CORE IDEA 1: THE CELL AND BIOMOLECULES OF LIFE
TOPIC 1.5: STEM CELLS

Learning Outcomes:

(t) describe the unique features of stem cells, including zygotic stem cells, embryonic stem cells and blood stem cells (lymphoid and myeloid), correctly using the terms:

i. totipotency (e.g. zygotic stem cells)
ii. pluripotency (e.g. embryonic stem cells)
iii. multipotency (e.g. lymphoid and myeloid stem cells)

(u) Explain the normal functions of stem cells in a living organism, including embryonic stem cells and blood stem cells (lymphoid and myeloid)

(v) Discuss the ethical implications of the application of stem cells in research and medical applications and how human induced pluripotent stem cells (iPSCs) overcome some of these issues. (Procedural details of how iPSCs are formed are not required).

Use the knowledge gained in this section in new situations or to solve related problems.

References:

Reece, J. B. et al. (2018). Campbell Biology (11th Ed). Chapter 19: DNA Technology, pp. 460 – 465.

Note: This textbook is available in our library. You may wish to borrow the book to supplement your reading when necessary.

1. What are Stem Cells?

1.1 Definition

The stem cell is an undifferentiated **and** unspecialised cell that can divide over long periods and can produce specialised cell types in the body.

1.2 Properties

All stem cells are different from other cells in the body in three main ways:

1. **Stem cells are <u>undifferentiated</u> and <u>unspecialised.</u>**
    - They **do not have any tissue-specific structures** that allow them to perform specific functions.
        - E.g. stem cells do not produce haemoglobin to carry oxygen through the bloodstream like a red blood cell
    - However, unspecialised stem cells can differentiate to become specialized cells, e.g. red blood cells.
2. **Stem cells are capable of <u>long-term self-renewal.</u>**
    - Stem cells can divide and produce copies of themselves (i.e. **<u>proliferation</u>**), to replenish their cell count.
    - Stem cells undergo mitotic division to produce two genetically identical daughter cells via:
        - **symmetrical division**
          which form 2 daughter stem cells
        - **asymmetrical division**
          where one daughter cell **remains a stem cell** while the other daughter cell becomes a **progenitor cell** which undergoes further division and differentiate into other specialised cell types.
        - A progenitor cell is an immediate descendent of a stem cell that is fate-restricted. E.g. progenitor daughter cells of haematopoietic stem cells can only differentiate into various blood cell types (e.g. red blood cells, mast cells, neutrophils) and not other cell types.

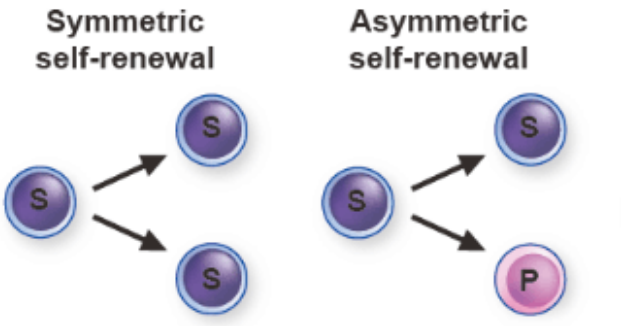

Fig. 1.1 Types of cell division in stem cells

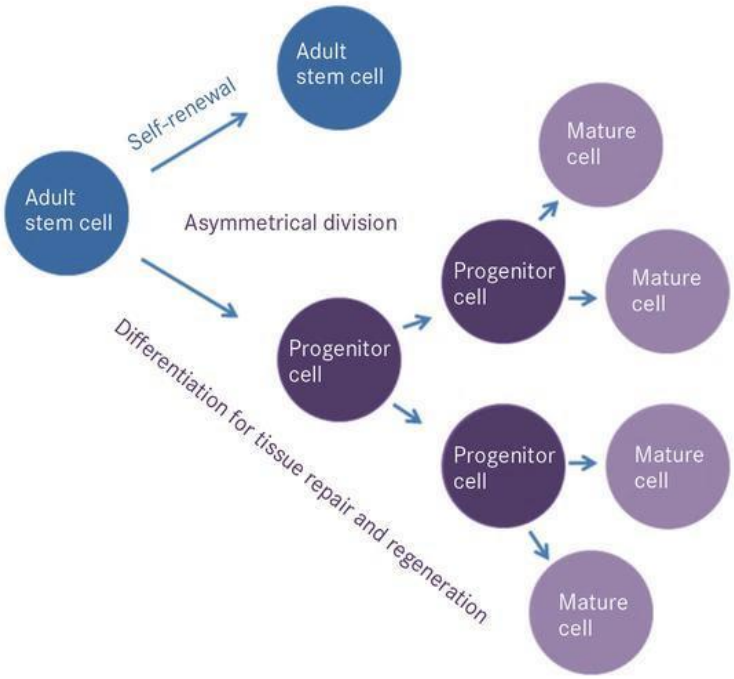

Fig. 1.2 Division and differentiation of progenitor cell

3. Stem cells can <u>differentiate.</u>

- Stem cells have the potential to become other more specific cell types. These new cells used to replace damaged or diseased cells of the tissues and organs in the body.

