



STEM CELLS

An introduction to aging science brought to you by the
American Federation for Aging Research

WHAT ARE STEM CELLS?

Stem cells are cells that, in cell cultures at least, have the ability to divide forever. They also have the capacity to develop into specialized populations of cells. There are stem cells in developing embryos, and in recent years, scientists have confirmed the existence of stem cells in adult humans. Recent data suggest that stem cells are not only active in embryos, but act throughout our lives, replacing worn and damaged mature cells.

Before the first stem cells were actually identified, they were merely assumed to exist. As evidence for their existence, researchers cited bone marrow transplants. In the treatment of certain cancers, chemotherapy destroyed all of the cells of the bone marrow. That treatment was followed by transplants of bone marrow from healthy donors.

The small volume of transplanted bone marrow eventually gave rise to enough cells to repopulate the body with red blood cells, white blood cells and platelets.

The source of all of those cells was presumed to be stem cells, and that presumption has proved correct.

Stem cells are best understood in terms of how committed they are to becoming any particular type of cell. The categories into which they fall include:

- Totipotent stem cells

- Pluripotent stem cells
- Multipotent stem cells
- Adult stem cells

Totipotent stem cells

Human cells can be divided into sex or germ cells (eggs and sperm) and somatic cells (all of the rest). When a sperm cell and an egg cell unite, they form a one-celled fertilized egg. This cell is totipotent, which means that it has the potential to give rise to any and all human cells, such as brain, liver, blood, or heart cells, as well as extra-embryonic tissue, such as the placenta, necessary for embryonic development. The first few cell divisions in embryonic development produce more totipotent cells. After four days of embryonic cell division, the cells begin to specialize.

Pluripotent stem cells

On the fourth day of embryonic development, the ball of cells forms itself into an outer layer, which will become the placenta, and an inner mass, which will form the tissues of the developing human body.

These inner cells, though they can form nearly any human tissue, cannot do so without the outer layer, and so are not totipotent, but pluripotent. As these pluripotent stem cells continue to divide, they begin to specialize further.

Multipotent stem cells

The offspring of the pluripotent cells become the progenitors of such cell lines as blood cells,

skin cells, and nerve cells. At this stage, they are multipotent, in that they can become one of several types of cells within a given organ (e.g., multipotent blood stem cells can develop into red blood cells, white blood cells or platelets).

Adult stem cells

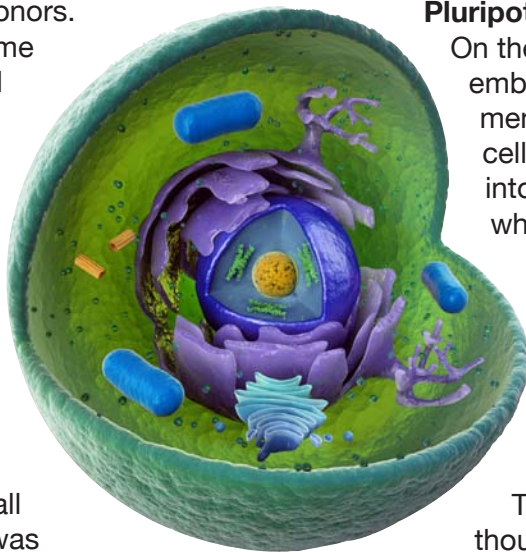
In recent years, scientists have identified multipotent stem cells in adult humans, which are used to replace cells that have died or lost function. Stem cells have been identified in adults for tissues including blood, brain, GI tract, and muscle. Researchers speculate that stem cells exist for many organs, although some have not yet been identified.

Recent research suggests that adult stem cells can be transformed into embryonic stem-cell-like cells that have the capacity to generate almost any cell type the body might need.

THE IMPORTANCE OF STEM CELLS

Studying stem cells and their functions is important not only to give us a greater understanding of early human development, including the development of birth defects, but also for our comprehension of medical diseases, such as cancer, that have their origins in abnormalities of cell division and cell differentiation.

The most exciting potential use for stem cells is “cell therapy,” treatment of disease by replacing damaged or dead tissue with stem cells. Currently, we employ transplantation of organs and tissues to replace those that are damaged, but the supply of donor organs is limited. Some of the diseases that scientists speculate might be treated with cell therapy include neurological diseases like Par-





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kinson's, Alzheimer's, stroke and spinal cord injury; both rheumatoid and osteoarthritis; and heart disease and diabetes. If successful, this regenerative approach would reduce the need for organ and tissue transplants.

STEM CELLS AND AGING

Most of the cells in our bodies are mature functional cells. Their primary role is not to divide but rather to perform the functions necessary for our survival (sensory cells sense stimuli, immune cells fight disease, etc.).

