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APPLICATION OF STEM CELL THERAPEUTIC AGENTS TO CONTROL CRITICAL DISEASE

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ABSTRACT

Stem cell research has been hailed for the potential to revolutionize the future of medicine with the ability to regenerate damaged and diseased organs. On the other hand, stem cell research has been highly controversial due to the ethical issues concerned with the culture and use of stem cells derived from human embryos. This article presents an overview of what stem cells are, what roles they play in normal processes such as development and cancer, and how stem cells could have the potential to treat incurable diseases. Ethical issues are not the subject of this review. In addition to offering unprecedented hope in treating many debilitating diseases, stem cells have advanced our understanding of basic biological processes. This review looks at two major aspects of stem cells. Three processes in which stem cells play a central role in an organism, development, repair of damaged tissue, and cancer resulting from stem cell division going awry. II. Research and clinical applications of cultured stem cells: this includes the types of stem cells used, their characteristics, and the uses of stem cells in studying biological processes, drug development and stem cell therapy; heart disease, diabetes and Parkinson's disease are used as examples.

INTRODUCTION: Stem cells offer opportunities for scientific advances that go far beyond regenerative medicine. They offer a window for addressing many of biology's most fundamental questions. Watching embryonic stem cells give rise to specialized cells is like peeking into the earliest development of the many tissues and organs of the human body.

Stem cell research may help clarify the role genes play in human development and how genetic mutations affect normal processes. They can be used to study how infectious agents invade and attack human cells, to investigate the genetic and environmental factors that are involved in cancer and other diseases, and to decipher what happens during aging [1].

Stem cells may also revolutionize traditional chemical medicine. Because embryonic stem cells can continue to divide for long periods of time and produce a variety of cell types, they could provide a valuable source of human cells for testing drugs or measuring the effects of toxins on normal tissues without risking the health of a single human volunteer.

In the future, thousands of Compounds could be quickly tested on a wide assortment of cell types derived from stem cells, making drug discovery more efficient and cost effective. Using nuclear transfer to produce stem cells could be particularly useful for testing drugs for disorders that are of genetic origin. For example, it is difficult to study the progression of Alzheimer's and Parkinson's diseases in the brains of

live patient but by using the cells of an Alzheimer's patient to create stem cell lines with nuclear transfer, scientists could trace the development of the disease in a culture dish and test drugs that regenerate lost nerve cells with no danger to the patient [2].

What are Stem Cells and why are they important? Stem cells have two important characteristics that distinguish them from other types of cells. First, they are unspecialized cells that renew themselves for long periods through cell division. The second is that under certain physiologic or experimental conditions, they can be induced to become cells with special functions such as the beating cells of the heart muscle or the insulin producing cells of the pancreas.

Scientists primarily work with two kinds of stem cells from animals and humans: embryonic stem cells and adult stem cells, which have different functions and characteristics that will be explained in this document. Scientists discovered ways to obtain or derive stem cells from early mouse embryos more than 20 years ago. Many years of detailed study of the biology of mouse stem cells led to the discovery, in 1998, of how to isolate stem cells from human embryos and grow the cells in the laboratory. These are called human embryonic stem cells. The embryos used in these studies were created for infertility purposes through in vitro fertilization procedures and when they were no longer needed for that purpose, they were donated for research with the informed consent of the donor [3].

Role of Stem Cell in Cancer: Ontogeny (development of an organism) and oncology (cancer development) share many common features. From the 1870s the connection between development and cancer has been reported for various types of cancers. Existence of "cancer stem cells" with cell division has also been reported more recently. The connection between cancer and development is clearly known as teratocarcinomas.

As early as 1862, Virchow discovered that the germ cell tumor teratocarcinoma is made up of embryonic cells. In 1970, Stevens derived embryonal carcinoma cells from teratocarcinomas. A teratocarcinoma is a spontaneous tumor of germ cells that resembles development gone awry. This tumor may contain several types of epithelia: areas of bone, cartilage, muscle, fat, hair, yolk sac, and placenta. These specialized tissues are often adjacent to an area of rapidly dividing unspecialized cells. The teratocarcinomas are able to differentiate into normal mature cells when transplanted into another animal. This alternation between developmental and tumor cells status demonstrates how closely development and cancer are related [4].

McCulloch explored the connection between normal development of blood cells and leukemia. According to him, normal hematopoietic development requires the interaction of stem cell factor with its receptor, c-kit. A hierarchy of stem and progenitor cells differentiates and produces different sublineages of cells resulting from response to varied growth factors.

Malignancies of the hematopoietic system originate from two sources: those with an increased growth in an early stem cell produce acute leukemia, while those that arise from a decreased response to death or differentiation in a stem cell produce chronic leukemia. The present-day challenge is to decode the common molecular mechanism and genes involved in self-renewal for cancer cells and stem cells.

Role of Stem Cell in Clinical Applications: Rao and colleagues postulate that all stem cells, regardless of their origin, share common properties. These researchers have reviewed the literature for candidate "stemness" genes. They conclude that there are a set of candidate genes that are present in all stem cells and can serve as universal markers for stem cells. These codes for proteins are involved in self-renewal and differentiation. In addition they predict some differences in gene expression between different populations of stem cells [5].