- Once stem cells have differentiated to form progenitor cells, they have fate restricted and become 'committed' to becoming a particular cell type.

    - E.g. skin stem cells give rise to new skin cells when needed, to assist regeneration after damage and as part of the normal ageing process. These new skin cells are committed to the role of skin cells and do not play other roles.

- Stem cells can be triggered to differentiate by:
    - **internal signals** like presence / availability of different transcription factors.
    - **external signals** like chemicals secreted by other cells, physical contact with neighbouring cells or certain molecules in the cell's environment like growth factors.

- These signals result in **differential gene expression** i.e. certain genes become activated and other genes become inactivated. As a result, a differentiated cell develops specific structures and performs specific functions. ***(Recall: Concept on Differential gene expression in CI2.4-2.5:Organisation of Eukaryotic Genomes & Control of Eukaryotic Gene Expression.)***

  E.g. a mature, differentiated neurone has dendrites and axon that receive and send nerve signals.

2. Types of Stem Cells

Learning outcome (t):
Describe the unique features of zygotic stem cells, embryonic stem cells and blood stem cells, correctly using the terms totipotency, pluripotency and multipotency.

Stem cells can be categorised by

- **potency** of the cell i.e. ability of the stem cell to differentiate into different cell types
- **origin / source** of where the stem cells are obtained from

The higher the potency, the greater the ability of the stem cells to divide into more types of specialised cells.

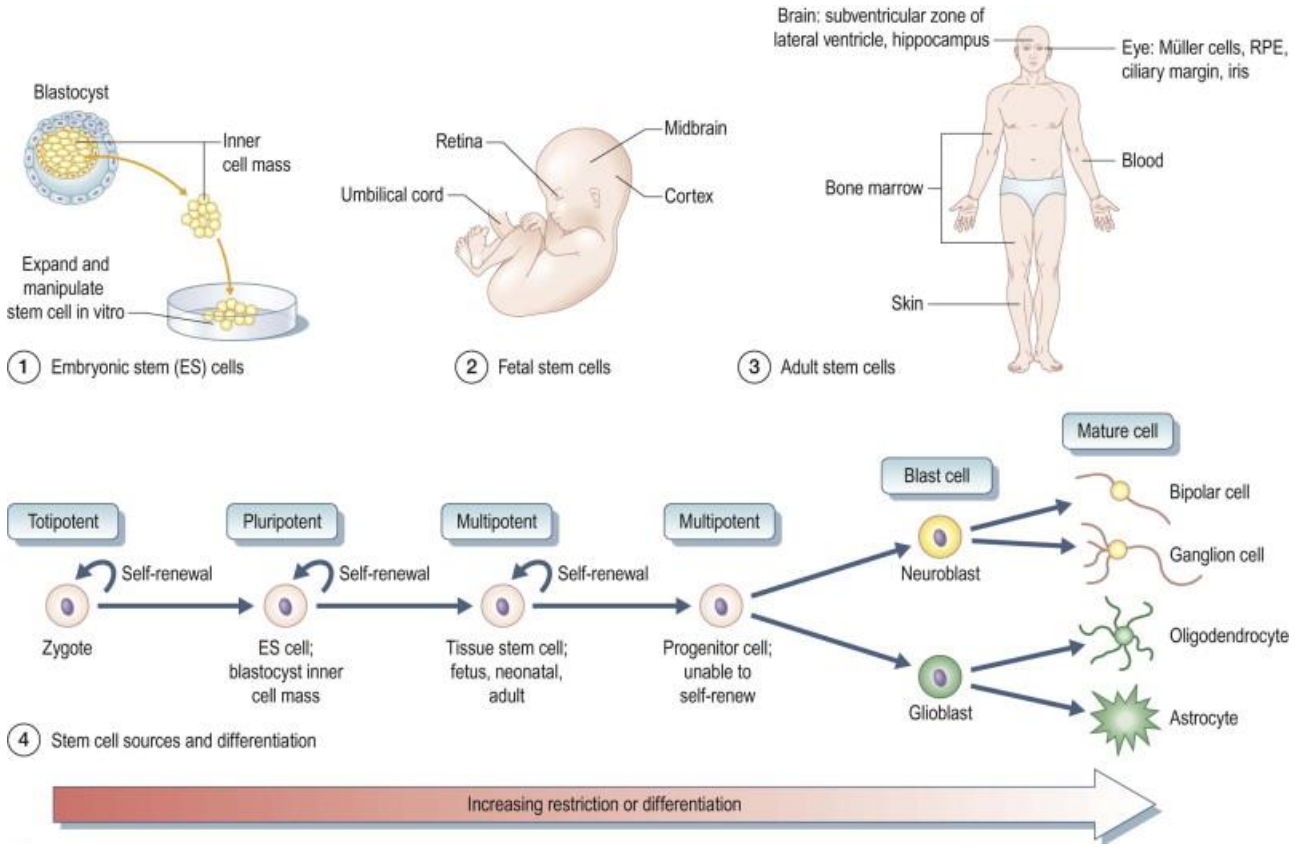

Fig. 2 The type of stem cells and their potential to develop.

