The Potential of Stem Cells

Ngan Tina Huang

In the past several years, human stem cell research has been placed at the forefront of public attention. Embryonic stem (ES) cells have tremendous flexibility in developing into specialized cells, so they offer hope to patients suffering from debilitating illnesses such as Parkinson's and Huntington's disease. In light of the moral issues that ES cells raise, some scientists turn to adult stem cells as a less controversial alternative. Already, some types of stem cells have found their way into tissue engineering applications, and with time, we expect to realize additional stem cell technology. Let us elucidate the unique potential of embryonic and adult stem cells by examining their history, biological basis, and applications.

Historical Overview

ES cells have already been characterized in the animal model. The development of ES cells can be traced from early studies with mouse teratocarcinomas, tumors in the gonads. It was found that teratocarcinomas produced differentiated embryonic carcinoma (EC) cells that contain a variety of cell types, including muscle, bone, and cartilage. From these observations, scientists began to realize the potential of EC cells in producing stem cells that were pluripotent—capable of giving rise to many cell types. However, since EC cells were often accompanied by genetic mutations, a novel idea was to derive pluripotent cells directly from blastocysts. This was successfully carried out in 1981 by Gail Martin and Martin Evans, independently.[1,2] Later, in 1995, James Thomson and colleagues derived ES cells from the rhesus monkey primate.[3] These studies provided the paradigm for later experiments.

Besides previous work in animal models, the interest in the human model was influenced by two significant events. The first breakthrough was the cloning of the sheep Dolly by Ian Wilmut and colleagues.[4] This event confirmed that cells can be genetically reprogrammed to produce a viable organism.[5] The second breakthrough was the derivation of human ES (hES) cells by Thomson and colleagues because it initiated a supply of hES cells for research.[6] These two events ushered the fantasy of human genetic reprogramming into reality.

Biological Basis

The basic biological aspects of embryonic stem cells are well known. In mammals, the fertilized oocyte and blastomeres of 2-4 and 8-cell-stage embryos are totipotent, capable of giving rise to all cell types. At the blastocyst stage, the inner cell mass (ICM) gives rise to ES cells that are pluripotent (Figure 1).[7] When grown in vitro, these ES cells have the unique ability to remain undifferentiated with unlimited self-renewal capacity and to spontaneously differentiate into somatic cells.[8] They can also aggregate into balls of differentiated cells known as embryonic bodies (EBs) (Figure 2). As cells within the EBs develop, they organize into three distinct layers—the ectoderm, mesoderm, and endoderm—from which various somatic cell types are derived.

ES Cell Applications

Several medical applications using mammalian ES cells have proved successful. One area is in Parkinson's disease, a degenerative disorder characterized by the loss of midbrain dopamine neurons. Björklund et al. (2002) showed that injections of mouse ES into the rat striatum produced dopamine-producing neurons in rat brains, leading to partial recovery of the disease.[9, 10] Another area is the treatment of damaged spinal cords. Derived from mouse ES cells, immature nerve cells that were injected into paralyzed rats showed improved mobility.[11] As scientists unravel the mysteries of hES differentiation, practical applications for humans will hopefully be in the near future.

One of the major goals of ES cell research is to understand how these cells can be directed toward specific lineages of differentiation. In mice, soluble factors are known to direct differentiation toward certain cell types. For example, interleukin-1 (IL-1) directs cells to become macrophages or neutrophils; retinoic acid induces neuron formation, and transforming growth factor beta (TGF-ß) induces myogenesis.[12, 13] The effects of soluble factors on hES are only beginning to be studied. Schuldiner et al. (2000) studied the effects of eight growth factors on the hES differentiation and found that each growth factor directed the cells to a unique set of differentiated cells.[14] They categorized the effects into three general types: (1) Activin-A- and TGF-ß1-induced mesodermal cells; (2) retinoic acid, epidermal growth factor (EGF), bone morphogenic protein-4 (BMP-4), and basic fibroblast growth factor (bFGF) activated ectodermal and mesodermal cells; and (3) ß nerve growth factor (ßNGF) and hepatocyte growth factor (HGF) directed all three embryonic germ layers. None of the growth factors could exclusively produce one single cell type.

Currently, researchers at the MIT Langer labs are studying hES cell differentiation. Supervised by Dr. Robert Langer and Dr. Shulamit Levenberg in the Department of Chemical Engineering, I am conducting research on the mechanism of hES differentiation toward endothelial cells. These blood vessel–forming cells generated from hES cells could be used for generating new blood vessels in ischemic regions of the brain, heart, and other tissues.

In January 2002, the publication of the first human therapeutic clone marks a new frontier for stem cell research and a step closer to practical therapeutic applications. Therapeutic cloning uses a patient's own genetic material to generate cells to treat debilitating diseases. Jose B. Cibelli's team at Advanced Cell Technology (Worcester, MA) successfully created a cloned human embryo to harvest hES cells for medical treatment.[15] This was carried out by replacing the genetic material in the donor egg with that of the patient and then coaxing the egg to divide. Once a blastocyst formed, the ICM was removed and grown in culture for stem cells. Cibelli hopes to derive nerve cells for healing damaged spinal cords and treating brain disorders.

Adult Stem Cells

In addition to embryonic stem cells, other types of stem cells are derived from adults, known as somatic stem cells. Somatic stem cells are characterized by their ability of self-renewal as well as their multipotency, the capability to give rise to many types of differentiated cells. Although once thought to be more rigid than ES cells, some adult stem cells have a plastic nature. For example, bone marrow cells can be induced to form muscle cells and neural cells.[16, 17]

Among adult stem cells, epithelial stem cells have achieved success in tissue engineering applications. In normal skin, epithelial stem cells are located in the basal keratinocyte layer, and they ensure the renewal of skin by giving rise to daughter cells that differentiate and migrate

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toward the suprabasal layers. Already, epithelial stem cells are used in the production of synthetic skin grafts for the treatment of burns and some skin diseases. Synthetic skin grafts are made by culturing keratinocytes onto a dermislike substrate, and the success of the graft depends on the ability of epithelial stem cells to replenish the cell supply. Several companies like Advanced Tissues Sciences, Inc. (La Jolla, CA) and Organogenesis, Inc. (Canton, MA) manufacture a commercially available skin substitute (Figure 3).

Outlook for Stem Cells

Stem cells have come a long way, but before they can be incorporated in clinical settings, several obstacles must be overcome. First, it is important to be able to direct the differentiation of pure cell populations in large quantities.[18] The availability of homogeneous cells would make stem cell treatment a feasible option for patients. Second, safety concerns must be met. The ES-derived cells should not cause teratomas or teratocarcinomas when transplanted in vivo, nor should they be immunologically rejected by the patient.[8] Therapeutic cloning seems a viable solution to immunologic incompatibility, but further studies are necessary to verify this. Finally, ES cells must be available for research purposes. Due to the ethical and moral aspects of this topic, hES research is currently still very limited, and the progress in this field is slow.

Although many questions still remain unanswered, it is clear that stem cells have a unique potential to treat many diseases. In both the embryonic and adult stem cell settings, we have tasted the promise for success in various breakthroughs. As research continues, we will gain more insight about the mechanism of stem cell differentiation and learn how to reprogram its course.

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