A heart-y new stem cell therapy that's sure to get your blood pumping

By Amanda Bedolla

Have you ever had a sharp pain in your chest and worried that you were having a heart attack? Heart attacks are the leading cause of death in the United States. According to the CDC, one in every four deaths is from a heart attack [1]. That translates to 655,000 Americans that die from heart attacks a year! I don't know about you, but I definitely struggle with a looming fear that one of my loved ones will be among the many people that suffer this fate. Predicting who might suffer from heart attack can be challenging—individual risk factors vary depending on race, age, lifestyle and genetics [2].

One particular form of cardiac disease associated with heart attack is sinoatrial node (SAN) dysfunction. SAN dysfunction targets the SAN, which is a cluster of pacemaking cells. These pacemaking cells generate electrical impulses known as action potentials, which are responsible for determining the rhythm and rate at which a person's heart beats [3]. They also have an intrinsic ability to generate action potentials without needing any sort of external stimulus. Action potentials involve the movement of sodium, potassium, and calcium ions in and out of a cell and is dependent on something known as membrane potential. Simply put, membrane potential refers to differences in the concentration of ions (charged particles) on either side of the membrane—this difference allows for rapid movement of ions in and out of the cell. [4] The movement of these ions causes the depolarization (when the charge inside a cell is more positive) and repolarization (when the charge inside a cell is more negative) of these cells to occur, which in turn triggers heart cells to contract enabling blood to be pumped throughout the body [5]. This is a fancy way to explain the movement of ions in and out of a cell, and the complex way the ion movement contributes to your heart beating.

If pacemaking cells are damaged or are unable to properly function, the ions don't flow accordingly, and the heart does not beat regularly. That means that the blood which supplies oxygen to the more distant parts of the body may be unable to supply an adequate amount of oxygen to those tissues. This can lead to cell death and, eventually, even death of the individual. Current therapies used for replacing damaged pacemaking cells are limited. The most common treatment is the use of an electronic pacemaker. An electronic pacemaker is an electrical device that must be surgically inserted under your skin near your heart. The device's role is to step in when your heart is not beating properly and generate electrical signals to correct your heart's irregular beating pattern. This mimics the natural electrical impulses that stimulate heart contraction [6].

Current research in the field of regenerative medicine is centered on therapies that would replace the artificial electrical pacemaker with a biopacemaker. The

biopacemaker can be created using a specific type of cell called a human induced pluripotent stem cell [7]. This type of stem cell can be differentiated into any cell type—including a pacemaking cell—through molecular pathway manipulations. This means that scientists may be able to take stem cells and turn them into cardiomyocytes (heart muscle cells) similar to the ones found in the SAN (pacemaking cardiomyocytes) in order to replace the damaged cells. This is more difficult than it might sounds because stem cells are very finicky to work with and the environment of the SAN is very particular. A current issue with the use of these stem cells is difficulty generating a homogenous population of pacemaking cells. This means that, in addition to cardiomyocytes, smooth muscle cells and fibroblasts (which are a structural cell found in connective tissue) are also generated when attempting to differentiate the stem cells [8].

Current research is focused on recreating the environment of the SAN and attempting to differentiate the stem cells within this environment. It is thought that the SAN environment itself may affect how the stem cells differentiate. To do so, we are comparing the fibroblasts found in the SAN with the fibroblasts found in other areas of the heart. Fibroblasts make up 45%-75% of the volume of the SAN and are essential support cells that form the structural matrix of the SAN [9]. They also provide growth factors and aid in cell to cell communication, which keeps the heart beating and blood pumping [8]. Gene expression analysis using a method called RNA-sequencing of SAN fibroblasts and other fibroblasts found in different regions of the heart will allow us to determine what makes the SAN fibroblasts so special. Better understanding the SAN fibroblasts at this level will allow us to determine the optimal environment for our pacemaking cardiomyocytes. Hopefully, this information will also help us recreate the SAN environment for improved production of stem cell-derived pacemaking cardiomyocytes. Ideally, once we are able to consistently generate cultures of pacemaking cardiomyocytes, these cells would take the place of the electrical pacemakers. This means that once these cells are implanted, they would continue to reproduce and eventually replace all damaged tissue! Talk about a heart stopping—or in this case, a heart starting—scientific innovation!

