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GENERATING STEM CELLS FROM NON-EMBRYONIC TISSUE

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Abstract

Stem cell research has been at the center of scientific, political and ethical debates. Stem cells have promised to propel the advances in medical therapies to the forefront due to their ability to differentiate into various types of cells and tissues. The interest of scientists for these cells was generated by the breakthrough discovery of Dolly the sheep, the first cloned mammal that was successfully engineered through somatic cell nuclear transfer procedure by the team of embryologist Ian Wilmut, at Roslin Institute, UK. The somatic cell nuclear transfer (SCNT) is a laboratory technique that is based on transferring the genetic information from a donor cell to a recipient unfertilized egg that had its nucleus removed ("Cloning Fact Sheet," 2009). The cell division is then induced through chemical and physical methods. This impressive discovery built the ground for stem cell research.

Keywords- stem cells; non-embryonic tissue; somatic stem cells; umbilical cord blood cells, astrosytes, oligodendrocytes.

Introduction

The procedure of cloning mammals proved to be inefficient in general. Moreover, it was invasive and results were not always repeatable (Hoog, Burning, & Hazekamp, 2000).Scientists had difficulties related to efficient reprogramming of the cells. As a result, the gene expressed using the technique was unregulated properly. On the other hand, Dolly's design proved that cells can be reprogrammed and a new cell, organ, tissue, or even organism can be generated. It was an important discovery since before scientists believed that once finished cell differentiation is permanent. The ability of scientists to reprogram cells raised concerns of religious groups that related reproductive cloning and the whole stem cell research to the intention of scientists to clone human beings and to control nature. That was not what scientists pursued though. Researchers aimed to use stem cells for therapeutic purposes, to

replace cells that were damaged by the disease with new healthy ones and were not even close in implying the engineering of human beings ("Cloning fact sheet," 2009). Due to these complex implications the research with stem cells was banned by the government and stagnated for years. The US states would obey the former President Bush, who instituted the law after the creation of Dolly, in 1997 that would forbid the research with embryonic stem cells. President Obama issued an Executive Order that allowed the removal of obstacles to responsible scientific research on human stem cells ("US policy on stem cell research", n.d.).

The ethical concerns surrounding the use of embryonic stem cells have strongly encouraged scientists and researchers to explore other therapies that yield equal or superior results to that of embryonic stem cells. The purpose of this research is to describe different types of adult or somatic stem cells and how they function. A comparative research between embryonic and adult stem cells will be analyzed. Some of the breakthrough technologies on stem cells would be emphasized, and advanced techniques for isolating stem cells discussed. This report is focused of new therapies that had been developed and applied in treating several diseases, such as leukemia, Parkinson, spinal cord injury, myocardial infraction etc.

Stem Cells

Stem cells are those special cells that can easily replicate in damaged, degraded tissues ("Stem Cells Basic," n.d.) to repair them. Liu in his research article on stem cells derived from endometrium defined stem cells as undifferentiated cells that are able to replicate themselves, but not self-renew (Liu, Xiang, D, Zhang, Allickson, & Xiang, Ch, 2011). Stem cells are unique because they can be programmed to differentiate into a special cell type, such as a bone cell (osteoblasts), or a muscle cell (cardio myocytes), or a hair cell, or a liver cell (hepatocytes) (Liu, Xiang, D, Zhang, Allickson, & Xiang, Ch, 2011). These cells are special because they are not like any other type of cells that compose human organism. These cells can divide in large quantities being very proliferative. Millions of cells can divide out of a few cells. They are capable to replicate over stretched periods of times depending on cell's type. On the other hand, stem cells don't specialize on a specific organ. They don't have same function as organs or tissues do. For example, a stem cell will not pump blood into human's heart same as the heart muscle pumps blood ("Stem cells basic," n.d.). Unspecialized stem cells can differentiate into specialized cells. This is a multiple layer process. With each step of differentiation of a stem cell there would be more cells, or tissues the cell is able to differentiates into ("Stem cells basic", n.d.).

Stem cells therapy comprises the techniques that replace sick, bad cells with the new, healthy ones. Moreover, stem cells can help in injuries, eye therapies, organ transplants to name a few. Researchers experiment with these cells for more than 20 years trying to solve important health problems. Embryonic stem cells were always appealing to scientists due to their ability to be pluripotent. They proved great results in cell therapies related to wound regeneration (Fu et al., 2006), some successes were achieved in Parkinson's animal models (Wolff et al., 2010), and spinal cord injury therapies (Nandoe Tewarie et al., 2006).