The job of generating new cells falls primarily to stem cells. Along the course of aging, however, our stem cells decline somewhat in their ability to divide and produce mature new functional cells. This decline may result from stem cell "burn out" — a result of having divided multiple times over the course of many years. Other possible contributors to this decline include accumulation of DNA damage in stem cells or a reduction in signals from other cells in the body telling them to divide. Thus, under normal conditions our organs

have a finite life span. Scientists speculate, however, that certain manipulations of adult stem cells can reset them to a more youthful state. This "fountain of youth," if harnessed, could allow us to rejuvenate our tissues, increasing the number of healthy years in our lives.

How are stem cells related to the diseases of aging?

A major consequence of aging is the aging of our tissues and the inability of our bodies to replace those aging tissues. Some of the diseases of aging to

which researchers hope to apply stem cell technology include neurological disorders, including Parkinson's and Alzheimer's disease, spinal cord damage and strokes; heart disease; diabetes; burns; and arthritis, both rheumatoid and osteoarthritis. Cultures of sufficient numbers of multipotent stem cells could conceivably be used in place of whole organs in transplantation.

HOW DO WE OBTAIN STEM CELLS?

Stem cells with the ability to regenerate the tissue of one specific organ (i.e. multipotent stem cells) can be obtained from other adult human organs. The only organ for which this procedure is regularly performed is blood: hematopoietic (blood, bone marrow, immune)

stem cells, which can be transplanted from one adult to another in order to repopulate the blood system of the recipient.

Hematopoietic stem cells are unique in that they are easily removable from live humans for transplantation. It is conceivable, however, that this procedure could be optimized for the transplantation of other multipotent adult stem cell types.

Stem cells with the ability to produce all possible adult tissues can be obtained from two major sources:

(1) the pluripotent stem cells of human embryos and (2) cells harvested from living adult humans and reprogrammed into an embryonic state.

The first possible source of pluripotent stem cells—embryonic stem cells—is isolated from either fertilized embryos created for *in vitro* use, but then not needed, or from terminated pregnancies. The researchers who have studied stem cells from both sources are only allowed to do so, according to federal guidelines, with the express and informed consent of the couples involved.

The second possible source of pluripotent stem cells—reprogrammed adult cells—was first generated through a process called somatic cell nuclear transfer. In this process, scientists remove the nucleus (the part of the cell that contains its DNA in the form of genes and chromosomes) from an unfertilized human egg cell. They then manipulate a

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human somatic (body) cell so that its nucleus is incorporated into the egg. This combination cell appears to have the potential to develop into a human. In the past two years, alternative methods have been emerging for reprogramming adult cells into a pluripotent state without the need to transplant them into an egg. While this research is in early stages, it raises the exciting possibility that we could eventually take a almost any cell from any adult and transform it into a “rejuvenated” cell with the capacity to regenerate new healthy cells.

Stem cells have already been used to treat cancer, allowing patients to survive after chemotherapy or radiation has destroyed their native hematopoietic system (bone marrow/blood/immune system). Transplants of donated bone marrow or umbilical cord blood (both are now often referred to as stem cell transplants) are given to provide the patient with stem cells that repopulate his or her bone marrow, blood, and immune system.

Among the cancers for which patient recovery has been aided by hematopoietic stem cell transplants are:

- Leukemia
- Hodgkin’s lymphoma

- Non-Hodgkin’s lymphoma
- Multiple myeloma
- Aplastic anemia
- Breast cancer
- Ovarian cancer
- Testicular cancer
- Sarcoma
- Neuroblastoma
- Brain tumors

THE FUTURE OF STEM CELL RESEARCH

Some ethical issues surrounding stem cell research remain controversial, and continued and open debate about the use of stem cells is critical. If these issues can be resolved, the future of science in this area shows tremendous promise. Among the areas being explored is the question of how to produce large numbers of stem cells in the laboratory. Stem cells that are “harvested” exist in small numbers; they then need to be cultured in the laboratory setting so that large volumes of them can be produced.

Scientists will be trying to identify the particular molecular signals that affect stem cells. Molecular

signals are chemicals in whose presence cells act in a certain fashion. Molecular signals released by surrounding tissues either tell stem cells to remain stem cells or they tell stem cells to differentiate into their specialized successors. Once we know what the various molecular signals are, we can manipulate stem cells, either by maintaining them as stem cells or by encouraging them to differentiate, depending on how we plan to use them.

A third area of future research concerns the delivery of stem cells to the tissues in which they are needed. Current practice involves either the injection of stem cells directly into the targeted tissue, or injection of the stem cells into the bloodstream without any guarantee that they will actually find their way to the appropriate tissues. “Targeted delivery” would ensure that the therapeutic stem cells are introduced to the organs and tissues that need them, where they need them.

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