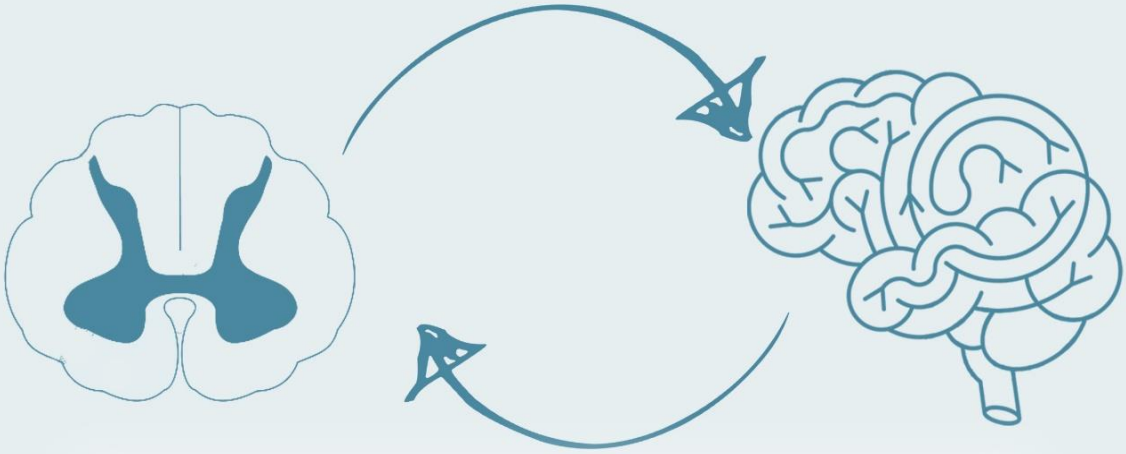


CNS

Biochemistry

0 slides 0 sheets

number 2

Done by نور الجايح

Correction **Abdullah Nimer**

Doctor **Diala Abu-Hassan**

This sheet covers the material up to slide number 38

There is no need to return to the sides since everything is included here

---

* **Stem cells** are primal cells common to all multicellular organisms that retain the ability to ***renew*** themselves through cell division and can ***differentiate*** into a wide range of specialized cell types.

* Stem cells are either found in **unspecialized** (undifferentiated) state, or **partial differentiated** state, following a specific lineage to reach a final functional cell.

* These cells have a group of special characteristics, which make them **distinctive** from other cells: -

1) Cell division: **Asymmetric division**: stem cells divide into two different daughters.

a) **First daughter cell** for **renewal** the population (self-renewal).

* Self-renewal: the ability to go through numerous cycle of cell division while maintaining the undifferentiated state.

b**) Second daughter cell** undergo **differentiation** path.

* How does asymmetric division occur?

Differential segregation of **transcription factors** and **cell membrane proteins** (such as receptors) between the two daughter cells.

After division both daughter cells have the same complete DNA, genes… but the genes that are activated in the cells that are responsible for renewal are different from the genes that are activated in the cell responsible for differentiation.

-What activates certain genes in certain cells?

Transcription factors; during division, differential segregation collect transcription factors that are responsible for pluripotency gene in one side and the transcription factor responsible to drive cell to differentiate into the other side, that gives us two different daughter cells.

The cells that are going to differentiate will not be converted directly to its final state, they will undergo a lot of consecutive stages; it will give progenitor cells, and intermediate cell types.

Progenitor cells: **partially** differentiated (not pluripotent cell or terminal cell)

e.g. hematopoietic stem cell.

2) Niche:

Each stem cell is surround by a specialized cellular microenvironment that provides stem cells with the support needed for self-renewal → called **stem cell niche**

*niche can be composed of one or more of the following:

- ✓ **Cells:** a single cell type, or a whole host of interacting. cells outside the stem cell`s linage, or they may derive primarily from the stem cells own descendant.
- ✓ **Extracellular Matrix**
- ✓ **Soluble factors** (TGF β, Notch, Wnt, FGF, EGF, SCF, insulin like growth factor & chemokine families).
- ✓ **Secreted or cell surface factors** (surface receptors and antigens).

*Each type of stem cell has its special niche component

The function of niche (why stem cell need a specific environment)

1) **Nutritive function**
2) Niche provides an area for stem cells to **communicate** between each other.
3) Niche might be agents of **feedback control** (control of stem cell pool size)

   *Each cell affects the other by secreting factors that maintain stem cells' own characteristics.
4) Niche are instrument of coordination among tissue component
5) Niche are hubs **of inter-lineage coordination**.
6) Demands on stem cells necessitate **special support for viability**.

3) Potency of stem cell:

* **Potency:** the ability to differentiate

* Stem cell have potential differentiated pole.