However, there are some side effects of the embryonic stem cells therapies. They proved that if non - programmed these stem cells can differentiate randomly into a tumor called taratoma. Taratoma is a tissue that is different from other tissues because it contains human components, such as hair, teeth, bone, eyes, hands and feet ("Tumor in baby's brain contained tiny foot", n.d.). Stem cells are also prone to tumourigenesis and it has been reported that in vitro cell lines obtained from embryo cells show a high incidence of deregulation in the controlling of imprinted genes (Pessina & Gribaldo, 2006). Moreover, serious genetic alterations have been found to occur in cell lines that have been cultured for long term purposes (Pessina & Gribaldo, 2006). Even though scientists were aiming to explore this still much unknown field of embryonic stem cells, they tried to look also at alternative ways through somatic stem cells that would benefit patients same way.

Somatic Stem Cells

Adult stem cells, the topic of our research, also called somatic stem cells are found in different tissues of an organism. These cells give rise to a small number of cell types. They are called multi potent ("What classes of stem cells are there?" n.d.), as opposed to pluripotent embryonic stem cells. These cells are involved in correction and repair of tissues destroyed by the disease. They help rebuild proper function. In the future, the differentiation of somatic stem cells may turn into a great solution for multiple new therapies. Research also calls these cells induced pluripotent stem cells, because they are produced through the expression of genes of interest.

Hematopoietic, Mesenchymal, Neural and Liver cells derive from somatic stem cells. Figure 1 shows different pathways of differentiation of adult stem cells into bone, tendon, ligament, cartilages, cardiac muscle, etc. Hematopoietic cells are isolated from blood or bone marrow. Mesenchyme multi potent stem cells differentiate into bone cells, cartilages, fat cells and tendons. These stem cells are isolated from women monthly period blood, abortions, hysterectomy, umbilical blood cord or the endometrium after the biopsy (Liu, Xiang, Zhang, Zllickson & Xiang, 2011). Neural stem cells found in the brain differentiate into nerve cells, also non-neuronal cells, such as astrocytes and oligodendrocytes. The Hepatocytes are cells from the liver, endodermal cells (NIH Center for Regenerative Medicine). There are also progenitor cells that have the tendency to differentiate similar to stem cells. These cells differentiate into a certain cell type, they are more specific then stem cells and have the ability to divide less proliferative than stem cells that replicate indefinitely ("Progenitor cells," n.d.).