A) Totipotent stem cells

- can differentiate into **any cell type in the adult body**, **including cells that form the extraembryonic tissues (e.g. the placenta)** needed for the development of the embryo,.

- Totipotent cells are found in the zygote as well as cells produced within the first 3 mitotic divisions (i.e. up to the 8-cell stage of embryonic development).

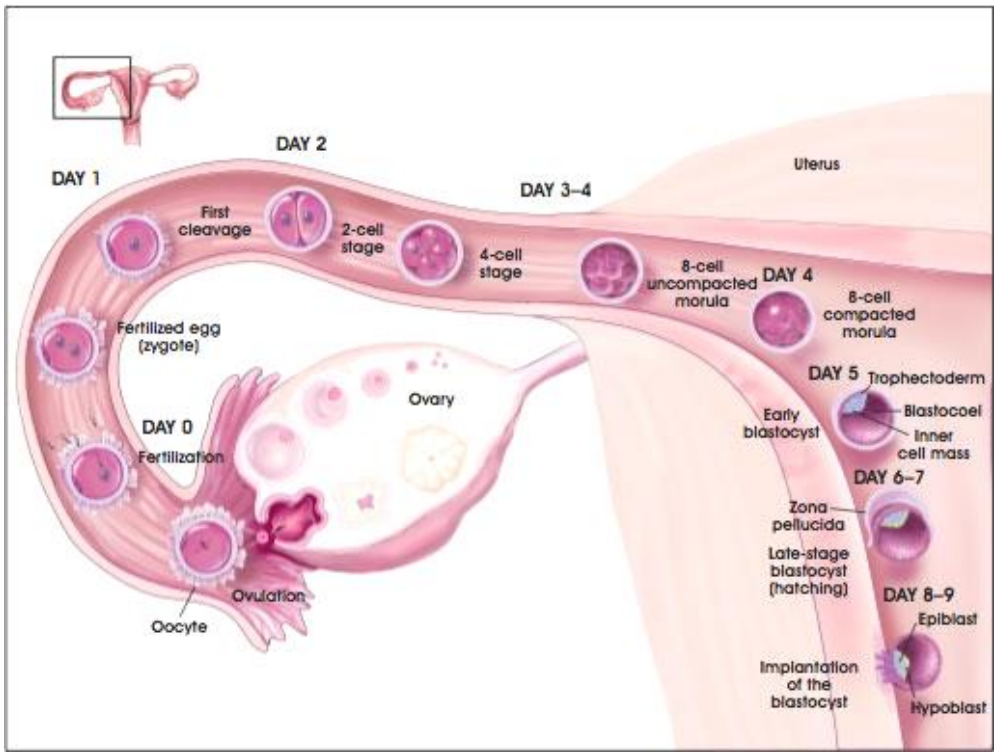

Fig. 2.1.1 Development of the Preimplantation Blastocyst in Humans

B) Pluripotent stem cells

- can differentiate into all cell types that develop to form the **three germ layers** (ectoderm, mesoderm and endoderm) (Fig. 2.1.2) but not cells that form the extraembryonic tissues.

- Pluripotent stem cells are found in **inner cell mass** of the blastocyst (early human embryo).

