Stem Cells

Prepared By

DR. Mohamed Kamal

Lecturer of Molecular Cancer Biology

Faculty of Science

University of Benha

Egypt.

Definition

Stem cells are self-renewing, pluripotent cells.

Historical view

Stem cells exist only in embryos, highly proliferative tissues such as the bone marrow.

In tissues with a high cellular turnover rate (skin and gastrointestinal mucosa), stem cells were thought to be limited in their ability to generate cells of different lineages with various differentiated phenotypes.

Stem cells were thought to be absent from brain and the heart

The Cell Biology Revolution

Self-renewing, multipotent, and perhaps pluripotent stem cells exist in every organ in the body

Characteristics of Stem Cells

A ‘‘true’’ stem cell must satisfy the following criteria:

(1) It must have unlimited self-renewal capacity (Telomerase Activity exercise).

(2) It must be able to divide into two types of daughter cells—one that replicates self-renewing phenotype and one that attains the phenotype of a subsequent differentiated state.

Origin and types of Stem Cells

Inner cell mass of an embryonic blastocyst **(Embryonic stem cells (ES))**

All mammalian tissues also contain stem cells

(Adult stem cells)

Adult stem cells can even differentiate into cell types of another tissue.

ES cells can be grown in cell culture and are capable of producing multiple cell types including vascular, neuronal, pancreatic, and cardiac muscle cells

Origin and types of Stem Cells

Table 4–3. Potential Plasticity of Stem Cells

Location of Stem Cell	Type of Cells Generated
Brain	Neurons, oligodendrites, skeletal muscle, blood cells
Bone marrow	Endothelial cells, blood cells, cartilage, bone, adipocytes, cardiac muscle, skeletal muscle, neuronal cells, skin, oval cells, gastrointestinal tract cells, thymus, pulmonary epithelial cells
Skeletal muscle	Skeletal muscle, bone, cartilage, fat, smooth muscle
Myocardium	Myocytes, endothelial cells
Skin	Keratinocytes
Liver	Liver cells
Testis and ovaries	Gonads
Pancreatid ducts	Islet cells
Fatty tissue	Fat, muscle, cartilage, bone

Stem Cell Therapy

Tissue regeneration

Parkinson's disease, diabetes, myocardial infarction, congestive heart failure, chronic limb ischemia, liver cirrhosis, and chronic lung Disease

Bone marrow mesenchymal stem cells may be an ideal source for therapy of human inherited or degenerative diseases

Bone marrow–derived cells of stromal origin have been shown to initiate pancreatic regeneration and to produce neurons

mesenchymal stem cells derived from the bone marrow of mice could differentiate into cells with visceral mesoderm,

neuroectoderm, and endoderm characteristics in vitro.

When single cells from this source were injected into early blastocysts, they contributed to most somatic cell types in the developed animal.

Stem Cell Therapy

Required factors for stem cell differentiation

Co-culturing of mouse multipotent adult progenitor cells, derived from the bone marrow, with astrocytes facilitated neuronal differentiation.

Pitfalls of stem cells therapy

Teratomas.

Stem Cells vs Cancer cells

Stem cells and cancer cells have a number of common characteristics

Are the stem cells present in various tissues the targets
for carcinogenic agents?

