ISSN 0017 - 8861

Estd 1923

Health

A JOURNAL DEVOTED TO HEALTHFUL LIVING

Email: admin@theantiseptic.in
subscription@theantiseptic.in

www.healthjournal.in

Vol. 104 No. 09 SEPTEMBER 2026 Rs. 20

COWDEN SYNDROME
(MULTIPLE HAMARTOMA SYNDROME)

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ROLE OF STEM CELLS

Stem cells are one of the human body's master cells with the ability to grow into any one of the body's more than 200 cell types.

Stem cells differ from other kinds of cells in the body. All stem cells□regardless of their source□ have three general properties:

- They are capable of dividing and renewing themselves for long periods;
- They are unspecialized (undifferentiated); and
- They can give rise to specialized cell types (differentiation).

When a stem cell divides, each new cell has the potential either to remain a stem cell or become another type of cell with a more specialized function, such as a muscle cell, a red blood cell, or a brain cell.

Different types of stem cells:[1]

Totipotent stem cells can differentiate into embryonic and extraembryonic cell types. Such cells can construct a complete, viable, organism. These cells are produced from the fusion of an egg and sperm cell. Cells produced by the first few divisions of the fertilized egg are also totipotent.

□ **Pluripotent** stem cells are the descendants of totipotent cells and can differentiate into nearly all cells,i.e. cells derived from any of the three germ layers.

□ **Multipotent** stem cells can differentiate into a number of cells, but only those of a closely related family of cells.

□ **Oligopotent** stem cells can differentiate into only a few cells, such as lymphoid or myeloid stem cells.

□ **Unipotent** cells can produce only one cell type, their own, but have the property of self-renewal which distinguishes them from non-stem cells (e.g. muscle stem cells).

Until recently, scientists primarily worked with two kinds of stem cells from animals and humans: **embryonic stem cells** and non-embryonic **"somatic"** or **"adult" stem cells.**

Embryonic stem cells:

Scientists discovered ways to derive embryonic stem cells from early mouse embryos nearly 30 years ago. The detailed study of the biology of mouse stem cells led to the discovery, in 1998, of a method to derive stem cells from human embryos and grow the cells in the laboratory. These cells are called **human embryonic stem cells.** In 2006, researchers made another breakthrough by identifying conditions that would allow some specialized adult cells to be "reprogrammed" genetically to assume a stem cell-like state. This new type of stem cell is called induced pluripotent stem cells (iPSCs).

Embryonic stem cell lines are cultures of cells derived from the epiblast tissue of the inner cell mass (ICM) of a blastocyst or earlier morula stage embryos. A blastocyst is an early stage embryo approximately four to five days old in humans and consisting of 50 150 cells. ES cells are pluripotent and give rise during development to all derivatives of the three primary germ layers: ectoderm, endoderm and mesoderm. In other words, they can develop into each of the more than 200 cell types of the adult body when given sufficient and necessary stimulation for a specific cell type.

Adult stem cells (somatic stem cell):

An adult stem cell is thought to be an undifferentiated cell that can renew itself and can differentiate to yield some or all of the major specialized cell types of the tissue or organ. The primary roles of adult stem cells in a living organism are to maintain and repair the tissue in which they are found.

The history of research on adult stem cells began about 50 years ago. In the 1950s, researchers discovered that the bone marrow contains at least two kinds of stem cells. One population, called **hematopoietic stem cells**, forms all the types of blood cells in the body. A second population, called **bone marrow stromal stem cells** (also called **mesenchymal stem cells,** or skeletal stem cells) which can generate bone, cartilage, fat, cells that support the formation of blood, and fibrous connective tissue.

In the 1960s, scientists who were studying rats discovered two regions of the brain that contained dividing cells that ultimately become nerve cells. Despite these reports, most scientists believed that the adult brain could not generate new nerve cells. It was not until the 1990s that scientists agreed that the adult brain does contain stem cells that are able to generate the brain's cell types.

In a recent study, U.S. researchers have reprogrammed cells found in circulating blood into cells that are molecularly and functionally indistinguishable from embryonic stem cells, a revolutionary achievement that provides a readily accessible source of stem cells and an alternative to harvesting embryonic stem cells. Making pluripotent stem cells from blood, which is one of the easiest tissues to obtain, provides an easy strategy for generating patient-specific stem cells that are valuable research tools and may one day be used to treat a number of diseases.[2]

Location of adult stem cells:

Adult stem cells have been identified in many organs and tissues, including brain, bone marrow, peripheral blood, blood vessels, skeletal muscle, skin, teeth, heart, gut, liver, ovarian epithelium, and testis. Stem cells may remain quiescent (non-dividing) for long periods of time until they are activated by a normal need for more cells to maintain tissues, or by disease or tissue injury.