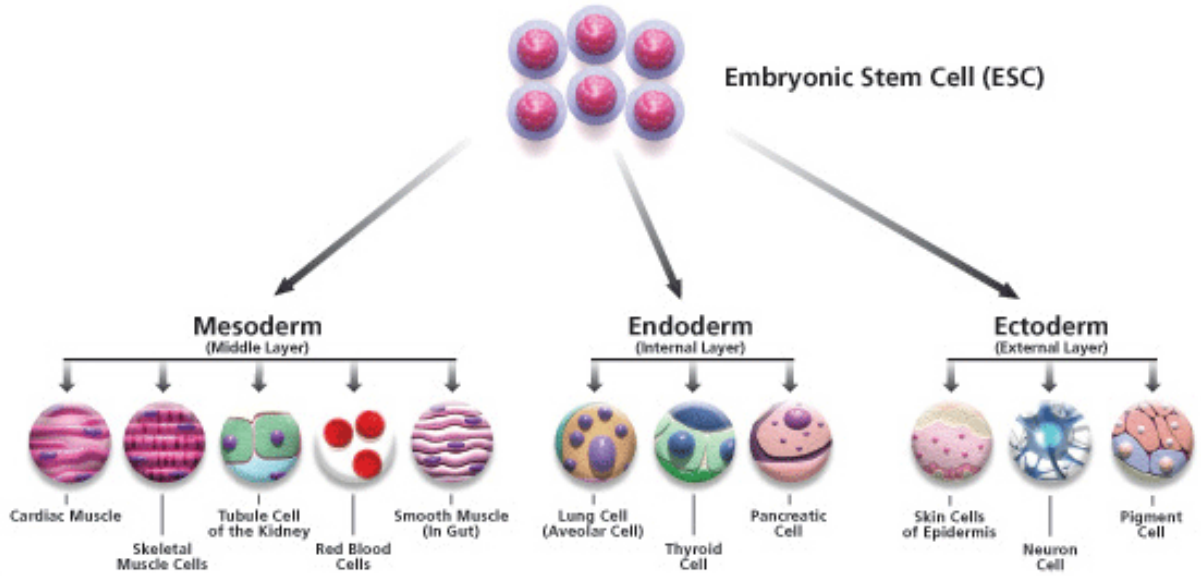

Fig. 2.1.2 The 3 germ layers of an embryo (ectoderm, mesoderm and endoderm) that eventually give rise to the different types of tissues and organs in the adult.

C) Multipotent stem cells

- Can differentiate into **multiple but limited number of related cell types.**
- found among differentiated cells in a tissue or organ, e.g. bone marrow, intestinal tract, skin
- E.g. Haematopoietic (blood) stem cells in the bone marrow can differentiate into all the cells of the blood, such as red blood cells, white blood cells and platelets etc., but not other cells from a different tissue like neurones.
- Research has also been shown that ASCs can differentiate into cells of a different lineage when appropriate chemical signals are provided in-vitro, e.g. haematopoietic stem cells can produce neurones. This property is known as **plasticity**.

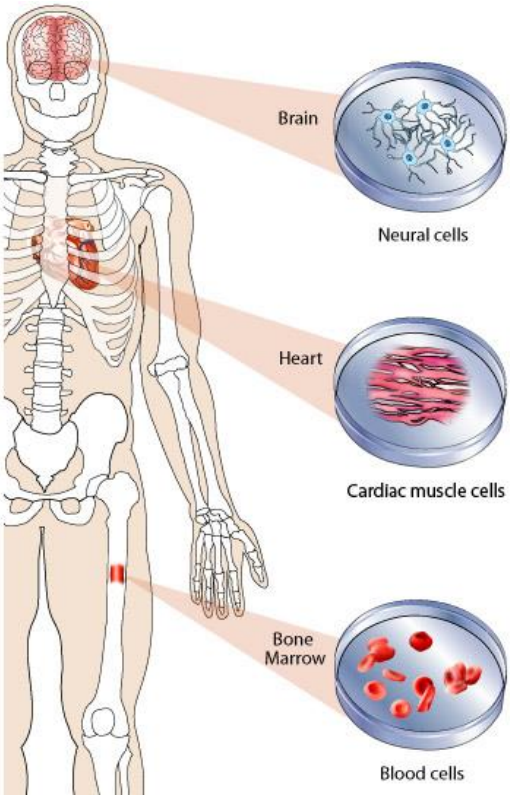

Fig. 2.1.3 Multipotent stem cells

Totipotent zygotic stem cells can differentiate into all the adult body cell types including extraembryonic membranes.

Pluripotent embryonic stem cells can differentiate into all the adult body cell types except cells that form extraembryonic membranes.

Multipotent adult stem cells e.g. blood stem cells, can only differentiate into a limited number of related specialised cell types.