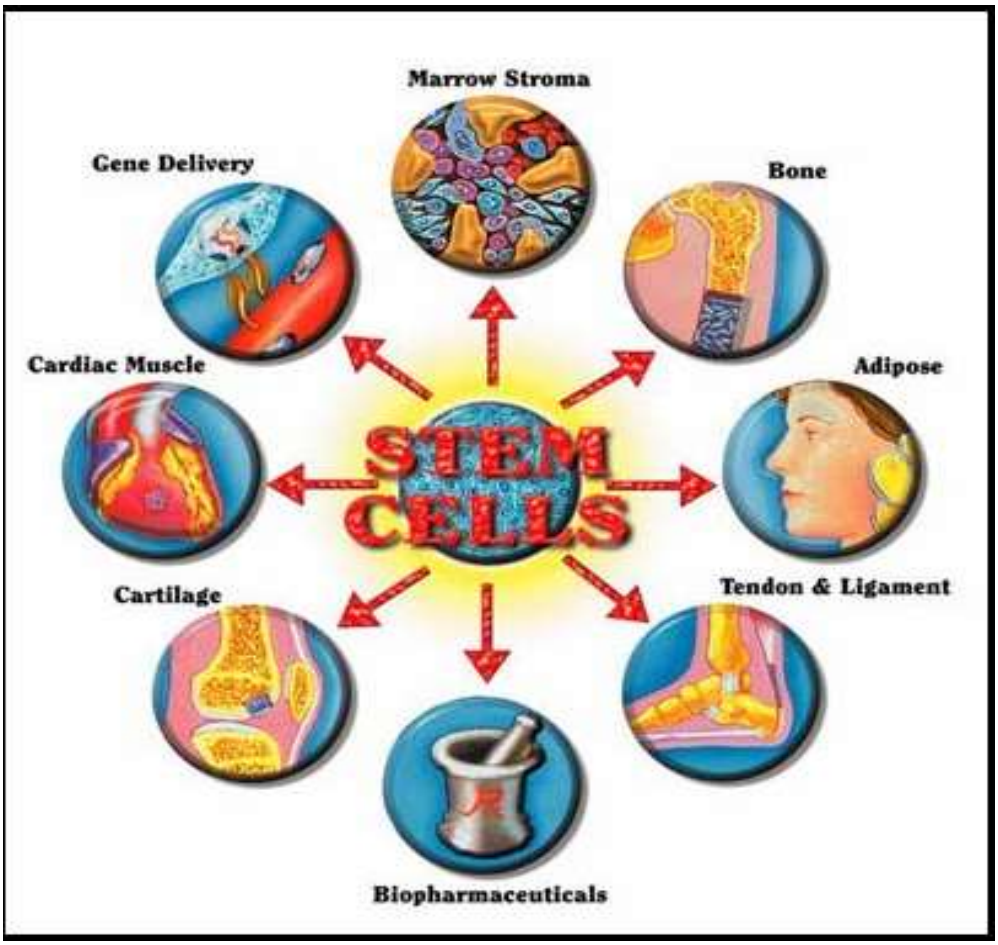

Figure 1 Stem cells differentiation. Stem cells can differentiate if reprogrammed into bone, cartilage, tendon, ligaments, cardiac muscle, etc.

Embryonic vs Somatic Stem Cells

There is a main difference between embryonic and somatic stem cells that has to be considered in order to separate the two. Embryonic cells can differentiate into any type of the body; they can even emerge into a whole organism, they are magically pluripotent. Embryonic stem cells can renew without stopping and have unlimited differentiation capacity. They may be used to generate somatic or adult stem cells (Wobus, 2001). On the other hand, somatic cells differentiate into cell types of their tissue origin. They are specific. A cell from liver will differentiate into a liver cell and a cell from the skin into a skin cell. They can't differentiate into any type of organ, or tissue, or cell like embryonic cells do. Embryonic cells grow easy in a cell culture in vitro, as opposed to adult stem cells that are hard to isolate from tissues and difficult to grow (Wobus, 2001). Researchers believe that somatic cells are less likely to be rejected by the immune system and most likely will not be rejected in organ transplantation. On the other hand, embryonic stem cell may or may not be rejected (Wobus, 2001). More studies have to be done to find out how embryonic stem cells work in transplants. It's still a much unknown pathway. The main function of somatic stem cells is the tissue regeneration. There have been a number of recent discoveries of adult stem cells that have proven to be very useful as alternative embryonic stem cell therapies (Pessina & Gribaldo, 2006). As we stated before adult stem cells are found in various tissues of the body. Those sources include bone marrow, umbilical cord blood, peripheral blood, neuronal stem cells, muscle mesenchyme stem cells, pancreatic stem cells, corneal limbic stem cells, mammary stem cells, salivary gland, skin, thymic tissue progenitors, dental pulp, adipose tissue, and hepatic tissue (Pessina & Gribaldo, 2006). Off these adult cells isolated, there are few that stand out for their unique ability for therapeutic treatment, bone marrow stem cells, umbilical cord blood stem cells, very small embryonic-like stem cells (VSELs), induced pluripotent stem cells (iPSs) and gestational amniotic fluid. This report will also cover some of the pathways the adult stem cells are isolated from.

