

Will stem cells transform medicine?

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CME

ETHICS CME, Part 3 of 3

Target audience: All physicians

Learning objectives:

1. Define stem cells.
2. List the sources of stem cells and explain their differences.
3. Articulate the potential role for stem cells in treating various diseases.
4. Describe ethical and moral objections to the use of stem cells.

Faculty credentials/disclosure:

Michael A. E. Ramsay, MD, is president of Baylor Research Institute, an affiliate of Baylor Health Care System. He has no significant financial relationships to disclose. No unapproved/off-label uses of any product are addressed in the article.

Before beginning this activity, please read the instructions for CME on p. 241. This page also provides important information on the method of physician participation, estimated time to complete the educational activity, medium used for instruction, and dates of release and expiration. The quiz, evaluation form, and certification appear on pp. 241–243.

In 1998, human pluripotent stem cells—self-renewing, unspecialized cells that can develop into all of the specialized cells of the body—were first isolated and grown in cell culture. Harold Vargus, director of the National Institutes of Health, told the US Congress, “Stem cell research has the potential to revolutionize the practice of medicine and improve the quality and length of life. There is almost no realm of medicine that might not be touched.” Illnesses and diseases that cannot be treated effectively by conventional medications and therapies are the driving force for scientists to explore the potential of stem cells to regenerate in place of damaged cells. Can this scientific technology really hold the future of medicine? Will there be therapies for Parkinson’s disease, Alzheimer’s disease, spinal cord injuries, insulin-dependent diabetes, or heart failure by using stem cells to grow new organs or tissues? Can these cells be studied to understand the normal development process and where derangements occur? Do we now have a resource to better screen the effects of new drugs and toxins on the human, as opposed to extrapolating data from animal studies?

Stem cells are undifferentiated, early predecessor cells that have, under certain circumstances, the unique ability to self-renew indefinitely. In response to the appropriate signals, they can differentiate into mature, specialized cells. In humans, stem

cells have been identified and can be obtained from the embryo, the fetus, and the adult. They are found in the inner cell mass of early embryos, in some tissues of the fetus, in the umbilical cord and the placenta, and in several adult organs and tissues, including bone marrow, where blood cells can generate for a lifetime. Stem cells vary widely in their ability to generate an assortment of cell types. Some, including most adult stem cells, have limited ability to differentiate into certain specialized tissues. The most limited stem cells are termed *multipotent*, while stem cells capable of developing into more specialized tissue types are termed *pluripotent*. Cells having the capacity to develop into organs or organisms are *totipotent*. Some organs, such as skin and liver, can regenerate themselves during the life of an organism, yet other tissues, such as brain or heart, seem to be incapable of self-repair. The challenge is to understand why some stem cells can develop into virtually any tissues while the potential of others is very limited.

For transplanted donor stem cells to be effective in repairing damaged and diseased organs, immune-mediated rejection of the cells must be controlled. Current stem cell transplantation, such as from bone marrow and blood, requires a close cross-match between donor and recipient, along with the use of immunosuppressive agents. This demand carries the risk of significant side effects; therefore, techniques to overcome tissue rejection are being sought. This search includes the ethically controversial technology of somatic cell nuclear transfer, or cloning, in which a cell nucleus is transferred from a somatic cell into an egg from which the nucleus has been removed. Somatic cell nuclear transfer can produce a line of stem cells that is genetically identical to the recipient’s cells and thus avoid the complication of immune-mediated rejection.

Adult stem cells are undifferentiated cells found in minute quantities in differentiated tissue such as bone marrow, brain, adipose tissue, skin, liver, skeletal muscle, dental pulp, gastrointestinal tract lining, and pancreas. Adult stem cells are not only scarce but are difficult to maintain in tissue culture and rapidly mature into their differentiated states. The success of bone marrow transplantation in increasing the survival of patients with leukemia and other diseases has stimulated research into the potential role of the hematopoietic stem cells. Growing evidence

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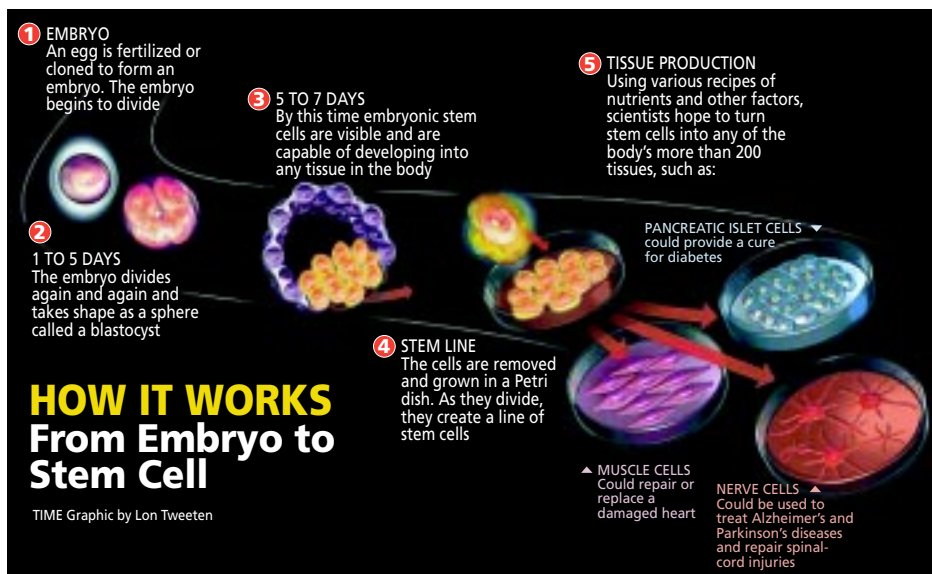


Figure. How stem cells are produced from embryos. Copyright 2001, Time Inc. Reprinted by permission.

exists that these particular cells are pluripotent and can generate other tissue types such as liver, cardiac and skeletal muscle, and neuron-like cells. Evidence also suggests that stem cells found in umbilical cord blood are more immature and less reactive immunologically. Stem cells from human fat tissue have been reported to form cartilage, bone, and muscle cells, but conclusive evidence is lacking that these were indeed fat stem cells and not other stem cells that had migrated to fat tissue.