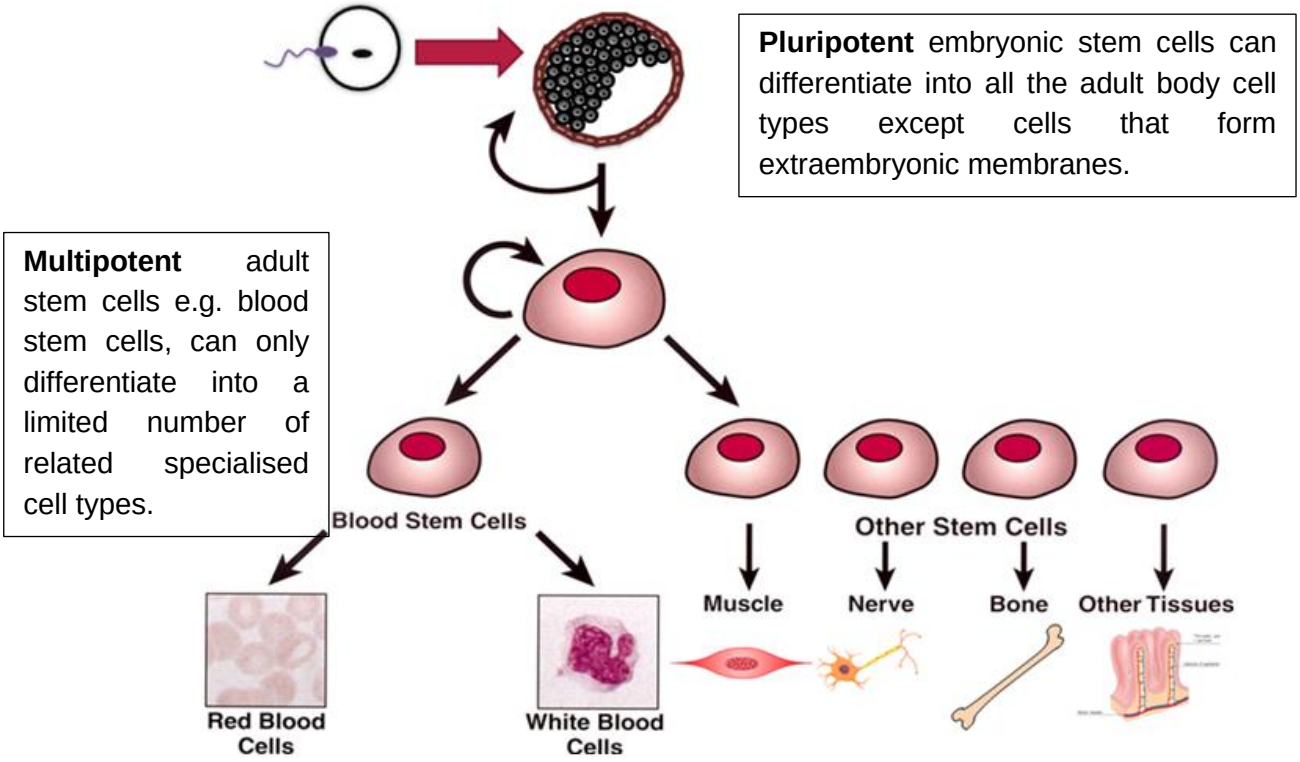

Fig. 2.1.4 Summary of different levels of potency.

