NATIONAL CENTER FOR CASE STUDY TEACHING IN SCIENCE

Can Stem Cells Bring Magic to Medicine?

by
Ashleigh Garrett and Joni H. Ylostalo
Department of Biology
University of Mary Hardin-Baylor, Belton, TX

Introduction

Carl was the star receiver of his high school football team. During an important game against their toughest rival, his team was leading by 14 points when Carl caught the ball 20 yards from the end-zone on the right side of the field and started to sprint toward a likely touchdown. Just as he was about to break the goal line, a free safety from the other team dove full force toward Carl and hit his helmet against Carl's knee from the inside. After the play was over, everyone got up except for Carl who appeared to be in agony on the field. When the trainers reached him, they immediately saw that his knee was severely twisted. Carl was rushed to the hospital, afraid that his season, and maybe even his career, was over. After multiple x-rays and images were taken of Carl's knee, the doctor met with Carl and his mom.

"I'm afraid your knee is not in great shape, Carl," the doctor stated frankly.

"How so?" asked Carl with concern.

"The damage caused to your knee is quite extensive and I would suggest that you consider stem cell therapy to aid in the healing process and to speed the recovery," said the doctor in a serious tone.

"What are stem cells?" asked Carl and his mom together.

Part I – What Are Stem Cells?

"If you're ok with it, I'd like to explain some of the history of stem cells," replied the doctor.

"Sure," responded Carl, who had always enjoyed history.

"Very well then. Going back many years, Darwin's theory of evolution, published in 1859, stated that all organisms stem from a common ancestor. As the hypothesis was becoming widely accepted as theory by scientists, Ernst Haeckel applied Darwin's ideas to embryology. This was explained in the German publication *Anthropogenie* in 1868 (later translated as the *History of Creation*), where he stated that the common ancestor of all species was unicellular. Haeckel then extended this idea concerning the origin of species to his understanding of a *zygote* (fertilized egg), which is formed when a haploid (half the chromosome numbers) sperm and a haploid egg join to form a diploid (full set of chromosomes) cell. The zygote then divides and, after many cell divisions, results in an embryo and ultimately a multicellular human. In his book,

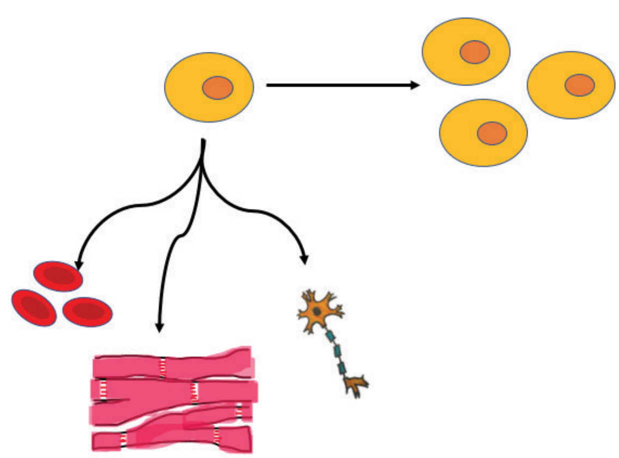

Figure 1. A stem cell can self-replicate and it can differentiate into one of the three germ layers. The stem cell shown above can differentiate either to erythrocytes, cardiac cells, or a neuron.

Case copyright held by the **National Science Teaching Association (NSTA)**. Originally published February 20, 2023. Please see our **usage guidelines**, which outline our policy concerning permissible reproduction of this work. *Credit:* Licensed photo ©Paul Topp | Dreamstime.com, ID 34046383.

Haeckel refers to the zygote as a "stem cell" because of the exponential growth that gives rise to all cells in the human body. One cell can divide and result in many cells to make an organism, raising the question of how one cell eventually results in different kinds of cells such as erythrocytes, cardiac cells, and neurons." (See Figure 1.)

"That's fascinating. Please continue!" said Carl.