Differentiation pathways of adult stem cells:

Hematopoietic stem cells give rise to all the types of blood cells: red blood cells, B lymphocytes, T lymphocytes, natural killer cells, neutrophils, basophils, eosinophils, monocytes, and macrophages.

Mesenchymal stem cells give rise to a variety of cell types: bone cells (osteocytes), cartilage cells (chondrocytes), fat cells (adipocytes), and other kinds of connective tissue cells such as those in tendons.

Neural stem cells in the brain give rise to its three major cell types: nerve cells (neurons) and two categories of non-neuronal cells astrocytes and oligodendrocytes.

Epithelial stem cells in the lining of the digestive tract occur in deep crypts and give rise to several cell types: absorptive cells, goblet cells, paneth cells, and enteroendocrine cells.

Skin stem cells occur in the basal layer of the epidermis and at the base of hair follicles. The epidermal stem cells give rise to keratinocytes, which migrate to the surface of the skin and form a protective layer. The follicular stem cells can give rise to both the hair follicle and to the epidermis.

Trans differentiation:

A number of experiments have reported that certain adult stem cell types can differentiate into cell types seen in organs or tissues other than those expected from the cells' predicted lineage (i.e., brain stem cells that differentiate into blood cells or blood-forming cells that differentiate into cardiac muscle cells, and so forth; regeneration of pancreatic beta cells by reprogramming other pancreatic cells). This strategy may offer a way to reprogram available cells into other cell types that have been lost or damaged due to disease.

Embryonic vs. adult stem cells:

Adult stem cells, and tissues derived from them, are currently believed less likely to initiate rejection after transplantation. This is because a patient's own cells could be expanded in culture, coaxed into assuming a specific cell type (differentiation), and then reintroduced into the patient. This represents a significant advantage.

The potential uses of human stem cells:

There are many ways in which human stem cells can be used in research and the clinic. Studies of human embryonic stem cells will yield information about the complex events that occur during human development. Some of the most serious medical conditions, such as cancer and birth defects, are due to abnormal cell division and differentiation. A more complete understanding of the genetic and molecular controls of these processes may yield information about how such diseases arise and suggest new strategies for therapy.

Human stem cells could also be used to test new drugs. Cancer cell lines, for example, are used to screen potential anti-tumor drugs.

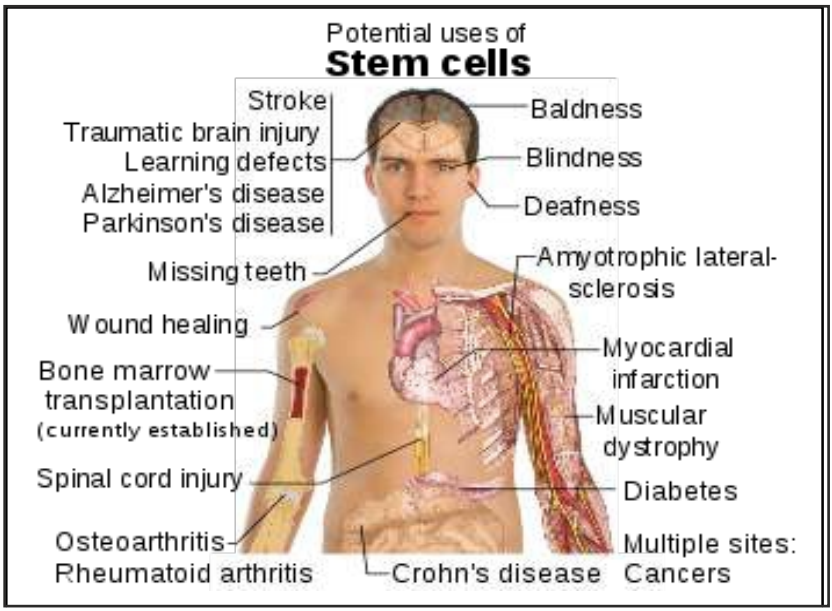
Perhaps the most important potential application of human stem cells is the generation of cells and tissues that could be used for **cell-based therapies.** Stem cells, directed to differentiate into specific cell types, offer the possibility of a renewable source of replacement cells and tissues to treat diseases including Alzheimer's diseases, spinal cord injury, stroke, burns, heart disease, diabetes, osteoarthritis, and rheumatoid arthritis.

The use of adult stem cells in research and therapy is not as controversial as embryonic stem cells, because the production of adult stem cells does not require the destruction of an embryo. Additionally, because in some instances adult stem cells can be obtained from the intended recipient, (an autograft) the risk of rejection is essentially non-existent in these situations. Consequently, more US government funding is being provided for adult stem cell research.

Adult stem cell treatments have been successfully used for many years to treat leukemia and related bone/blood cancers through bone marrow transplants.