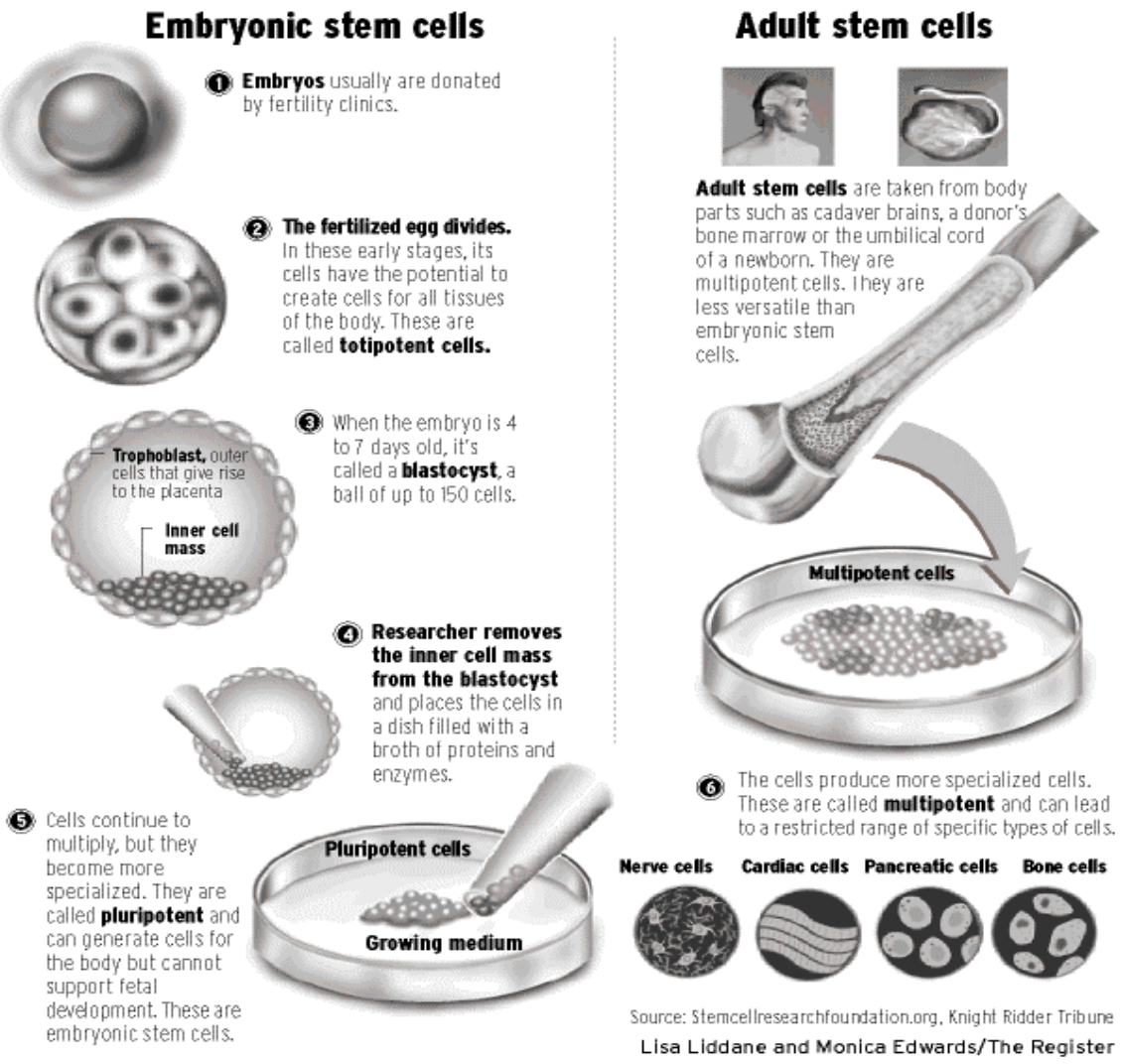

Fig. 2.2.3 Comparing ESC and ASC

3. Function of Stem Cells

Learning outcome (u):
explain the normal functions of stem cells in a living organism, including embryonic stem cells and blood stem cells (lymphoid and myeloid)

3.1 Embryonic Stem Cells

- Embryonic stem cells (ESCs) play a crucial role in the **early development** of a living organism.

- ESCs are derived from the **inner cell mass** of the **blastocyst**, which is a pre-implantation stage embryo around 4-5 days after fertilization.

- ESCs are **pluripotent**, meaning they can **differentiate into any cell type of the three primary germ layers** - endoderm, mesoderm, and ectoderm.

- Key Functions

    - **Formation of the Embryo**: The pluripotent ESCs in the inner cell mass of the blastocyst give rise to the entire body of the organism, including all specialized cell types and organs such as the heart, lungs, skin, and reproductive cells.

    - **Differentiation into Germ Layers**: As the blastocyst implants in the uterus, the ESCs begin to differentiate and form the three embryonic germ layers - endoderm (giving rise to organs like the digestive system), mesoderm (forming tissues like muscle and bone), and ectoderm (developing into the nervous system and skin).

    - **Self-Renewal**: ESCs have the remarkable ability to self-renew indefinitely through continuous cell division, producing more pluripotent stem cells identical to themselves. This property allows them to proliferate and maintain their undifferentiated state **during early embryonic development**.

- In summary, the primary function of embryonic stem cells is to **initiate the formation of the embryo** and **differentiate into all the specialized cell types and tissues** that make up the various organs and systems of a living organism.

- Their pluripotency and self-renewal capabilities are essential for proper embryogenesis and development.