The seemingly unlimited potential of embryonic stem cells has created enormous scientific interest. Embryonic stem cells are found in the inner cell mass of the human blastocyst that exists from the fourth to the seventh day after fertilization. The ethical debate around the use of these cells centers on the fact that the blastocyst is destroyed by the removal of the stem cells. Moral and religious arguments revolve around whether the blastocyst is human life and should be protected or whether it can be considered the earliest of "organ donors." Pluripotent embryonic stem cells have been shown to self-renew continuously over >2 years. The technique of growing human embryonic stem cells in an undifferentiated state is complicated and requires the use of mouse embryonic fibroblasts in a medium containing bovine serum. This situation presents certain theoretical hazards, such as the spread of viruses or infective material from the animal cells.

The resulting culture of human stem cells contains cell types representing all 3 layers of embryonic tissue (Figure). The types include rhythmically contracting cardiomyocytes, epithelial cells, neural cells displaying axons and dendrites, cells with liver and pancreatic function, and cells with hematopoietic precursor structure. Tumors found in humans may arise from these cell types; teratomas may contain tissues from all 3 embryonic layers. The role of genetic and biochemical controls is being studied to determine the stimuli required for the stem cells to differentiate into particular specialized cells.

The potential for embryonic stem cells to provide an unlimited source of cells, differentiated in vitro, for transplantation therapies involving the liver, the pancreatic islet cells, and the nervous system is real. Animal studies have been able to partially restore insulin function in diabetic mice, relieve Parkinson's dis-

ease symptoms, and restore neural function in rodents with transected spinal cords.

Enormous challenges remain in translating this animal research into treatment modalities for humans. Techniques must be developed to establish whether stem cells will function properly after transplantation and will be incorporated into existing tissues. Some cells, such as pancreatic islet cells or hematopoietic cells, will require less complex incorporation and, therefore, may provide early vehicles of success. However, substantial gaps in the knowledge of stem cell science still remain, such that widespread clinical application is years, even decades, away.

Those who seek to develop stem cell technology into clinical medicine must respect the social, ethical, political, legal,

and economic issues that face a democratic society. A very clear responsibility of the scientific community is to articulate the potential role for stem cells in treating the previously untreatable.

Obstacles to the development of embryonic stem cell science are based on legal, religious, moral, and ethical grounds. Stem cell research touches on the most fundamental issues, such as the definition of human life and the moral and legal status of the human embryo. Religious organizations have to wrestle with the definition of when human life begins. Is it at the earliest opportunity for cell growth, or does it require embryonic implantation in the uterus? Should new cell lines be derived from "excess" embryos that are produced by in vitro fertilization techniques and otherwise would be destroyed after one embryo has been successfully implanted? Could these early embryos be considered organ donors? There is also the potential for creating embryos with the somatic cell nuclear transfer technique that does not even involve fertilization of an egg by a sperm. These are some of the significant ethical dilemmas that must be dealt with, not only by science but also by society.

Federal funding for research has been limited to supporting the use of the approximately 60 existing cell lines and will not support the development of new lines. This limitation in the number of available cell lines raises concerns. Existing lines might become contaminated by environmental and mutation factors that would limit their usefulness. The majority of these lines are held by 2 organizations: the University of Wisconsin and the University of Gothenburg. Another concern is that cell line cultures may be prone to develop chromosomal mutations as they age. Two significant risks associated with embryonic stem cell transplantation are tumor formation and immune rejection. In a small number of studies, when the stem cells have been allowed to differentiate before transplantation, tumor formation has not occurred. It may be possible to add "growth factors" to transplanted stem cells to stimulate the production of a particular cell type. An exact genetic match between a recipient and stem cell could theoretically be induced by using somatic cell nuclear transfer to create histocompatible stem cells.

Private funding, however, has supported biotechnology companies that can produce stem cells at will. Such companies have created embryos specifically for research using eggs and sperm donated by volunteers who are unrelated and have no reproductive intent.

Scientific research involving the cells of a human embryo represents a serious challenge to the moral and ethical fiber of society. The potential benefits of this technology in treating diabetes, organ failure, and brain and spinal cord damage must be weighed against the moral objections to the various techniques of obtaining stem cells.

As a society, we are obligated to balance what we are *capable* of doing against what we *should* be doing. These decisions are critical, since they shape the future of medicine and health care for our communities. The future of medicine is now, and the tough decisions must be made today. Actor Christopher Reeve, who was paralyzed from the neck down after being thrown from a horse, is a prominent supporter of the Spinal Cord Injury Unit at the Washington University School of Medicine in St. Louis. After witnessing the recovery of similarly injured rats after the injection of stem cells, Reeve commented, "Never before has there been such a powerful tool, such a resource that can give so much hope. And to have it just sitting here right in front of us, ready to go while all this debate rages on, is really frustrating."

The responsibility placed on all of us—scientists, citizens, and political and religious leaders—is great.

Suggested reading

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