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THE THERAPEUTIC POTENTIAL AND HOLISTIC APPLICATIONS OF STEM CELLS IN REGENERATIVE MEDICINE.

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ABSTRACT:

Stem cell research has been conducted over half a century, and this little leap is proving a giant stride for regenerative medicine and medical conditions. Stem cells are the cells found in the embryo, umbilical cord and other blood tissues. They are harvested and injected with a view to differentiating them into millions of healthy cells. This therapy has been very effective but since it is in the initial stages, more research needs to be carried out. A number of obstacles such as ethical, moral and social constraints thwart the therapeutic use of these cells for humankind. Research conducted on mice gives promising and fructifying results, and consequently this therapy is being used to treat a number of disorders. Through this therapy the genetic scientists can control and command the cells before differentiating into other cells.

Thus, it is possible to mold the cells into what is exactly demanded by the body, for example, skin cells, blood cells or muscle cells. A number of guidelines have been prescribed by National Institution of Health, and US Food and Drug Association, so that there is no anomaly or misuse of this therapy in clinical trials. The transplantation of these cells, although very expensive, has given astonishing results. Nevertheless, there appear several side effects also- a condition that has to be looked into carefully before this therapy is accepted universally and holistically. This research intends to explore how this therapy can be used for elimination of diseases, and what scope this research has in the future for human life. To complete this research, a number of experiments conducted successfully in the US have been taken into account and given their efficacy further horizons where this therapy can be used have been explored. The therapy holds a lot for future as it has the potential to stop the medicine use by eradicating the root cause of the disease.

INTRODUCTION

Stem cell research has been the centre of scientific research for a number of decades and is used extensively for regenerative medicine. A lot of

research has been done, and various other experiments are being conducted with a view to eradicating the genetic diseases. But as is the wont, with its potential there emanate a number of complications, side-effects and ethical dilemmas that pose a hindrance to the use of this revolutionary panacea to controlling the genetic disorders and tumors in the cells. Although the effects of stem cell therapy vary from individual to individual, in many cases anomalies and disorders such as weakness, dizziness, fatigue, headache, shivering, sickness and mild fever, have been observed during the clinical trials. These symptoms are mild and transient; they are avoidable by using different kinds of stem cells in the therapy. For instance, Mesenchymal Stem Cell Therapy, an IRB (institutional Review Board) approved clinical research, has been very effective in the diagnosis, prevention and treatment of human conditions. But for the therapy to be implanted on a large and holistic manner, it is necessary to follow the guidelines, safety procedures, dosage, and mode of administration of stem cells into the human genome. It is expected that MSCs and various other kinds of stem cell therapies hold a promising and revolutionary future for humanity. This research paper will address the limitations of stem cell therapy and the possible side effects. This paper also focuses on the protocols that are to be followed before its application to health conditions. This research also aims at how the future of stem cell therapy overcomes the limitations encountered in its application on medical conditions. The paper looks forward to the scope of applications of stem cell therapies for combating rapidly permeating diseases related to spinal cord injuries, cardiac arrest, neurological disorders and diabetes mellitus.

Regenerative Medicine

Stem cell therapy is one of the latest researches conducted in medical sciences. The meaning of this therapy is how we can repair, replace, regrow the cells, tissues and organs in a human body. The purpose of this therapy is to treat the cells in a manner that the human body starts functioning normally as all the bodily functions are restored to proper functioning. As a result of its tremendous potential and success, this therapy is also known as a regenerative medicine-a medicine which regenerates the dead or decaying cells and tissues. What is remarkable in this therapy is that the stem cells are used in such a way that the body's repair and growth mechanisms are activated, thereby giving the body an opportunity to heal itself without restoring to operations and surgeries. Thus, it is a magical therapy that can restore and rejuvenate all dead cells and tissues, giving organs life and sustainability. In other words, this therapy has replaced the chemicals, drugs and gadgets with the biological regenerative medicines.

KINDS OF STEM CELLS

Cells are the tiniest units of a human body, and are also called microscopic building blocks given the fact that they are dynamic in that they have the ability to reform themselves by millions every second. These cells are not specialized which means that they have not grown into a particular kind of cell earmarked for a specific functioning. Since the stem cells can develop into other kinds of cells, this

process is called differentiation. This is what is most useful for the scientists as they can use the stem cells right at this stage and develop them into particular kinds of cells. There are around 37 trillion cells in a human body that grow, change, reform and modify on their own. Although every cell has the same set of genes there are around 226 different kinds of cells in the body. Out of these, stem cells are those cells that manifest the potential to develop into different kinds of cells, and their basic function is to act as a workshop for repairs. What is remarkable is that these cells can create replicas of themselves thereby creating millions of copies of themselves once they are transfused. For example, the stem cells infused into the nerves will increase exponentially thereby creating millions of nerve cells.