Type of potency:

1) **Totipotent:** "toti"=whole, they develop early on, with unlimited potential and can differentiate to **any type of cell in addition to extra embryonic tissues** like placenta.
2) Pluripotent: "pluri"=many, they are found in embryo only, and can give **all types of cell derived from the three germ layers** (***ectoderm**: skin cells, neuron, pigment cell ***mesoderm**: lung cells, thyroid cells, digestive cells like pancreatic cell * **endoderm**: smooth, skeletal and cardiac muscle cell, RBCs, tubule cell of kidney)
3) **Multipotent**: "multi"=several, they found in adult, and can give **several types of cells** for example (hematopoietic stem cells)
4) **Unipotent:** gives only one type of cells.

- **How to check the pleuripotency of cell?**

The totipotent & pleuripotent can gives cells of the 3 germ layers as we said earlier, so, by exposing stem cells to certain conditions we initiate their differentiation, they use a specific marker that detect if cells are capable to give the 3 type of germ cells or not, if yes, they consider pleuripotent cells.

4)trans-differentiation vs. developmental plasticity.

***Developmental plasticity:** The multiplicity of stem cell differentiation options.

When the cell had already differentiated it can't go back to be a stem cell - while in vitro might be able to initiate undifferentiation -.

***trans-differentiation:**

A change or transformation in stem cell differentiation from one cell type to another even if they different in their embryonic origin.

Trans-differentiation specially found in **cancer cell**, as they transform from ectoderm to mesoderm, accordingly they will lose their characteristic and function.

Types of stem cell:

1) **Embryonic stem cell (ESCs):** pleuripotent cells, found in inner cell mass of mammalian blastocyst, develop before implantation in uterus, they are able to differentiate into all the specialized embryonic tissue, derived from 3 germ layers.

2) **Adult stem cell (ASCs)**: they found in many areas like **bone marrow**, **umbilical cord**, **brain**, or either as a small population of stem cells in certain tissues, they act as a repair system for the body replacing specialized damaged cells

- **What make embryonic stem cell pleuripotent cells?**

Transcription factors which influence the expression of proteins in these cells.

- **Pluripotency transcription factors of ESCs:**

1) Oct4
2) Nanog
3) Wnt-β- catenin signaling
4) Other TFs

Don't forget that their function is to activate certain genes to preserve the pleuripotency of cells.

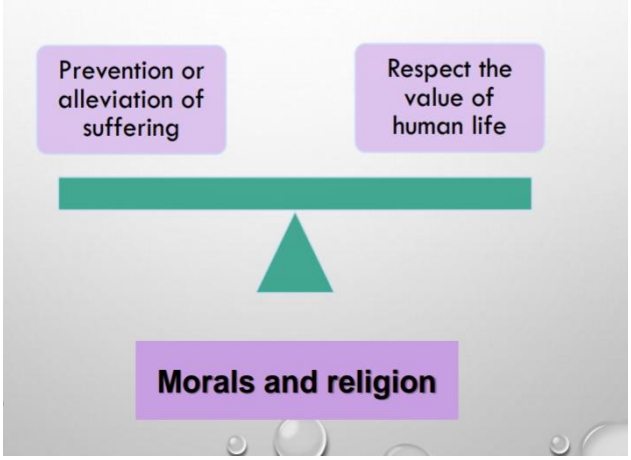
Human embryos cloning:

Hwang's work was able to offer an alternative to the use of actual human embryos by **cloning several human embryos**, helping to eliminate the need for new embryos.

Hwang claimed he had successfully cloned 30 human embryos, claims that have now been shown to be **lies.**

The ethical dilemma of embryonic stem cell:

There is a problem in using ESCs between morals, religion and ethical aspects; Islam & Judaism permit usage of ESCs before day number 40, while Christianity does not, for its belief that zygote is a human being.



To solve this dilemma, some Japanese scientists tried to generate **induced pleuripotent stem cells** (IPSCs).

IPSCs were obtained by transducing embryonic and adult fibroblasts with **defined transcription factors.**

Those scientists converted differentiated cell (fibroblasts to pluripotent stem cells activation of transcription of pleuripotent factors (OCT3/4, SOX2, c-Myc, KLF4).

They do that by taking **a skin biopsy** and picking **fibroblast** then exposing them to **a viral victor** that contains genes of these transcription factors, accordingly they will activate their expression, finally **fibroblasts** were successfully converted back **to stem cell**.

In 2006 → **Takahashik, Yamanaka**: induction of pleuripotent stem cell from mouse embryonic and adult fibroblast cultures by **defined factors**.

In 2007 →a group of scientists could achieve the induction of pleuripotent stem cells from **adult human fibroblasts by defined factors**.