Astrosytes, Oligodendrocytes and Neurons. The human brain was an interesting research subject that was studied by scientists for years and still is considered to be an unknown organ. Moreover, scientists were under the impression that brain cells were incapable to regenerate. With time, researchers discovered that stromal cells isolated from the bone marrow of the leg bone of the rat, are able to differentiate into brain cells, if induced (Kopen et al, 1999). The cells extracted from bone marrow called stromal cells, showed the ability to replicate efficiently; they proved high levels of expression. The induced stromal cells would differentiate into neurons, cells of the Nervous System. Stromal cells also are able to differentiate into astrocytes and oligodendrocytes in vitro. Astrocytes are cells that look like stars; they are big and are part of the Central Nervous System tissue (Reynolds and Weiss, 1992). Oligodendrocytes are special cells of the brain that have the function of covering the axons, that are prolonged continuities of neural cells (Baumann & Pham, 2001) .Figure 3 shows patterns of differentiation of how adult stem cells, such as astrosytes, oligodendrocytes and neurons. Each type of cell in the picture is marked with a different color to ease comparison between the three. Researchers tried to transplant these stem cells to new sites and discovered that they are able to integrate into different parts of the brain (Kay, 1997). Various therapies were developed based on stromal cells induction and differentiation (Kay, 1997). Trying to understand the process of cell differentiation scientists were able to develop theories of reconstruction of brain cells after injury or disease. Researchers tried to induce stromal cells in rodents first. The adult stromal cells, which are mesenchemial stem cells, were injected into the heart of mice. They differentiated into astrocytes (Kopen et al, 1999). Through this experiment researchers found out how to reprogram mesenchemial stem cells so that they differentiate exceptionally into neurons. And what is very convenient is that the highly invasive procedure of brain stem cells extraction is avoided Instead, cells are obtained from the bone marrow, a less invasive procedure and a safer technique also, much easier to tolerate by patients. The experiments repeated in humans worked great. Human mesenchemial stem cells were isolated in vitro (Azizi et al, 1998). The results were consistent with the results obtained in rodents. Cells were marked with a special dye to get a good visualization of the expression (Azizi et al, 1998).

Very Small Embryonic Like Stem Cells (VSELs)

Very small embryonic-like stem cells (VSELs) are valuable to stem cells research because they are capable of differentiating into cells of all three germ layers, which categorizes them to be pluripotent (Rogerson & Harris, 2011). Their size makes them very unique, which ranges from 3 to 7 microns in humans (Rogerson & Harris, 2011). VSELs have been isolated from bone marrow cells and are mobilized in the peripheral blood upon stress-inducing situations. Studies have concluded that VSELs play a central role in the regeneration of cells and tissues. A study at the University of Louisville, School of medicine showed that mice with myocardial damage responded favorably to VSELs promoted therapy. After 35 days of VSELs treatment, mice presented improved global and regional left ventricle systolic function, compared to the mice that were not treated with VSELs (Rogerson & Harris, 2011). Additionally, VSELs are believed to have all of the potential of embryonic stem cells for the generation of all cells, without the problem of tumorigenesis that has been associated with embryotic stem cells (Rogerson & Harris, 2011).

Induced Pluripotent Stem Cells (iPSs)

Induced pluripotent stem cells are newly emerging cells that have the identical functionality of pluripotent stem cells, or embryotic stem cells. However, the full extent of their capabilities, advantages and disadvantages are still being researched by scientists (Rogerson & Harris, 2011). iPSs isolation has continued to be difficult for researchers. The first method used retroviruses as vectors to transport the critical gene to be expressed. Still, lentiviruses are considered unsafe for therapies in humans, as retroviruses are known as cancer causing agents (Rogerson & Harris, 2011). However, researchers continue to explore methods of isolation for iPSs, as they have valuable potential in the future of stem cell therapy.

Conclusion

The ever evolving field of stem cells research holds great promises for the cure and treatment of a multitude of genetic diseases, health disparities and injuries associated with trauma and sickness. While the exploration of adult stem cells therapies have reduced the ethical issues associated with embryonic stem cells therapy, there is still a great need for continued research on them, such as isolation technique improvements and short term and long term risks reduction. There has been a lot accomplished in utilizing adult stem cells for therapeutic purposes and scientists are confident that many more accomplishments and discoveries are to come in the area of adult stem cells research. Still there are questions to be answered. The regulation of endogenous stem cells is not as well understood yet. The full capacity of neural stem cells is not a fact until the pathways of differentiation are better examined and control of their proliferations achieved. The location of adult stem cells and the places to which they move for differentiation are still unresolved. More experimentation is needed and research done. We think that the future of biotechnology relies on stem cells research that would bring new biopharmaceuticals and promising personalized therapies to be used to treat diseases traditional medicine can't cure. This article is a research on stem cells and also a strong support for the technology of stem cells, which could benefit tremendously in our opinion millions of patients worldwide, as well as would move scientific research forward.

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