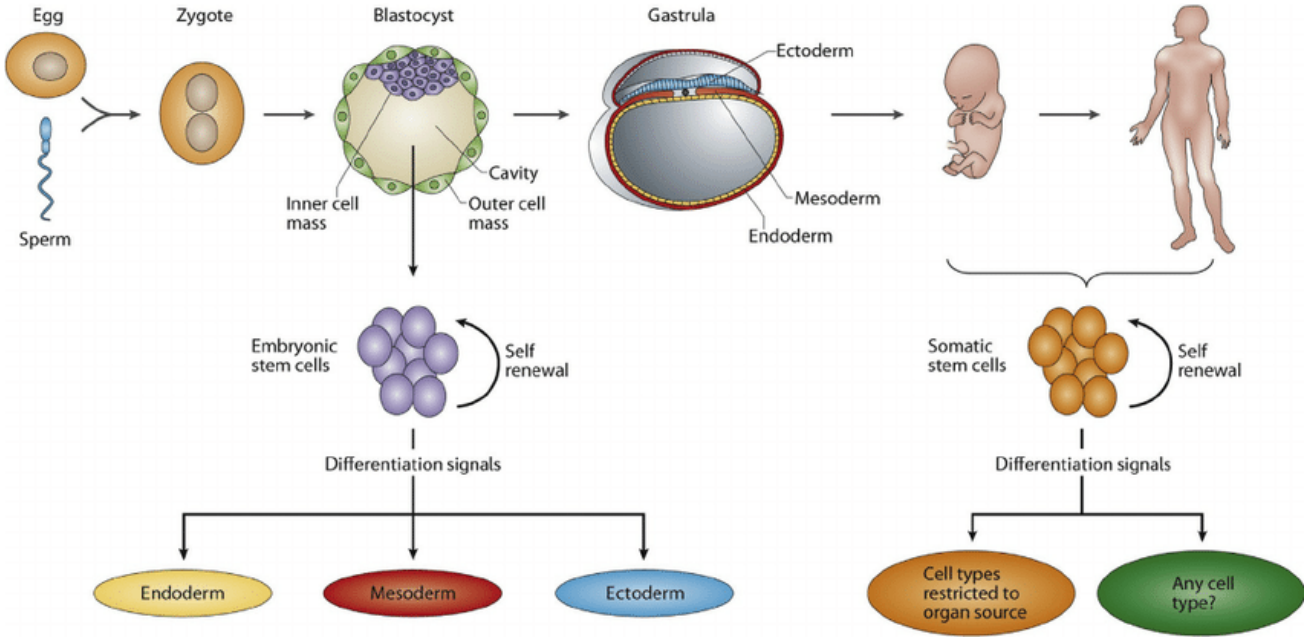

Fig. 3.1.1 Embryonic stem cells (ESCs) are important for development of a fetus

3.2 Blood Stem Cells

- Blood stem cells, also known as **hematopoietic stem cells (HSCs)**, play a crucial role in the normal functioning of the **blood and immune systems** in a living organism.

- Key functions

  - **Production of All Blood Cell Types**: HSCs produce all types of blood cells, including red blood cells (RBCs), white blood cells (WBCs), and platelets (Fig. 3.2.1). Through a process called **hematopoiesis**, HSCs differentiate into lymphoid or myeloid progenitor cells, which further mature into the different blood cell lineages.

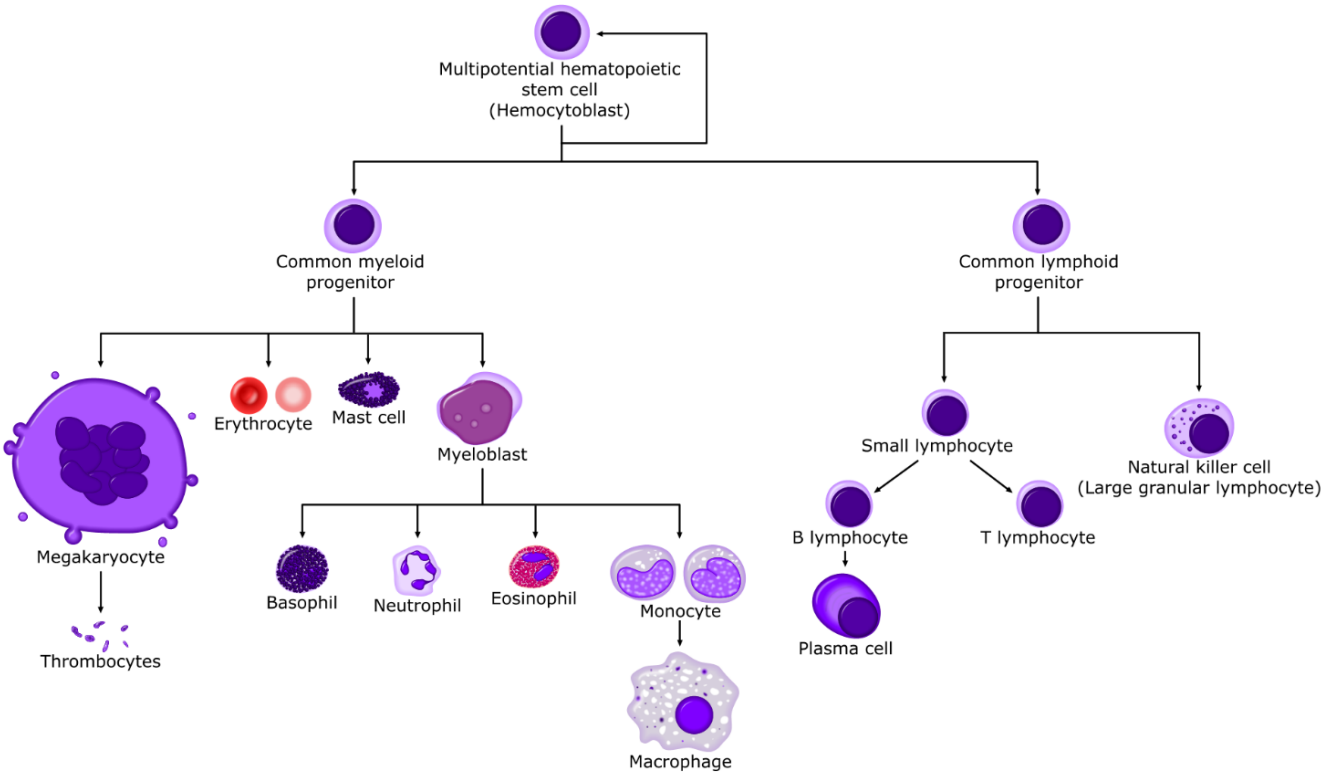

Fig. 3.2.1 Haematopoietic stem cell differentiation

  - **Lifelong Blood Cell Replenishment**: HSCs have the remarkable ability of **self-renewal**, allowing them to **replicate** themselves and **maintain a pool of undifferentiated stem cells**. This self-renewal capacity ensures a **continuous supply** of new blood cells throughout an organism's lifetime, replacing those that are lost due to normal turnover or injury.