"Meanwhile, in Russia, a scientist named Alexander Maximov was studying connective tissues and cells of the blood. In the early 1900s he demonstrated that all cells of the blood come from a common precursor cell. Maximov had confirmed the theory of *hematopoiesis*, that all blood cells come from hematopoietic stem cells. This meant that these cells could differentiate into multiple different cells, also known as multipotency, because of the niche or microenvironment in which they reside."

"So, what happened next?" asked Carl's mom, sounding as interested as her son.

"These key studies resulted in further experiments elucidating the origins and characteristics of stem cells. Much research was carried out in embryology to better understand the development of organisms and roles of various stem cells in the developmental process. As time progressed, many more scientists made contributions to this field by discovering various types of stem cells, understanding stem cell functions, and using stem cells in the medical field. Whole new fields of the life sciences developed, including regenerative medicine that aims to use cells and cell products for treating and even curing diseases. The discovery of adult stem cells in the bone marrow, embryonic stem cells in the early embryo, and the eventual discovery of stem and progenitor cells throughout the body, led to seminal scientific breakthroughs, such as cloning of the first mammal, Dolly the sheep. Considering all these discoveries, scientists today define stem cells as cells that can *self-renew* (produce copies of themselves) and *differentiate* (form other cells)."

Questions

1. How are stem cells different from other cells?

2. Why do scientists care so much about these cells?

3. What medicinal applications do you think there are for stem cells?

Part II – What Types of Stem Cells Are There?

"But where do stem cells come from?" Carl asked the doctor.

"I was almost there, but I need to get a drink first," the doctor said as he looked around for a glass of water.

"Here you go," two nurses nearby said simultaneously, startling the doctor who was surprised to see others listening to him too.

"So, you were asking about the origin and characteristics of stem cells. We can address that by learning about the location of these cells in our bodies. Various stem cells are naturally found throughout the body from early embryonic development through adult life serving the general functions of tissue development and maintenance with specific roles in tissue repair and replacement.

"You can find different types of stem cells almost anywhere in a healthy person. The first one is a zygote, which is formed when a sperm fertilizes an egg. The zygote undergoes many changes during embryonic development to eventually form the organism. A zygote is the only *totipotent* stem cell, which means that it can generate any cell in the organism. Around five days after fertilization, a rapidly dividing ball of cells is formed, known as the *blastocyst*. The blastocyst contains the outer *trophoblast* cells that work with the maternal cells to form the placenta and nourish and protect the developing embryo, whereas the inner group of cells, called the *inner cell mass (ICM)*, contains *embryonic stem cells (ESCs)* and forms the embryo." (See Figure 2.)

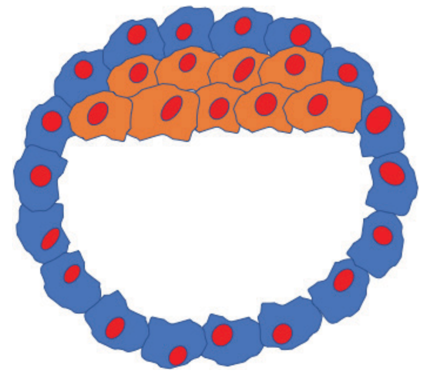

Figure 2. A blastocyst is an embryonic developmental stage that contains trophoblasts on the outside (shown in blue) and the inner cell mass or ICM (shown in orange) in the inside. The ICM contains embryonic stem cells (ESCs) that are pluripotent.

"Please explain more about the potency of stem cells," another nurse chimed in, startling the doctor again.

