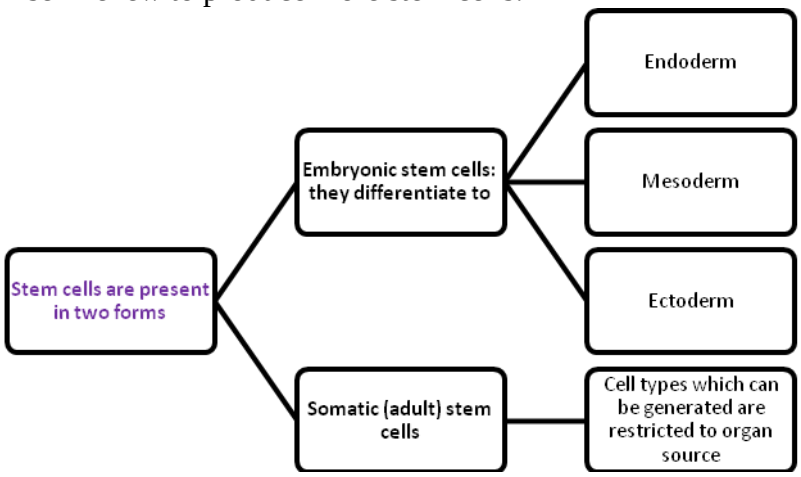
Unit IX – Problem 3 – Genetics: Regenerative Medicine

- **Regenerative medicine**: it focuses on new approaches for replacement of cells, tissues and organs which are affected with disease.
- **Stem cells**: they are undifferentiated cells which have the ability to:
  - Differentiate into specialized cells.
  - Can self-renew to produce more stem cells.



- **Categories of stem cells based on their ability to differentiate:**

Stem cell type	Description	Example
Totipotent	Each cell can develop into a complete organism	Cells from early embryo (1-3 days)
Pluripotent	Cells can form any cell type (over 200!)	Cells from blastocyst (5-14 days)
Multipotent	Cells can form a number of other tissues	Umbilical cord blood and adult tissue
Oligopotent	Can differentiate into few types of cells	Lymphoid and myeloid stem cells
Unipotent	Can only differentiate into a single type of cell	Skin cells

- **Embryonic stem cells:**
  - They are derived from inner cell mass of blastocyst (an early stage embryo which is capable of differentiating into all the cell types of the human body-pluripotent).
  - **Stages of embryogenesis:**
    - ✓ Fertilization → zygote → equal divisions (creating totipotent cell mass which will differentiate at the 4^{th} day to blastocyst).
    - ✓ An outer layer known as trophoblast will develop and become the placenta.
    - ✓ An inner cell mass (pluripotent) will develop and give rise to many types of cells but not all types necessary for fetal development. These pluripotent stem cells can differentiate into:
      - ❖ Endoderm: lung and pancreatic cells.
      - ❖ Mesoderm: cardiac and gut muscle cells.
      - ❖ Ectoderm: neuronal and epidermal cells.
  - **How stem cells determine what tissue to become?**
    - ✓ Chemical & physical signals inside & outside cells → changes in gene activity → ceullular differentiation.
  - **Stimulation of embryonic stem cells to differentiate:**
    - ✓ Embryonic stem cells in culture → differentiate and form embryoid bodies → which can be induced to differentiate into the desired type of cell/ tissue.
    - ✓ Notice that control of this differentiation process can be achieved by adding growth factors, changing chemical composition of the culture medium, adding inhibitory factors… etc.