Role of Stem Cell in Heart Disease: Cardiovascular disease is a leading cause of death worldwide killing 17 million people each year, especially due to heart attack and stroke. In the United States, heart disease is the number one cause of death. The high rate of mortality associated with heart diseases is the inability to repair damaged tissue due to the full differentiation of heart tissue. Interruption of blood supply to the tissue causes infarction of the myocardium and death of myocardiocytes.

A recent report used a swine model of atrioventricular block and transplanted human ES cell-derived cardiomyocytes into the pig's heart to work as a pacemaker. The ES cells survived, functioned and integrated well with the host cells. The researchers used embryoid bodies to select spontaneously beating areas of culture (cultured myocytes will actually beat in synchrony just like a heartbeat). This study bodes well for future myocardial regeneration using human ES cells.

Adult stem cells have also been used in cell therapy for the heart; skeletal muscle myoblast transfers showed contraction but did not differentiate into cardiomyocytes and did not integrate with the host myocardium. Ideally, both contraction and integration with host myocardium should have occurred in order for the therapy to be effective. Endothelial progenitor cells transplants halted the degenerative process but did not initiate regeneration [6].

Role of Stem Cell in Diabetes: Elevated glucose levels in the blood are responsible for diabetes. Diabetes affects 16 million Americans (5.9 percent of the population) and is the seventh leading cause of death. Worldwide it afflicts 120 million people and the World Health Organization estimates that the number will reach 300 million by 2025.Type I diabetes, or juvenile onset diabetes, is an autoimmune disease that causes destruction of the insulin-producing beta cells in the pancreas. Insulin injections are given to diabetics but they cause surges in blood glucose levels followed by a drop in the glucose levels and lack fine tuning.

Pancreas transplantation has been performed in diabetics as more recently has pancreatic islet cell transplantation. The latter has the advantages that it does not require whole organ transplantation. However, the need for immunosuppression to prevent rejection of allogeneic islet transplants and a serious shortage of organ donors are lingering problems. The Edmonton protocol, developed by Shapiro and colleagues, is promising. This procedure transplants a large amount of islet cells and uses a glucocorticoid-free type of immunosuppression regimen.

In early clinical testing it reversed diabetes in all of the patients tested [7].

Stem Cell Therapy for Diabetes: Cells need to be able to self-regenerate and differentiate. Also it has been observed that the presence of all the islet cell types is preferable to only beta cells since the former are better able to respond to changing levels of glucose in the blood. Growth must be balanced with ability to produce insulin. The insulin producing cells tend not to divide and those which divide actively do not produce insulin.

Adult stem cells from the pancreas have been elusive so far. However, a recent report of a clone from mouse pancreas that can generate both pancreatic and neural cell lines is exciting, as is a second report that adult small hepatocytes (liver cells) can be induced to produce insulin. Both reports offer hope for using adult stem cells as a treatment and cure for diabetes

Role of Stem Cell in Parkinson's disease: Parkinson's disease is the second most common neurodegenerative disease following Alzheimer's. Approximately 1.5 million people in the United States suffer from Parkinson's disease, which is caused when 80% or more of dopamine producing-neurons in the substantia nigra of the brain die. Normally, dopamine is secreted from the substantia nigra and transmitted to another part of the midbrain. This allows body movements to be smooth and coordinated.

Patients with Parkinson's disease are treated with the drug levodopa (or L-dopa), which is converted to dopamine in the body. Initially effective, the treatment's success is reduced over time and side effects increase, leaving the patient helpless.

It has been recognized that dopamine-producing cells are required to reverse Parkinson's disease. Since the 1970s, many types of dopamine-producing cells have been used for transplantation. These include adrenal glands from the patient, human fetal tissue and fetal tissue from pigs. Limited success has been achieved with these cells. Rat and monkey models of Parkinson's were used to test fetal mesencephalic cells. Success with animal models led to clinical trials [8].

Fetal tissue transplantation has been performed in 350 patients, including trials using pig fetal tissue. So far, the success of reversing Parkinson's disease using fetal tissue has been limited at best. However, in the most successful cases, patients have been able to lead an

independent life without L-dopa treatment. The limitations include (i) lack of sufficient tissue for the number of patients in need, (ii) variation in results between patients ranging from no benefit to reversal of symptoms, and (iii) Occurrence of uncontrolled flailing movements (called dyskinesias).

CONCLUSION: This review has summarized the role of stem cells in basic biological processes in vivo, namely in development, tissue repair and cancer in Part I. Part II focused on cultured stem cells and their uses, describing the different sources of stem cells, their properties and their research uses and clinical applications.

Remarkable progress has been achieved in studying stem cells. The most exciting use of cultured stem cells is the promise for curing many devastating diseases like Parkinson's and diabetes. However, more basic research remains before stem-cell based therapy is widely used.

Of the stem cells discussed, ES cells have the most capacity to differentiate into a variety of cells and their proliferation capacity is also unsurpassed by any other cell type. There are three major problems with ES cells; ethical issues, immunological rejection problems and the potential of developing teratomas.

In the future, ideally, somatic stem cells from the patient will be extracted and manipulated and then reintroduced into the same patient to cure debilitating diseases. This would preclude the use of embryonic stem cells for cell therapy, eliminate the ethical objections against stem cell research, and also resolve immunological rejection problems. However, at present the cell proliferation and differentiation potential of embryonic stem cells remains far more likely to produce a cure than do the somatic cells.

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