Stem cells are of two kinds: embryonic stem cells and adult stem cells. As the name suggests, embryonic stem cells develop in the embryo at a very early stage, even post 3-4 days of fertilisation in the lab dish. Through the process of cell division, the stem cells divide and renew themselves thereby creating a reservoir of stem cells in the embryo. Adult stem cells on the other hand are found in bone marrow, and unlike the embryonic cells they multiply thereby creating millions of other cells including the RBC. Therefore, these cells are also known as totipotent or omnipresent stem cells. The embryonic stem cells have been widely used by the genetic scientists for repairing other cells of the body as these cells can change and develop them into other 226 kinds of cells right from the embryonic stage. Since these cells are taken from the embryo developed after IVF, and once these cells are used, the embryo is wasted, there come a number of ethical issues in the use of this therapy in treating human diseases.

Mesenchymal Stem cells

Of all the stem cells, MSCs have been called the most prospective of adult stem cells due to their multipotent nature and ability to transform into other cell types. MSCs are also called versatile cells given their tremendous ability to differentiate into multiple cell types. Consequently, they are the most widely used in stem cell therapy for medicinal purposes. They are better than the embryonic cells as the embryonic cells not only have a higher tendency of getting rejected by the immune system but also cause a risk of inflammation and damage to the tissues. Another advantage of the MSCs is that they can be extracted from a number of body parts such as the bone marrow, fat, umbilical cord etc. They can be easily harvested and conveniently used for medicinal purposes. It is for this quality that MSCs are also called immune-suppressive as they are not subject to rejection that is observed in case the foreign cells are used for the therapy. In all the clinical trials the MSCs derived from the umbilical cords were brand new cells that were thoroughly accepted by the immune response of the body. Moreover, while using the MSCs for therapy there is no HLA matching (a prerequisite to match patients and donors for blood or marrow transplants) required, no blood loss is there, and there is no rejection at all.

Safety concerns, protocol and guidelines for stem cell treatment

As the stem cell therapy is used universally at the clinics there have to be a number of precautions and concerns in order that the therapeutic procedure is not misused or carried out anomalously. A number of unregulated clinics offer to treat patients with MSCs although they are not approved by FDA (US Food and Drug Association)and IRB. Such unregulated clinics lack the foresight and experience to use such therapies and can hinder the expected results. The use of unsterile equipment by these clinics has also led to unsafe and ineffective treatment. If the sterilization protocol is not adhered to, there remains a heavy risk of infection and contamination to the other cells in the body.

Differentiation of stem cells into mature cells.

We have studied that various kinds of stem cells are infused selectively into different body organs with a view to developing millions of new cells. How does this happen and how does a stem cell develop into different cells? This process is known as cell fate decision which means that every stem cell has the power to decide what it intends to develop or mature into. There are many reasons behind it but the exact nature of this functioning is complex. Cells have the tendency to send and receive signals from outside and inside, and as such there is a communication network among millions of cells. The proteins and hormones produced by the body also give the stem cells an impetus to develop or divide into other cells. These signals, proteins and hormones carry an expression into the genes that helps a cell to develop and mature. As per a research conducted at "McMaster Stem Cell and Cancer Research Institute," the stem cells know how and where to develop, for instance into blood cell or neural cell. The stem cells are gifted with a tendency called Pluripotency that allows them the choice to develop into any of the remaining 226 cells in the human body. The evidence behind the functioning of the cells comes from how the DNA is arranged inside the cells, which in turn can be detected by the specific proteins deposited on the surface of the stem cells. "Dr. Bhatia, a professor in the Department of Biochemistry and Biomedical Sciences at the Michael G. DeGroote School of Medicine," says, "it is like going on a secret trip." If one is going to Jamaica, he needs light clothes and swimwear but if the same person wants to go to Alaska he needs heavy clothes and protection from ice. Same is the case with the cells. They know what is the need of the hour, and accordingly they equip themselves for the future journey. Through the use of ontogenetic and sonogenetics techniques the cells can be forced to change the course of their way and commanded into developing into different kinds of cells. Thus the cells are not always free; they have to obey the command. During the research conducted by Dr. Bhatia and his team it was found that when the scientists isolated the stem cells by new protein markers on the cell surface, a great number of specialized cells were formed, "nearly five times as many blood cells and twelve times as many neural cells compared to when the stem cells had to be forced into those cell types." Scientists are able to make predictions also on the nature of how the cells