"I'd be happy to," said the doctor, taking a quick sip of water. "ESCs can differentiate into any cell in the human body, except the extra-embryonic tissues, such as the placenta. This ability or potency is called *pluripotency* (Figure 3). The newly forming embryo needs to grow by producing large numbers of every cell type to develop from a blastocyst to a fully developed fetus. However, as the organism matures from an embryo into a fetus and then into an adult, stem cells start to lose potency. Some stem cells are able to differentiate into many different cell types in the body, but not all of them. This is called *multipotency* and applies to many adult stem cells that reside throughout the body and partake in tissue homeostasis (Figure 3). *Mesenchymal stem cells (MSCs)* can be found in various connective tissue sites, including bone marrow and cartilage and can differentiate into at least bone, fat, and cartilage. *Hematopoietic stem cells (HSCs)* reside in the bone marrow and are responsible for generating all the cells of the blood including lymphocytes and myeloid cells, such as monocytes and neutrophils. *Adipose-derived stem cells (ADSCs)* share similar characteristics to MSCs, such as differentiation into fat, bone, and cartilage, and can be found in fat throughout the body. Myeloid stem cells originate from HSCs but can only differentiate into a few cell types and are thus called *oligopotent* (Figure 3). *Unipotent stem cells*, such as cardiac and hepatic (liver) stem cells can only result in one kind of cell, cardiomyocytes for cardiac stem cells and hepatocytes for hepatic stem cells (Figure 3). Unipotency can be an advantage, as cells in the heart tissue should only be cardiomyocytes (heart cells), not bone or cartilage cells. Since the cardiac stem cells are unipotent, there is very little chance of

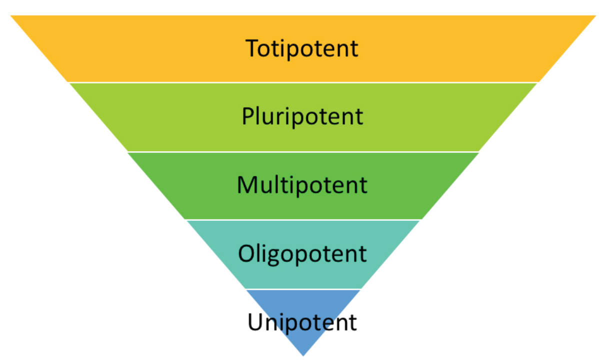

Figure 3. This diagram shows the hierarchy of stem cell potencies from the most general to the most specific, starting with totipotent stem cells that can turn into any cell in the body to unipotent that can only differentiate into one type of cell.

them giving rise to any other cells, besides cardiomyocytes, which is important to the proper functioning of the heart, including coordinated contraction."

"It's amazing how all these cells have a specific potency and function in our bodies," said Carl.

"I agree," continued the doctor. "All these stem cells have a potency of some sort and are naturally found in the human body. Additionally, research is trying to determine how our body generates these cells in the first place to study whether stem cells could be made artificially in the lab setting."

Questions

1. Describe the various stem cell potencies.

2. When thinking about therapeutic applications of stem cells, does the stem cell potency matter? Please explain.

3. If a person needed liver cells, would you use a pluripotent stem cell or a unipotent stem cell? Why?

Part III – Are All Stem Cells Natural?

"What do you mean by 'artificially made'? Aren't all stem cells natural?" Carl's mom asked.

"Let me address that next. So far, we've been discussing stem cells that can be found throughout the body, but to try to understand how stem cells work, scientists started to wonder if it were possible to sustain the pluripotency of cells throughout one's life. The only naturally occurring pluripotent stem cells are the ESCs that can be obtained from the ICM of the blastocyst. In the process of extracting the ESCs, the blastocyst is destroyed, which prevents the blastocyst from developing into an embryo and eventually a fetus. This renders human ESC isolations legally controlled and even prohibited in many countries, as many people see ethical issues in destroying the blastocyst and hence inhibiting the remaining developmental process of the embryo."

"I can see how some people might have a problem with destroying embryos for science," another nurse blurted out, quickly looking a little embarrassed by the sudden stare of the crowd that was getting bigger and bigger.