References

1. Salim S. Virani, M., PhD, FAHA, Chair, Alvaro Alonso, MD, PhD, FAHA, Emelia J. Benjamin, MD, ScM, FAHA, Marcio S. Bittencourt, MD, PhD, MPH, Clifton W. Callaway, MD, FAHA, April P. Carson, PhD, MSPH, FAHA, Alanna M. Chamberlain, PhD, Alexander R. Chang, MD, MS, Susan Cheng, MD, MMSc, MPH, FAHA, Francesca N. Delling, MD, MPH, Luc Djousse, MD, ScD, MPH, Mitchell S.V. Elkind, MD, MS, FAHA, Jane F. Ferguson, PhD, FAHA, Myriam Fornage, PhD, FAHA, Sadiya S. Khan, MD, MSc, Brett M. Kissela, MD, MS,

Kristen L. Knutson, PhD, Tak W. Kwan, MD, FAHA, Daniel T. Lackland, DrPH, FAHA, Tené T. Lewis, PhD, Judith H. Lichtman, PhD, MPH, FAHA, Chris T. Longenecker, MD, Matthew Shane Loop, PhD, Pamela L. Lutsey, PhD, MPH, FAHA, Seth S. Martin, MD, MHS, FAHA, Kunihiro Matsushita, MD, PhD, FAHA, Andrew E. Moran, MD, MPH, FAHA, Michael E. Mussolino, PhD, FAHA, Amanda Marma Perak, MD, MS, Wayne D. Rosamond, PhD, MS, FAHA, Gregory A. Roth, MD, MPH, FAHA, Uchechukwu K.A. Sampson, MD, MBA, MPH, FAHA, Gary M. Satou, MD, FAHA, Emily B. Schroeder, MD, PhD, FAHA, Svati H. Shah, MD, MHS, FAHA, Christina M. Shay, PhD, FAHA, Nicole L. Spartano, PhD, Andrew Stokes, PhD, David L. Tirschwell, MD, MS, MSc, FAHA, Lisa B. VanWagner, MD, MSc, FAST, Connie W. Tsao, MD, MPH, Vice Chair, and On behalf of the American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee, Heart Disease and Stroke Statistics—2020 Update: A Report From the American Heart Association
Circulation, 2020. 141(9): p. e139-e596.

2. Jun Wanga, E.K., Subeena Sood, Randy L. Johnson, Xander H. T. Wehrensb,, and James F. Martina, Pitx2 prevents susceptibility to atrial arrhythmias by inhibiting left-sided pacemaker specification Proc Natl Acad Sci USA, 2010.
3. Kashou AH, B.H., Chhabra L. , Physiology, Sinoatrial Node. StatPearls [Internet], Updated 2020 Oct 6.
4. Kenta Tsutsui, O.J.M., Syevda G. Sirenko-Tagirova, Larissa A. Maltseva, Rostislav Bychkov, Mary S. Kim, Bruce D. Ziman, Kirill V. Tarasov, Yelena S. Tarasova, Jing Zhang, Mingyi Wang, Alexander V. Maltsev, Jaclyn A. Brennan, Igor R. Efimov, Michael D. Stern, Victor A. Maltsev, and Edward G. Lakatta, A coupled-clock system drives the automaticity of human sinoatrial nodal pacemaker cells. Sci Signal, 2018.
5. Rudy, Y., Molecular Basis of Cardiac Action Potential Repolarization. Annals of the New York Acadamy of Sciences, 2008. 1123(1): p. 113-118.
6. Kwang Jin Chun, H.B.G., Jin Kyung Hwang, Seung-Jung Park, Young Keun On, June Soo Kim, Kyoung-Min Park, Is transjugular insertion of a temporary pacemaker a safe and effective approach? . PLOS ONE, 2020.
7. Lee, J.H., et al., Human pluripotent stem cell-derived atrial and ventricular cardiomyocytes develop from distinct mesoderm populations. Cell stem cell, 2017. 21(2): p. 179-194. e4.
8. Feng Liu, Y.F., Xiaojie Hou, Ying Yan, Haiying Xiao, Dongchuan Zuo, Jing Wen, Linli Wang, Zhichao Zhou, Xitong Dang, Rui Zhou & Bin Liao, Enrichment differentiation of human induced pluripotent stem cells into sinoatrial node-like cells by combined modulation of BMP, FGF, and RA signaling pathways. Stem Cell Research and Therapy, 2020.

9. Patrizia Camelliti , C.R.G., Ian LeGrice , and Peter Kohl, Fibroblast Network in Rabbit Sinoatrial Node: Structural and Functional Identification of Homogeneous and Heterogeneous Cell Coupling. Circulation Research, 2004. 94(6).