Key research events

- **1908** - The term "stem cell" was proposed for scientific use by the Russian histologist Alexander Maksimov. It postulated existence of haematopoietic stem cells.
- **1960s** - Joseph Altman and



Gopal Das present scientific evidence of adult neurogenesis, ongoing stem cell activity in the brain; their reports

- **1963** - McCulloch and Till illustrate the presence of self-renewing cells in mouse bone marrow.
- **1968** - Bone marrow transplant between two siblings successfully treats.
- **1978** - Haematopoietic stem cells are discovered in human cord blood.
- **1981** - Mouse embryonic stem cells are derived from the inner cell mass. Gail Martin is attributed for coining the term "Embryonic Stem Cell".
- **1992** - Neural stem cells are cultured in vitro as neurospheres.
- **1997** - Leukemia is shown to originate from a haematopoietic stem cell, the first direct evidence for cancer stem cells.
- **1998** - James Thomson and coworkers derive the first human embryonic stem cell line.
- **2001** - Scientists at Advanced Cell Technology clone first early (four- to six-cell stage) human embryos for the purpose of generating embryonic stem cells.
- **2003** - Dr. Songtao Shi of NIH discovers new source of adult stem cells in children's primary teeth.
- **October 2006** - Scientists at Newcastle University in England create the first ever artificial liver cells using umbilical cord blood stem cells.
- **January 2007** - Scientists at Wake Forest University report discovery of a new type of stem cell in amniotic fluid. This may potentially provide an alternative to embryonic stem cells for use in research and therapy.
- **June 2007** - Research reported that normal skin cells can be reprogrammed to an embryonic state in mice. In the same month, scientist Shoukhrat Mitalipov reports the first successful creation of a primate stem cell line through somatic cell nuclear transfer.
- **October 2007** - Mario Capecchi, Martin Evans, and Oliver Smithies win the 2007 Nobel Prize for Physiology or Medicine for their work on embryonic stem cells from mice using gene targeting strategies producing genetically engineered mice (known as knockout mice) for gene research.
- **November 2007** - Induction of pluripotent stem cells from adult human fibroblasts by defined factors" and Induced pluripotent stem cell lines derived from human somatic cells.
- **January 2008** - The first human embryonic stem cells without destruction of the embryo.
- **January 2008** - Development of human cloned blastocysts following somatic cell nuclear transfer with adult fibroblasts.
- **February 2008** - Generation of Pluripotent Stem Cells

from Adult Mouse Liver and Stomach: these iPS cells seem to be more similar to embryonic stem cells than the previous developed iPS cells and not tumorigenic, moreover genes that are required for iPS cells do not need to be inserted into specific sites, which encourages the development of non-viral reprogramming techniques.

- **March 2008** - The first published study of successful cartilage regeneration in the human knee using autologous adult mesenchymal stem cells is published by Clinicians from Regenerative Sciences.
- **30 October 2008 -** Embryonic-like stem cells from a single human hair.
- **1 March 2009** - Andras Nagy, Keisuke Kaji, et al. discover a way to produce embryonic-like stem cells from normal adult cells by using a novel "wrapping" procedure to deliver specific genes to adult cells to reprogram them into stem cells without the risks of using a virus to make the change.
- **9 March 2009** US President Obama lifted federal funding limits on human embryonic instituted by former President Bush.

Stem cells in hematology:

Hematopoietic stem cells (HSCs) are multipotent stem cells that give rise to all the blood cell types including myeloid (monocytes and macrophages, neutrophils, basophils, eosinophils, erythrocytes, megakaryocytes/platelets, dendritic cells), and lymphoid lineages (T-cells, B-cells, NK-cells).

Hematopoietic Stem Cell Transplantation (HSCT):3

HSCT involves the intravenous infusion of autologous (from the patient) or allogeneic (from another person) stem cells collected from bone marrow, peripheral blood, or umbilical cord blood to reestablish hematopoietic function in patients with damaged or defective bone marrow or immune systems.

Although some investigators have traced the origin of HSCT to the end of the 19th century, when patients were given bone marrow orally as a treatment for hematologic disorders, a more realistic starting point is a 1939 report of a patient who received 18 mL of intravenous marrow from his brother as a treatment for aplastic anemia.

Significant advances in transplantation science did not occur until the 1950s. At that time, 2 major preclinical developments advanced the field. The first was the observation that mice could be protected from the lethal effects of whole-body irradiation by exteriorizing and shielding the spleen or by using intravenous marrow infusion. The second was the identification and unraveling of transplantation antigens (ie, the human leukocyte antigen [HLA] system in humans).

