal oxygen consumption, there was a small yet statistically significant 1.4% improvement in LV ejection fraction over baseline at 6 months. The CCTRN also sponsored the TIME and LateTIME trials to assess the influence of BMMNC delivery timing on LV function [25–27]. Each of these double-blinded and placebo-controlled trials enrolled successfully reperfused MI patients and delivered 150×10^6 autologous BMMNCs by intracoronary perfusion either at day 3 or 7 (TIME) or at 2–3 weeks (LateTIME) after MI. Neither study detected any functional benefit by cardiac MRI at 6 months after cell treatment, regardless of delivery timing. Similar in cell dose and design, the SWISS-AMI study [28] compared BMMNC delivery at days 5–7 to delivery at weeks 3–4 after post-MI reperfusion and again detected no improvement in LV ejection fraction at 4 months. Collectively, these studies challenge the earlier reports of functional improvement, but they differ in using a double-blinded study design and in targeting patients with significantly worse baseline cardiac function (for example, the median ejection fraction of SWISS-AMI patients was 37%). It seems unlikely to us that this difference in baseline cardiac function underlies the difference, however, because the REPAIR-AMI trial found that the patients with the worst ejection fractions showed the greatest improvement with treatment. Results are eagerly awaited from the 3000-patient enrollment, multicenter Phase 3 trial (the BAMI trial), which is currently underway in Europe, as it will help clear up some of the conflicting results in the field (clinical trial identifier NCT01569178 [29]).

2.1.2. Mesenchymal stem cells

Numerous trials have been conducted using MSCs purified from bone marrow, which are adult cells characterized for their osteogenic, chondrogenic, and adipogenic differentiation potential [30,31]. Less than 0.01% of the cells isolated from bone marrow are considered MSCs [32,33], therefore obtaining clinically relevant cell numbers requires ex vivo expansion.

The first clinical trial investigating the intracoronary injection of MSCs reported an improvement in LV ejection fraction and increased myocardial perfusion 3 months after treatment [33], echoing the results reported using BMMNCs at the time. A few studies have directly