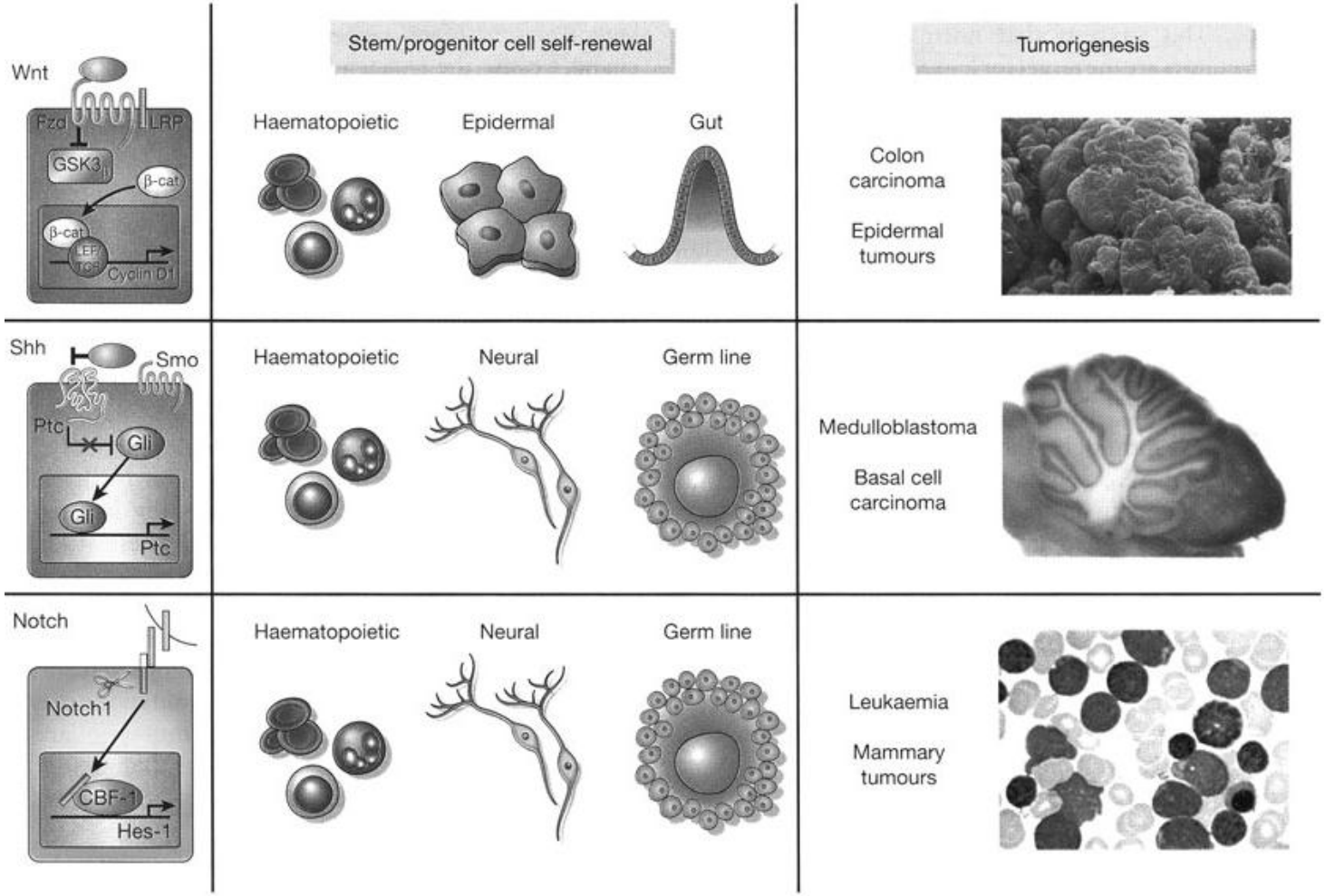
Cell surface receptors profile of expressed genes determined by DNA microarray for murine and human HSCs overlaps with genes expressed in cancer cells.

Also, a ras-like gene, Eras, is expressed in mouse ES cells, which may give these cells tumor-like properties.

Cancer cells acquire the machinery for cell proliferation that is expressed in normal tissue stem cells. However, cancer cells lose the feedback systems to know when to stop proliferating and to start differentiating.

Stem Cells vs Cancer cells

Similar Signal Transduction



Stem Cells vs Cancer cells

Stem cells are the origin of Cancer

1- Stem cells already have the machinery for self-renewal turned on and it would require fewer genetic or epigenetic manipulations for a cell to become a cancer cell than if they had to turn all these genes on de novo.

2- stem cells by their vary nature are set up to proliferate for several population doublings and thus have greater opportunity for carginogenic mutations to accumulate than in most mature cell types.

3- Generation of heterogenous cell types (variable expression of cellular differentiation markers in cancers.

Examples: Variable expression of myeloid markers in chronic myeloid leukemia
Neuronal markers in neuroectodermal tumors
Estrogen receptor in breast cancer

4- Anchorage Independent Growth (1 in 1000 to 1 in 5000 cells were able to form colonies in soft agar).

Isolation of Cancer Stem cells

1) Colony Forming Assays

2) In vivo colony forming masses

3) Gene expression DNA microarrays

4) Identification of specific markers for specific stem cells

5) Isolation of stem cells based on their specific marker expression using FACS.

6) Characterization of the isolated stem cells for confirmation

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Role of Cancer Stem Cells in the management of cancer

Biomarkers Discovery

Stem cells may be the cell population for which biochemical markers need to be developed and implemented clinically to discern which breast neoplasms to treat aggressively and which may be more indolent and less dangerous. This would be a big help, for example, in discriminating which breast ductal carcinomas in situ (DCIS tumors) should undergo more extensive surgery and chemotherapy or hormonal therapy and which may be managed less aggressively. Similarly, such markers could be used to determine which prostate cancers should be excised, irradiated, or left for ‘‘watchful waiting.’’

Role of Cancer Stem Cells in the management of cancer

Drug Targets

In addition, it is the cancer stem cell population for which therapies should be targeted and developed. Currently available chemotherapeutic drugs were developed largely on the basis of their ability to shrink a tumor mass in an experimental model and in a human clinical trial. Since most cells in a cancerous tissue have limited proliferative potential, the ability of a drug to decrease a tumor mass largely reflects the ability of the drug to kill this less aggressive, potentially less dangerous type of cell, leaving behind the more proliferative clones. Thus, drugs more specifically targeted to the cancer stem cell population should result in more effective

and durable responses.

Questions