- **There are two accessible sources of human embryonic stem cells:**
  - ✓ Early embryos created by IVF (أطفال الأنابيب):
    - ❖ *Either those which are not needed for infertility treatment (spare embryos).*
    - ❖ *Or embryos which are created specifically for research.*
  - ✓ Therapeutic cloning:
    - ❖ *What is cloning*? → it is the production of multiple exact copies of a single gene, DNA fragment, cell or organism.
    - ❖ *There are three types of cloning:*
      - ➢ DNA cloning (recombinant DNA technology):
        - The gene of interest is cut using restriction enzymes.
        - It is then joined with plasmid (cloning vector).
        - Plasmids are self-replicating, allowing the new recombinant DNA molecule to produce its gene product in its new environment.
        - Plasmids are not the only cloning vectors that can be used, but they are very common.
      - ➢ Reproductive cloning:
        - It is the production of a genetic duplicate of an existing organism.
        - Somatic Cell Nuclear Transfer (SCNT) is the most common cloning technique: the nucleus of an unfertilized egg is removed → a nucleus of somatic cell is transferred to the egg → egg is stimulated with shock and starts to divide → blastocyst is generated (exact DNA match to the organism from which somatic cells where taken). → implantation in uterus to cause birth!
        - Example: Dolly (in 1996).
      - ➢ Therapeutic cloning:
        - Using the process of Somatic Cell Nuclear Transfer (SCNT) to create an embryo. However, this embryo is destroyed and harvested for stem cells!
        - The obtained stem cells can be used to treat disease or regrow damaged tissues.
- **Ethical debate (الجدال الأخلاقي):**
  - ✓ Supporting opinions:
    - ❖ Excess IVF embryos which will be destroyed anyways can be used in research.
    - ❖ Therapeutic cloning produces cells in a petri dish, not a pregnancy.
  - ✓ Opinions against embryonic stem cells research:
    - ❖ Embryo is a human and has the right to live → destroying it is a murder.
    - ❖ There is a risk of commercial exploitation of the human participants in embryonic stem cell research.

- **Somatic stem cells (adult stem cells):**
  - **Definition**: they are undifferentiated cells found among differentiated cells in a tissue or an organ, capable to differentiate to major specialized cell types (multipotent).
  - **Function**: maintaining and repairing tissue in which they are found.
  - **Found in:**
    - ✓ Bone marrow.
    - ✓ Umbilical cord blood.
    - ✓ Peripheral blood.
    - ✓ Amniotic fluid.

- ✓ Many tissues and organs.

- **Therapy using these cells is accepted ethically.**
- **Transdifferentiation of somatic cells:**
  - ✓ Recently somatic stem cells have been shown to have the ability to cross lineage boundaries and to give rise to cells not normally found in the organs or tissues of residence.
- **Hematopoietic stem cells give rise to two major progenitor cell lineages:**
  - ✓ Myeloid progenitor.
  - ✓ Lymphoid progenitor.

- **Human embryonic stem cells vs. human somatic stem cells:**

Embryonic stem cells	Somatic stem cells
Pluripotent; very flexible, have the potential to make any body cell	Multipotent; limited flexibility, can not become any cell type
Immortal; one cell line can potentially provide an endless supply of cells with defined characteristics	Limited longevity; difficult to maintain in cell culture for long time
Can be grown relatively easily in culture	Harder to grow in culture
Availability; embryos from IVF clinic	Many unknown; not all adult stem cells have been identified yet
Immunogenic; cells from a random embryo donor are likely to be rejected after transplantation.	Immune response is unlikely; patient's own cells
Tumorigenic; (teratomas or teratocarcinoma)	Tend not to form tumors
Ethical controversy and legal restrictions	No ethical controversy

- **Induced pluripotent stem cells (iPS cells):**
  - They are somatic stem cells genetically re-programmed to an embryonic stem-cell like state by being forced to express genes and factors to maintain the properties of embryonic stem cells.
  - They are not derived from human embryos. Therefore, there are no ethical issues.
  - **Patient's specific iPS cells are genetically matched:**
    - ✓ Eliminate the concern of immune rejection of implanted cells.
    - ✓ Circumvent problems with organ transplantation (shortage of donor organs and limited availability of matched tissues).
  - **Clinical uses of iPS cells:**
    - ✓ Drug development and drug toxicity tests.
    - ✓ Study development and genetics.
    - ✓ Understanding birth defects.
    - ✓ Cell therapies: type-I diabetes, heart disease, Parkinson's disease, Alzheimer's disease and others.
- **Other types of stem cells:**
  - **Embryonic germ cells**: pluripotent.
  - **Cancer stem cells.**
  - **Endogenous pluripotent somatic cells**: pluripotent.