"To circumvent some of these issues, in 2006 a researcher named Yamanaka and his team published their work that described a method to revert an already differentiated cell back to its embryonic state. We call these cells *induced pluripotent stem cells* or *iPSCs*. While these cells removed many of the ethical concerns associated with the use of ESCs, the process that is used to generate them is unfortunately not very efficient and relatively complicated and time consuming. In the initial work, *retroviruses*, or viruses that insert their genome into the host cell genome, were used. Yamanaka used retroviruses to carry genes for the *transcription factors* (master regulators of transcription) that were essential for the pluripotency of embryonic stem cells into adult differentiated cells. These differentiated cells, such as fibroblasts, then developed into pluripotent stem cells, sharing many of the characteristics of ESCs, but no embryos were destroyed in the process of obtaining them. Since the initial work, several other techniques to obtain iPSCs have been developed, including the use of mRNAs or proteins for the key pluripotency transcription factors. In addition, micro RNAs (miRNAs) that can silence specific mRNAs in adult cells and reprogram the cells into pluripotent cells have been used."

Questions

1. How are iPSCs different from other stem cells?

2. Are there any drawbacks of using iPSCs? Please explain.

3. Do you think ESCs should be used at all for medical approaches, considering iPSCs now exist? Why or why not?

Part IV – How Could Stem Cells Be Helpful?

"That is absolutely amazing," Carl's mom said with genuine excitement in her voice.

"How can stem cells be helpful, in cases like my knee then?" Carl asked.

"Well, now that we've learned about the specific characteristics of stem cells to self-renew and differentiate, we have a better idea of how they might help in the field of regenerative medicine. As many stem cells exist in our bodies, they can be isolated, expanded outside the body, and even manipulated with relative ease, and hence could be extremely valuable for medical approaches. Currently, numerous applications for stem cells are being studied through basic research, translational research, and *clinical trials*. These include stem cell therapy in transplantation, Alzheimer's disease, Parkinson's disease, epilepsy, diabetes, arthritis, spinal cord injury, heart regeneration, and many more. Some of the studies employ *autologous* (from the patient) stem cells, whereas others use *allogeneic* (from another human) stem cells. Stem cell clinical trials are typically designed to develop new treatments or prevent specific diseases."

"Can you talk more about clinical trials? I've heard of those, and I think we have some ongoing in our hospital," a nurse asked.

"I'd be happy to. Most clinical trials are either Phase I (initial safety studies), Phase II (initial efficacy studies and continued safety studies), Phase III (large trials to determine efficacy and risk-benefit), or Phase IV (optimal use of already approved therapies), and employ an experimental group that receives the treatment, as well as a control group that receives a placebo."

"I've heard about double-blind clinical trials," another hospital worker stated as the crowd further increased.

"Double-blind clinical trials happen when two or more parties don't know the intervention assignment. In single-blind clinical trials, one party is unaware of the intervention assignment. Blinding is used to minimize patient and investigator bias in interpreting the effects of the treatment, as these could confound the clinical trial results and stop the treatment development."

Questions

At this point, searching the internet for current studies of stem cells would be helpful. Many primary research and review articles can be found utilizing the PubMed search engine through National Institute of Health (NIH) (https://pubmed.ncbi.nlm.nih.gov/). Also, ongoing and recently concluded clinical trials that test the safety and efficacy of stem cell therapies in real patients can be browsed through the NIH clinical trials search engine (https://clinicaltrials.gov/). Browse a stem cell type in which you are most interested through the PubMed search engine and read through the first few abstracts. Also, check the current clinical trials website by utilizing the same stem cell type you used in the first search, and browse through the first few clinical trials listed in the search results. Answer the following questions after your online searches.

1. What stem cell did you search through the PubMed site? List three recent publications regarding the stem cell type you searched.

2. What type of clinical trials were ongoing with the stem cell type you searched on the clinical trials site? What diseases were they targeting?

Part V – Jigsaw Activity

This activity will help you review stem cells and learn even more about the different types of stem cells while sharing your findings and hearing from fellow students.

Instructions

1. Obtain a stem cell card with a number on it from your instructor. Each student should have a stem cell card. Do not look at the back of the card if a two-sided card was provided for you.