are going to differentiate into and also what tissues will be formed after differentiation. In another research by "Jianping Fu, an assistant professor in mechanical engineering and biomedical engineering," and his team, the study of stem cell mechanics helped them to understand the force that cells exert on the materials on their surface as well as on the materials they are attached to. Once the researchers observed the cells differentiating according to the mechanical stiffness of the substrate, they decided to measure the cellular traction forces throughout the culturing process to see if they could predict how the cells would differentiate. Using a technique called fluorescent microscopy, the researchers measured the bending of the micro posts in order to quantify the traction forces. Fu claims, "Our study shows that if the stem cells determine to differentiate into one cell type then their traction forces can be much greater than the ones that do not differentiate, or that differentiate into another cell type. Thus, we can use the evolution of the traction force as early indicators for stem cell differentiation." Another factor that gives the power of transformation to a cell comes from OCT4. "Laszlo Nagy, professor and director of the Genomic Control of Metabolism Program," after her experiments on stem cells asserts that "We found that the stem cell-specific protein OCT4 primes certain genes that, when activated, cause the cell to differentiate, or become more specialized." Thus it can be understood that the presence of this protein has the power of constricting the range of cell types into which the cells were supposed to differentiate. The latest research on the stem cells indicate that OCT4 acts as a transcription factor that controls the tendency of a cell to mature or develop into. With the help of this protein found on the DNA of the cell, and through signals, the scientists can both help initiate or repress the transcription of specific genes. Presently, the genetic scientists are using genomic approaches that help them to customize the embryonic cells, and there is no doubt that "OCT4 is an integral and necessary component of signal-regulated transcriptional processes required for tissue-specific responses."

Stem Cells Applications

Apart from the embryonic and mesenchymal stem cells, the recently induced tissue specific progenitor stem cells (TSPSCs) and pluripotent stem cells have shown promising and exciting results in regenerative medicine. The aim of regenerative medicine deals with the elimination of the current use of medicines by eradicating the root cause of the diseases and dysfunctions. There are a number of ways in which the stem cells are administered and transplanted from one body part to the other. The first one is called IV stem cell therapy which refers to the transfer of these cells intravenously. Intrathecal therapy employs injecting the stem cells directly into the spinal cord and into other damaged tissues and organs.

The embryonic stem cells that have the power of differentiating into 226 other cells under specific culture conditions can be transformed into "hepatocytes, retinal ganglion cells, chondrocytes, pancreatic progenitor cells, cone cells, cardiomyocytes, pacemaker cells, eggs, and sperms

which can be used in regeneration of tissue and treatment of disease in tissue specific manner." Similarly, the tissue specific progenitor stem cells have also been experimentally forced to change into a number of mature and developed cells. Take, for instance, the inner stem cells of our ears can be differentiated into auditory hair cells. The stem cells of the dental pulp can be transformed into serotonin cells. With the help of genome approaches, the TSPSCs have been transplanted into various body organs and through it the scientists have been successful in the regeneration of tibialis muscles from mesoangioblasts. Cardiac tissues have been regenerated from MSCs and corneal tissues from limbal stem cells. On further research the genetic scientists found that "The 3D-culture of TSPSCs in complex biomaterial gives rise to tissue organoids, such as pancreatic organoid from pancreatic progenitor, intestinal tissue organoids from intestinal progenitor cells, and fallopian tube organoids from fallopian tube epithelial cells." Apart from the applications of these cells, the MSCs can also differentiate into regenerating the cartilage, muscular tissues and bones. Research also shows that the use of the MSCs has been conducive to the treatment of liver cirrhosis, removal of the heart scar formed after a cardiac arrest. and also to produce hair follicles.

It is to be noted that of all the research conducted on the stem cells in the past fifty years, the most conducive has been the use of Haematopoietic stem cells for transplantation. It is the most popular therapy used in regenerative medicine. Similar to the MSCs these cells are derived from the bone marrow, umbilical cord blood or peripheral blood. This therapy is very effective as during transplant the cells can be taken from a donor or from the person under treatment. In other words, this therapy can be autologous, allogeneic and syngeneic, thereby giving the genetic scientists ample opportunities to transplant them from one person to the other. HSCs have been very productive as the transplantation helps us to fight the ailments caused by the anomalous working of the haematopoietic system, which leads to diseases such as anaemia and leukaemia.