Advantage of IPSCs:

1) Evade ethical problems.
2) Use of autologous cell, to avoid immune response.
3) Skin biopsy is less invasive than harvesting bone marrow (iliac crest).
4) Patients specific.
5) Safer.

*embryonic stem cell, live in **colonies**

*ESCs & IPSCs are similar in morphology.

Yamanaka's comparison of IPSCs & ESCs:

They are indistinguishable in:

1) Surface antigens (markers).
2) Gene expression and their micro-array.
3) Telomerase activity.
4) Epigenetic status of pleuripotent cell specific genes.
5) Promoter activity.
6) Teratoma formation: Their ability to produce cancer or tumors.
7) Their ability to proliferation and renew themselves
8) In vitro differentiation into cells of the whole body

Adult stem cells:

Undifferentiated cells found throughout the body.

*function → they divide to replenish dying cells and regenerate damage tissue in normal conditions (RBCs regeneration/ intestinal regeneration…) or to repair damaged tissues like wound healing.

Types of adult stem cells:

1) Bone marrow stem cells:

a. **Hematopoietic stem cell:** they found in bone marrow and give variety of blood cells.

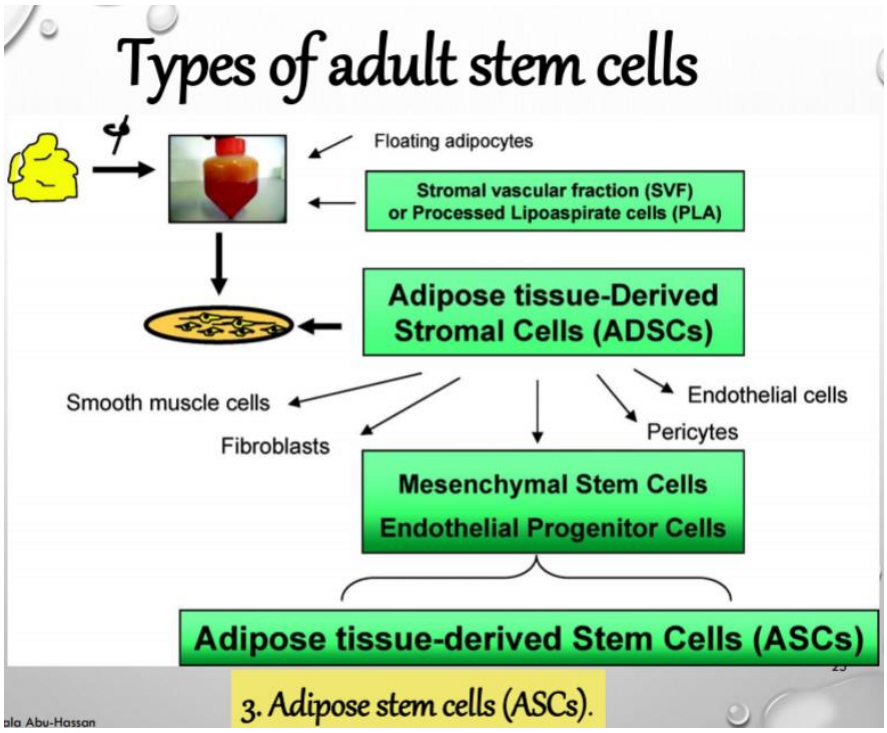
b. **Somatic stem cells (bone marrow stroma cells):** such as mammary stem cells and mesenchymal stem cells (osteoblasts, chondrocytes, myocytes, adipocytes, neuronal cells).

2) **Neural stem cells:** which counter our previous conviction that brain cells didn't regenerate, now they have found that in certain areas, we have a group of cells that regenerate certain brain cells.

***Neurosphere:** floating heterogeneous aggregation of cells, contain a large proportion of stem cells responsible for adult neurogenesis in subventriculare zone, which lines the **lateral ventricles of the brain**, and **the dentate gyrus of the hippocampal formations.**

3) adipose stem cells:

Extracts after liposuction, they can differentiate to a variety of cell like smooth muscle cells, fibroblast, or endothelial cell. They try to use them to treat diseases of eye but nothing is approved clinically, it still under research



4) Umbilical cord stem cells:

There are two types of cell

a) **Mesenchymal stem cells** inside the **cord tissue**

b) **Hematopoietic stem cells** of **cord blood**

5) olfactory adult stem cell:

They are found in the olfactory mucosal cells, they regenerate axons of the olfactory nerves and the olfactory epithelium.

6) tissue stem cell: in the cornea, and the trabecular meshwork of the eye, this region contains a small population of stem cells; about 300,000 cells.