2. Find other people in the classroom with the same stem cell type and assemble into a group. There are five different stem cell types: iPSCs, ESCs, HSCs, MSCs, and ADSCs.

3. Discuss the history, characteristics (potencies), and applications for the particular stem cell on your cards (every member in your group should have the same stem cell). You can get information from this case study and the internet search engines mentioned above. During this step, you will become a "subject matter expert" on your stem cell. Check the back of the card after initial discussions, if a two-sided card was provided for you, for additional information.

4. Now break from your group, find other people with the same number on their card, and assemble into a new group. Every student in the new group will have the same number, but a different stem cell.

5. In the new groups, take turns explaining and discussing the stem cell card you are holding as a "subject matter expert." You will be teaching the others who are holding a different stem cell card. Each person will have a turn, allowing everyone to learn about all of the stem cells.

Part VI – Carl's Knee Injury

"So, what do you think about stem cells after hearing about them?" the doctor asked Carl and his mom.

"We've definitely learned a lot, and stem cells seem really interesting and something that might help Carl to recover," Carl's mom replied.

"I'm just curious about what the damage to my knee was," Carl asked hesitantly.

"You have a dislocated knee that resulted in tears in your anterior cruciate ligament, also known as the ACL, and your medial collateral ligament, also known as the MCL," the doctor explained and showed images and diagrams of Carl's knee (Figure 4).

"The stem cell therapy sure sounds promising," Carl continued, with some hope showing in his teary eyes as he looked at the doctor first and then at his mom.

"I think we have a long road ahead of us, but I certainly am excited about the potential of stem cell therapy for Carl's knee injury," Carl's mom chimed in.

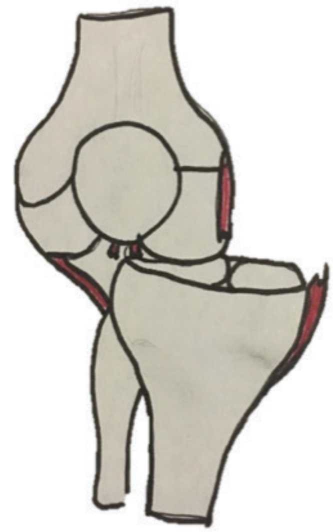

Figure 4. The damage to Carl's knee.

Questions

1. Which stem cell do you think would be most beneficial for Carl's knee? Why?
2. How could these stem cells be obtained? Would they be autologous or allogeneic?
3. Is there a guarantee that these stem cells will differentiate into the desired cell type? Why? What is the desired cell type?
4. Do you see any ethical concerns with the stem cell you chose? Please explain.

Part VII – What Type of Stem Cell?

As Carl's mom was walking to the cafeteria to get a cup of coffee and a snack for Carl, she overheard the nurses who had gathered earlier in Carl's room talking about one of their patients, "Jessie." Jessie had battled severe epilepsy for many years, making her condition life-threatening as the seizures were now occurring more frequently and were longer in duration. Jessie was treated with stem cells as a last resort, in hopes of improving her condition and stopping the further deterioration. For the treatment, her doctors had decided to extract stem cells autologously and then differentiate them into neural cells on culture dishes with nutrient-containing media and differentiation inducing factors. The neural cells were then injected into specific places in Jessie's brain using stereotactic surgical methods. The stem cells were relatively easy to obtain and more of them were available if needed, as they were self-renewing. The cell injections were able to lower the excitatory function of neurons in Jessie's brain and reduce the inflammation, resulting in suppression of the number of seizures she experienced and making her life much easier and less dangerous. Carl's mom found the discussion extremely interesting and encouraging, considering what she and Carl were thinking about, however, she did not hear what stem cell had been used in the therapy for Jessie.

"Stem cells sure seem magical," she said to herself as she walked back to Carl's room with a coffee and two pastries.

Questions

1. What type of stem cell was used?

2. What led you to this conclusion?

3. Would any other types of stem cell be appropriate for the treatment? Explain.