Failures during the therapeutic use and transplantation

Although the use of the stem cells has proven to be very effective, there have been a number of incidents when this application either failed or resulted in a number of side effects. Besides pain in the mouth and throat, and nausea, the transplant is prone to a number of infections. Since the stem cells take at least 6 months to differentiate into the white blood cells, the infection caused by bacteria, virus and fungus is very probable. At this time, the human body is frail and vulnerable, and in the event of reduced immunity, the infections become rampant. The symptoms of GVHD (graft versus host disease) have been reported even after 90 days of transplant. The onslaught of this disease is identified by severe rashes and infections on the skin. It must also be noted that many a time the human body does not accept the cells, whether they come from the same human body or from the donor. In such a scenario, the time, efforts and expenditure are wasted.

Although most of the time, the therapy proved effective in the treatment of cancer, it was observed that in some cases the cancer relapses even after three years of the transplantation. Looking at these failures and future risks, NIH (national institute of health) has created a number of guidelines for further research. According to the first regulation, it is mandatory on the part of the scientists to take the cells from an in vitro embryo developed in a lab dish, and not a natural embryo. A written consent from the donor is required along with other legal documentation. No donation or payment is to be made to the donor under any circumstances. There are a number of areas in which this research and therapeutic use has been prohibited. For instance: "Research related to human germ line gene therapy and reproductive cloning; Clinical trials involving xenogeneic cells; Any clinical research on Xenogeneic-Human hybrids; Use of genome modified human embryos, germ-line stem cells or gametes for developmental propagation; Research involving implantation of human embryos (generated by any means) after *in vitro* manipulation, at any stage of development, into uterus in humans or primates; Breeding of animals in which any type of human stem cells have been introduced at any stage of development, and are likely to contribute to chimeric gonadal cells." Therefore, every regulated clinic using this therapy has to present the "FDA-issued Investigational New Drug Application number," in order to show that the procedure followed is in consonance with the international standards set for transplant. The therapy although effective is out of the means of every patient as the transplant and post operative care are enormously expensive. Moreover, its use is not universally available on the globe.

Religious and ethical constraints in the therapeutic use of the stem cells

As with every research on the human body, the stem cell research has also often been thwarted on religious and ethical grounds. We are not God, and we lack omniscience-this is the view of moralists, priests, rabbis and spiritualists against this research. Our purposes are not philanthropic and instead they are governed by selfishness. It is feared that this revolutionary technology can be misused similar to the organ trade, which is still practiced in manty countries. Buying stem cells from a fit donor is not a difficult job, and with the help of this therapy the rich might use the stem cells of the poor in order to prolong as well as immune themselves. In the eyes of religious proponents, we are playing with the sanctity of human life by using the stem cells in therapeutic and regenerative medicine. They are very much against the use of these cells as they are mostly gathered from the embryo and the fetus. Once the cells are taken after the IVF, the embryo gets destroyed thereby killing the potential of one human life. Opponents of this therapy consider this research as synonymous with cloning thereby bringing the objection that humans cannot be the creator. Creation is the act of God, and any such attempt on the part of man is highly unethical. Some moralists even fear that this therapy is not flawless and as such there are chances that some real Frankenstein may be erroneously created by this

research. Even if the stem cells are harvested from a dead fetus, the opponents condemn this practice as they call it taking life from the dead as a dead fetus is cadaverous in nature. The debate continues between the moralists and the scientists as ever!

The future prospects of Stem Cell therapy

As the research is undergoing, the genetic scientists intend to use the therapy in a number of ways with a view to eradicating diseases that are called untreatable as of now. Scientists hope that this therapy will play a revolutionary role in tailoring and customizing to each patient's requirement by using patient specific stem cells for genetic makeup. Regenerative medicine is under development which will help the patients suffering from the incurable neurological disorders, such as OCD, Multiple Sclerosis and Parkinson's disease. Pluripotent stem cells research makes the scientists very confident as these cells have provided them a big platform to understand the underlying mechanism behind these neurodegenerative dysfunctions. Stem cells can be used to reverse the ageing process by rejuvenating the dead cells and tissues.

Conclusion

Stem cell research has been taking place for the last fifty years, and it can now be said that this therapy is a game changer with reference to human medical conditions and diseases. Although a number of obstacles whether ethical, genetic or psychological are left to be combated, there is no doubt in saying that stem cell therapy has brought a very conducive effect in regenerative medicine and transplantation. Further research on this therapy brings promising results of the effective use of therapy in eliminating neurological disorders and also the so far untreatable neurodegenerative diseases. The therapy holds a bright future as the stem cells can be stored and there is a tremendous growth of tissue banks in every country. Thus, stem cells give us a chance to fight with the unpredictable and contingent diseases that might erupt anytime in the near future. With the help of this research, we hope that time is not far when these cells will be used to the extent of providing longevity and immunity to human life.

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