Function & uses of stem cell:

1) To study the **specific signals and differentiation**.

2) **genetic therapy** → if a patient has a mutation in a certain gene that express a liver protein, we can take hepatocytes or fibroblasts to create IPSCs, then by a recombination process we target the mutant gene and remove it then insert the healthy genes, then we initiate the differentiation of these cell to hepatocyte and return them back into the liver to produce the protein of interest (under-research).

3) **Cell based therapies**

4) stem cell for **cancer treatment by activation of chemotherapeutic agents**.

5) **Drug testing:** instead of treat patients with drugs that have a lot of aggressive side effects, especially if the patient is immunocompromise, in vitro we take a tissue biopsy from these patients and expose it to drugs, now we can get approximate image for that treatment and its side effect.

* This leads us to **personalized medicine**, to understand how two patients of a same disease, and same drugs, response differently to treatment (mainly in cancer therapy).

stem cell therapy limitations:

1) Carcinogenicity → mainly in ESCs, they have a **carcinogenic potential**

When injected in mice, they were able to form teratoma.

*if stem cells were injected they may form teratomas, while injecting differentiated cells didn't have the same risk.

2) immune rejection: immune rejection chances increase when ESCs were used, while it decreases in Autologous cells usage.

*note: there is only one report that reveals an immune rejection in Autologous cell in mice.

3) Infection: there should be a cross infection control before transfer stem cell from one person to another.

Limitation of using adult stem cells:

1) Lack of stem cell markers resulting in difficulties to **separate and identify cells**.

2) In-vitro systems for manipulating adult stem cell populations is often **not well-defined**.

3) multipotency of ASCs

4) In-vivo: our understanding of how adult stem cells are regulated within their niche is in its infancy (our lack of knowledge of their specific biology limits our ability to use them).

Cancer stem cell:

They are **tumor cells** that have the essential properties of **self-renewal**, **colonel tumor initiation capacity**, **colonel long term repopulation potential** and **plasticity**.

***note:** cancer stem cells can explain the reoccurrence of some cancers.

Why we interest in stem cell research?

1) **Therapeutic** potential.

2) **Organ transplantation**

3) **Functional genomic studies** to understand human embryonic gene expression, genomic data mining, and bioinformatics.

4) **To study biological processes to understand human developmental disorders** like birth defect, cancer, etc.

5) Creating **human disease models** for disease etiology and drug discovery and development.

6) **Cell-based therapy and regenerative medicine.**

Stem cells and neurodegenerative disease.

Neurodegenerative diseases: a wide range of acute & chronic conditions in which neuron and glial cells in the brain and spinal cord are lost or damaged.

***acute:** ischemic stroke or spinal cord injury.

***chronic:** Parkinson disease, Alzheimer disease, or amyotrophic lateral sclerosis (ALS).

*** Type of stem cell used to treat neurodegenerative diseases:**

1) Embryonic stem cells ***2) adult stem cells***

- Clinical trials using stem cells have already been performed or initiated (e.g. for the rare, fatal, autosomal recessive neurodegenerative disorder Batten disease)
- **No stem cell-based therapy has yet been proven beneficial for any neurodegenerative condition**
- Despite this fact, unproven treatments for several neurodegenerative diseases are offered at "clinical" around the world without rationale and with poor scientific and clinical basis.
- Ethical, regulatory, societal, and economical issues need to be addressed

Main considerations when we use stem cells to treat neurodegenerative diseases:

- What is required for the stem cell-based approach **to be clinically competitive.**
- **Risks** to the patient that are **acceptable**, depending on disease **severity**. Animal models may not fully predict their toxicity, occurrence of immune and other biologic responses, and the risk for tumor formation after implantation in patients.
- **The variability between neurodegenerative diseases** in the degree of disability that they cause and in the therapeutic options that are available (Don't start a treatment until you are sure the benefits outweigh the risks).
- Parkinson disease (PD) ⟶ symptomatic treatment
- Amyotrophic lateral sclerosis (ALS) ⟶ no efficient treatment

So, the usage of stem cell depends on type of disease and difficulty of its treatment, and predictable improvement after treatment, cost, ethics… for example: patient can learn to live with Parkinson disease, unlike Alzheimer or paralysis due spinal cord injury "cost effective".

- **The cell type to be regenerated and transplanted**

  PD ⟶ dopamine neurons

  ALS ⟶ motor neurons

- Stroke and Alzheimer's disease-several cell types

    - The stem cell-based approach should show **substantial improvement of functional deficits in animal models before their use in clinical application**, to determine the biological mechanism underlying the observed effects of a stem cell–based treatment in an animal model. E.g. reconstruction of neuronal circuitry.

Thank you