Surgery to Stem Cells: Possibilities of Cardiac Regeneration

By Anirudh Penumaka

The human heart beats approximately two and a half billion times during one's lifetime. In the western world, cardiac diseases are the leading cause of death, and the impact of cardiovascular disease in the developing world may soon rival that of infectious diseases (1). As the prevalence of cardiac diseases increases, there is an increased demand for novel treatment, and cardiac stem cells hold enormous therapeutic potential. While most injuries to the heart lead to permanent loss of cardiac tissue, researchers find that the heart may heal after injury using its own small pool of stem cells. Researchers now aim to manipulate stem cells to repair damage to the heart after injuries such as heart attacks.

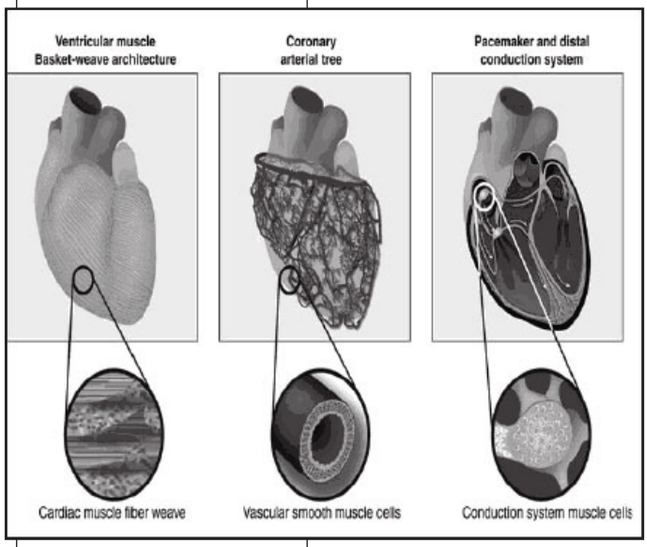

Figure 1. The different systems that comprise the heart muscle. Stem cells or progenitor cells introduced into the heart must be able to functionally integrate with the surrounding tissue. (11)

credit: (11)

Stem cells hold enormous potential in regenerative medicine: embryonic stem (ES) cells can become any of the myriad cell types that make up our body. A recent development that increased optimism for the use of stem cells is the discovery of induced pluripotent stem (iPS) cells (2). Like ES cells, these stem cells hold great potential to perform cardiac regeneration, but they are created from other cells in the body, thus bypassing many ethical concerns associated with stem cell research.

The heart supplies vital oxygen and nutrients to all parts of the body, and a loss of function in its contractile activity causes tissue death, most importantly in the brain. The heart is composed of a few distinct cell types, including cardiomyocytes and vascular smooth muscle cells. It is usually the contractile cardiomyocytes that are lost in diseased portions of the heart, leading to heart failure over time (3). A heart attack occurs from a blockage in an artery supplying blood to the heart muscle. Due to lack of oxygen, parts of myocardium can die, disrupting its functional ability and increasing the risk of future heart failure.

Until recently, it was believed that once dead, cardiomyocytes are replaced with scar tissue and cannot regenerate whatsoever. But in 2009, Bergman et al. inferred the rates of renewal of human cardiomyocytes using radioactive carbon-14 that was incorporated into cardiomyocyte DNA during nuclear bomb tests. They discovered that cardiomyocytes regenerate at a very low rate (less than 1% every year) throughout life, and that less than 50% of cardiomyocytes are renewed during the average life span (4). Prior to this discovery, Beltrami et al. showed in 2003 that a small population of progenitor cells in the heart can differentiate into cardiac cell types. When they injected a specific lineage of cardiac progenitor cells into ischemic (dead) portions of the heart, they generated a large amount of mature myocytes (5).

Despite promising new advances, the therapeutic potential of cardiac stem cells is far from certain. Cardiac stem cells or other precursor cells can replenish a small percentage of cells after injury, but the same regenerative mechanisms are not active in the absence of injury (6). Therefore, while a small amount of regeneration occurs af-

ter injury, the body's regenerative system seems unable to completely replenish lost contractile cells. In addition, there is some uncertainty about the use of cardiac stem cells derived from bone marrow, because it is possible that their regenerative potential arises not from their ability to truly reconstitute cardiac cell types, but from their ability to secrete factors that improve functioning of nearby cells (7). Clinical trials using bone-marrow-derived cardiac stem cells provide ambiguous results, suggesting that benefits possibly arose through secondary effects such as secretion of factors that improve vascularization of surrounding tissue (8).

