Novel Biological Therapies Targeting Heart Failure: Myocardial Rejuvenation

Amanda J. Favreau-Lessard, PhD, Sergey Ryzhov, MD, PhD, Douglas B. Sawyer, MD, PhD*

KEYWORDS

• Heart failure • Rejuvenation • Cell therapy • Gene therapy

KEY POINTS

- Therapies targeting myocardial rejuvenation represent a promising area of investigation for advanced heart failure.
- Bone marrow–derived and cardiac-derived mesenchymal stem cells have exhibited some promising results, although further investigation is needed.
- Scarring and fibrosis, which occur in some forms of heart failure, require a search for ways to reprogram fibroblasts, or find strategies to rebuild cardiac tissue.
- Developmentally critical cell-signaling factors, such as NRG1β, SDF-1, or FSTL1, offer possible strategies to manipulate cardiac repair and rejuvenation.
- Gene delivery strategies are improving, allowing for induction of cardiac-specific expression of proteins involved in improving mechanical function, such as SERCA or Pim1.

INTRODUCTION

The great man is he who does not lose his child-like heart
—Mencius, Confucian Philosopher, ca 300 BC

Cardiovascular disease (CVD) is the leading cause of death across the globe, accounting for 17.3 million deaths per year.[1] In the United States, more than 1 in 3 adults suffers from some form of cardiovascular disease (85.6 million people), with 15.5 million experiencing coronary heart disease (CHD).[1] Among the types of CHD, 5.7 million people have heart failure (HF).[1] These statistics highlight the epidemic that is continually growing among the global population. Current therapies for HF with reduced ejection fraction focus on preserving left ventricular function as well as restoring cardiac function through the use of mechanical circulatory support devices or, in select patients, heart transplantation. The enormous growth in our understanding of heart biology as well as pathobiology leading to HF over the past several decades promises novel therapeutic approaches that will harness this biology to restore heart function.

Myocardial regeneration to some is the "holy grail" of HF translational research. Organ regeneration is an ancient concept. One of the most well-known stories of organ regeneration dates back to Greek mythology, where the Titan Prometheus, as punishment for deceiving Zeus, was forever chained to a rock where an eagle came each day to dine on his liver. Each evening his liver regenerated, whereupon the next day the eagle returned to continue its punishment. It is now well known that the adult liver indeed has remarkable regenerative potential, as does the bone marrow. The regenerative potential of the heart has also been recently established, at least

Center for Molecular Medicine, Maine Medical Center Research Institute, Maine Medical Center, 81 Research Drive, Scarborough, ME 04074, USA
* Corresponding author.
E-mail address: DSawyer@mmc.org

Heart Failure Clin 12 (2016) 461–471
http://dx.doi.org/10.1016/j.hfc.2016.03.008

in lower vertebrates and young mammals.[2,3] When the chest of a young zebrafish or mouse is carefully opened, and the apical segment of the ventricular myocardium is clipped away, some organisms will survive through a process of growing new myocardium in its place. This process involved mesenchymal stem cells proliferating and differentiating in an organized way to replace the missing heart muscle in young animals. The adult heart throughout life responds to injury and stress with activated expression of genes involved in cardiac development, the so-called fetal gene program. In addition, both mesenchymal and bone marrow–derived progenitor cells are activated by cardiac injury. And yet, these processes are inadequate to restore heart function. Therapeutic approaches that manipulate these signals and processes are the cornerstone of biologic therapies for HF.

Based on the ancient wisdom of the Confucian scholar, the "Mencius Paradigm" is a term we have coined to characterize the hypothesis that biologic signals and processes critical for cardiac development might be manipulated to improve adult heart function. In this context, we propose that the term myocardial "rejuvenation," rather than "regeneration," is a more realistic outcome of these clinically motivated translational research efforts. In this brief review, we describe the state of a number of approaches at various stages of development using biologics, many of which fit the Mencius Paradigm.

CELL-BASED THERAPIES FOR HEART FAILURE WITH REDUCED EJECTION FRACTION

Developmental biology research has created detailed knowledge over how pluripotent cell lineages differentiate in an organized and highly programmed way to become the functional heart. The recognition that progenitor or stem cells which can differentiate into cardiac cells exist both in the bone marrow as well as the myocardium has led to a number of completed and ongoing experimental efforts asking if these can be used to restore ventricular function. Although in general the results are encouraging, it appears we are still some distance away from applying these strategies in the clinic. We outline a few of the stem cell-based approaches describing how specific cell types are being examined as potential therapy for HF.

Bone Marrow–Derived Mesenchymal Stem Cells

Mesenchymal stem cells (MSCs) are thought to be one of the most promising cell-based therapies for cardiovascular disease. Bone marrow–derived (BM-) MSCs can differentiate into many mature cardiac cell types, including cardiomyocytes, cardiac fibroblasts, and smooth muscle cells.[4–6] This makes BM-MSCs attractive for cell-based therapies to treat cardiac injury and HF. Under the proper conditions, these cells will differentiate into multiple lineages, hence it is hypothesized that by providing these cells to the heart by direct injection they will develop into functional cells that promote cardiac repair and restoration of heart function (for more in-depth review see Refs.[7,8]). MSCs have been well reported to migrate to an injured site to promote repair by immune modulation through a secretome.[9,10] The MSC secretome is also thought to play an important role in MSC repair. The secretome includes cytokines, such as interleukins, growth hormones, and exosomes, containing factors including microRNAs.[9,10] Thus, these cells may enable rejuvenation at sites of cardiac injury through differentiation into new cardiac cells, as well as provision of the necessary factors to aide repair. BM-MSCs are being examined in clinical trials (**Table 1**) with some evidence of success.[11–13]

Cardiac-Derived Mesenchymal Stem Cells

In recent years, subsets of cells within the heart, rather than the bone marrow, have been characterized as "cardiac stem cells" or "cardiac progenitor cells" due to their unique multipotent properties. Endogenous cardiac progenitor cells, also known as cardiac-derived MSCs, have been characterized by their ability to differentiate to cardiac cell types, including endothelial cells, fibroblasts, and myofibroblasts.[18–23] Directing differentiation of progenitors toward cardiac myocytes and limiting their conversion into nonmyocyte cells, specifically fibroblasts/myofibroblasts, is an attractive approach to regenerate cardiac tissue after injury.[24] Two markers, adult stem cell antigen-1 (Sca-1) and c-Kit, are widely used to identify progenitors within CD45-negative nonhematopoietic cells in adult murine heart. The c-kit^{+}CD45^{-} cells, which are also found in the human heart, are undergoing clinical trials to repair cardiac injury.[25,26] Sca-1 positive murine cardiac progenitors have been characterized as small interstitial cells located adjacent to the basal lamina and in proximity with CD31-positive endothelial cells (EC),[27] indicating a close relationship between EC and progenitor cells. Additional characteristics of this population are strong cell surface expression of CD105 and low or negative expression of CD31/PECAM1 and absence of CD34 and CD45 hematopoietic cell markers. No expression of c-Kit was found on these cells.[22] Human cardiac