Further clinical advances, such as the understanding and development of chemotherapeutic

agents, progress in blood banking and transfusion sciences, and the availability of new potent antibiotic agents, led to the first successful transplantations in the late 1960s. Few fields in medicine better illustrate the effective use of translational science into the clinical arena, a fact that culminated in the awarding of the Nobel Prize in medicine to Joseph E. Murray and E. Donnall Thomas for their discoveries concerning organ and cell transplantation in the treatment of human diseases.

HSCT was undoubtedly one of the most important medical advances in the second half of the 20th century. Worldwide, approximately 30,000-40,000 transplantations are performed yearly, and the number continues to increase by 10-20% each year. More than 20,000 people have now survived 5 years or longer after HSCT.

Diseases treated by HSCT

HSCT has led to the cure of diverse forms of cancer, bone marrow failure, hereditary metabolic disorders, and severe congenital immunodeficiencies that would otherwise have been fatal.

Hematopoietic stem-cell transplantation is used to treat the following conditions:

Autologous transplantation

- Multiple myeloma
- Non-Hodgkin lymphoma
- Hodgkin disease
- Acute myeloid leukemia
- Neuroblastoma
- Germ cell tumors
- Autoimmune disorders Systemic lupus erythematosus (SLE), systemic sclerosis
- Amyloidosis

Allogeneic transplantation

- Acute and chronic myeloid and lymphoblastic leukemia
- Myeloproliferative disorders
- Myelodysplastic syndromes
- Multiple myeloma
- Non-Hodgkin lymphoma
- Hodgkin disease
- Aplastic anemia
- Pure red cell aplasia
- Paroxysmal nocturnal hemoglobinuria
- Fanconi anemia
- Thalassemia major
- Sickle cell anemia
- Severe combined immunodeficiency (SCID)
- Wiskott-Aldrich syndrome
- Hemophagocytic lymphohistiocytosis (HLH)
- Inborn errors of metabolism (eg, mucopolysaccharidosis,

Gaucher disease, metachromatic leukodystrophies and adrenoleukodystrophies)

The summary of in some specific disorders is as follows:

Acute myeloid leukemia: Allogeneic HSCT is the treatment of choice for all children with acute myeloid leukemia (AML)

with HLA-matched sibling in their first complete remission (CR1), and in adults this is reserved for those with high-risk features in their CR1. In adults with standard or good risk features, SCT is reserved for their second complete remission (CR2). HSCT is the only curative option for patients with primary refractory or relapsed AML.

Acute lymphoid leukemia: SCT indications in adults with acute lymphoid leukemia are similar to those for persons with AML.

Chronic myeloid leukemia: Ever since imatinib was introduced for the treatment of chronic myeloid leukemia (CML), the practice of recommending transplantation to eligible patients with CML has been changed. Currently, all newly diagnosed chronic phase CML patients younger than 20 years with HLA-identical donor or MUD and those younger than 40 years with HLA-identical sibling donor should be considered for HSCT. HSCT should also be considered for those with high-risk features and imatinib failure.

Myelodysplastic syndrome: Allogeneic HSCT should be considered for patients with myelodysplastic syndrome who are younger than 60 years and who have an HLA-matched sibling donor.

Chronic lymphocytic leukemia: Autologous and allogeneic HSCT have been used with success in young patients with chronic lymphocytic leukemia.

Non-Hodgkin lymphoma: A combination of high-dose chemotherapy and autologous or allogeneic HSCT has produced complete remissions in patients with relapsed disease and in those who do not achieve complete remission with primary therapy.

Hodgkin lymphoma: High-dose chemotherapy and autologous HSCT are the treatments of choice for patients with poor prognoses and early relapse after initial chemotherapy or induction failure (ie, resistant disease), second relapse after conventional treatment for first relapse, or generalized systemic relapse after initial chemotherapy.

Multiple myeloma: Although autologous HSCT does not produce a cure, event-free survival rates and overall survival rates are prolonged approximately 1 year compared with survival rates achieved by chemotherapy. Autologous HSCT is associated with a much lower mortality rate than allogeneic HSCT. Trials from France have shown the advantage of double autologous HSCT (tandem transplants) over single transplantation.

Testicular cancer: The achievement of disease-free survival in a minority of patients with severe disease suggests much better results if performed earlier.

Thalassemia: An 80% disease-free survival rate is achieved after allogeneic HSCT.

Sickle cell anemia: Sickle cell anemia is potentially curable with allogeneic HSCT.

Genetic disorders: Many genetic immunologic or hematopoietic disorders are potentially curable with allogeneic HSCT.

HSCT in patients with AIDS has not been shown to be very encouraging. However, transfecting the hematopoietic stem cells with retroviral vectors that cleave the RNA of the HIV virus is in the experimental stage.

To summarize, stem cells offer exciting promise for future therapies, but significant technical hurdles remain that will only be overcome through years of intensive research.

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