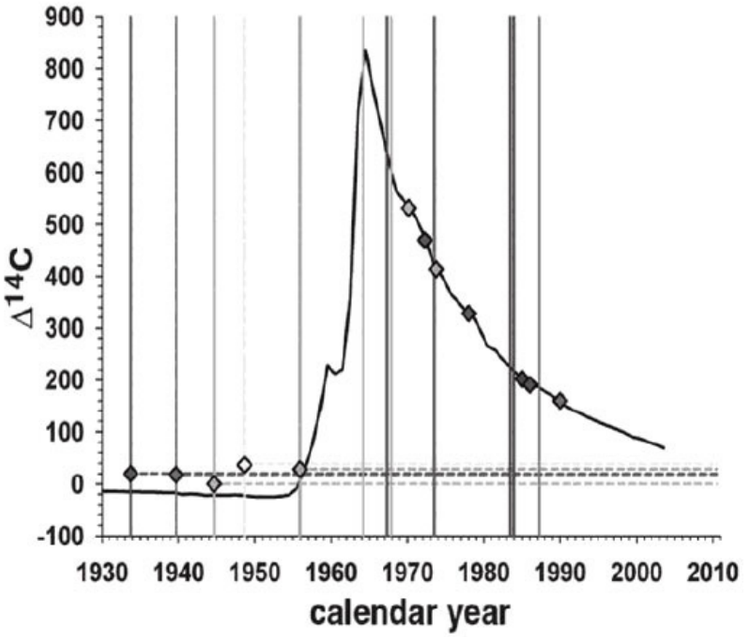

Figure 2. Carbon-14 levels in cardiomyocyte DNA for individuals born at various times in the 20th century. Carbon-14 levels spiked during the period when nuclear weapons were tested. (4)

Although there are many barriers to overcome prior to using ES or iPS cells, an alternative may be to utilize multipotent cardiac progenitor cells. These progenitor cells are more developmentally confined in that they can differentiate into only specific cardiac cell types (9, 10). Thus, one option for performing regeneration of an injured heart, called endogenous repair, is to induce the resident stem or progenitor cells to proliferate quickly and replace more of the diseased myocardium. Another approach, termed exogenous repair, involves introducing cardiac progenitors, iPS cells, or grafting cardiac tissue generated from these stem cells into the heart to replace damaged tissue.

Both strategies pose challenges. While endogenous repair would be less invasive and more comfortable for the patient, it requires optimizing technologies for guiding stem or progenitor cells to repair cardiac damage to the extent required. Exogenous repair is more invasive and involves introducing foreign tissue into a patient. Induced pluripotent stem cells (iPS) removed obstacles such as the immune rejection of foreign tissue by the host, yet there still exist unresolved questions, including whether these injected cells or grafted tissue can integrate and beat synchronously with the rest of the heart muscle.

Cardiac regeneration, a task that once seemed impossible, may progress into treatments for patients in the coming years. Clinical trials have begun, and bringing this treatment to the bedside requires technical advances in delivering cells to injured regions and precise evaluations of the benefits of stem cell based therapies. H

— Anirudh Penumaka '12 is a Chemical and Physical Biology concentrator in Adams House

References:
1. CDC. <www.cdc.gov/features/heartmonth> Jan, 2010.
2. S. Yamanaka, Cell 137, 13 (2009).
3. M.S. Parmacek, New England Journal of Medicine 361:1, 86 (2009).
4. O. Bergmann et al., Science 324, 98 (2009).
5. A.P. Beltrami, Cell 114, 763 (2003).
6. P.C.H. Hsieh, Nature Medicine 13:8, 970 (2007).
7. K.R. Chien, Science 306, 239 (2004).
8. R. Passier, Nature 453, 322 (2008).
9. S.M. Wu, Cell 127, 1137 (2006).
10. D.J. Garry, Cell 127, 1101 (2006).
11. K.R. Chien, Science 322, 1494 (2008).

credit: (4)