DID YOU KNOW? the nature of science

Red blood cells (RBCs) have a limited lifespan of approximately 120 days in circulation before they are removed and replaced by new RBCs. This process of continuous RBC regeneration throughout life exemplifies the lifelong blood cell replenishment function of hematopoietic stem cells (HSCs).

HSCs residing primarily in the bone marrow are responsible for producing all blood cell types, including RBCs, through a process called hematopoiesis. As RBCs age and become less efficient in carrying oxygen, they are cleared from the bloodstream by the spleen and liver.

To replenish the lost RBCs, HSCs differentiate into committed progenitor cells called myeloid progenitors, which further mature into reticulocytes (immature RBCs) and eventually become fully functional RBCs. This process occurs continuously throughout an organism's lifetime to maintain a steady supply of new RBCs.

The ability of HSCs to self-renew and differentiate into all blood cell lineages, including the erythroid lineage that gives rise to RBCs, is crucial for sustaining this lifelong RBC regeneration cycle. Without this capacity, the body would quickly become anemic due to the constant loss of aged RBCs.

In summary, the regeneration of RBCs every 120 days serves as a concrete example of the lifelong blood cell replenishment function of HSCs, highlighting their essential role in maintaining the body's oxygen transport and overall hematopoietic homeostasis throughout an organism's lifetime.

- **Immune System Maintenance**: HSCs are responsible for the **production of all immune cells**, including lymphocytes (T cells and B cells), natural killer cells, and various types of granulocytes (neutrophils, eosinophils, and basophils). These immune cells play crucial roles in **defending the body against pathogens and foreign substances**.

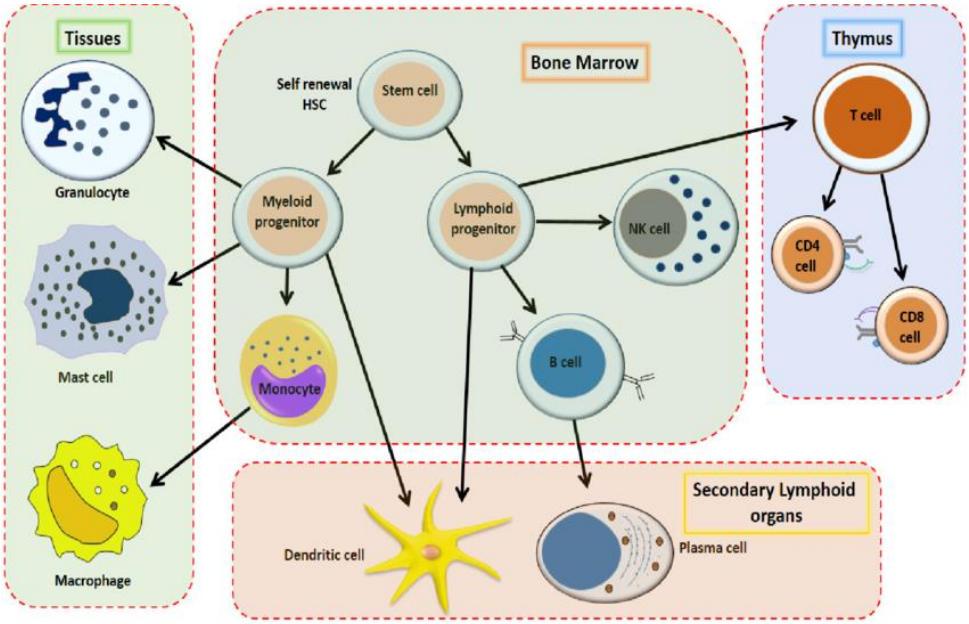

Fig. 3.2.2 Development and differentiation of HSC into different immune cell lineages

- **Tissue Homeostasis and Repair**: Under normal physiological conditions, most HSCs remain in a **quiescent or resting state (G_0 phase)**. However, they can be **activated in response to stress signals**, such as injury or infection, to rapidly proliferate and differentiate, replenishing the required blood cell types and contributing to tissue repair and regeneration.

- **Bone Marrow Transplantation**: HSCs are the basis for bone marrow transplantation, a life-saving procedure used to **treat various blood disorders**, cancers, and immune system deficiencies. HSCs from a healthy donor can be transplanted into a patient, allowing the reconstitution of their blood and immune systems.

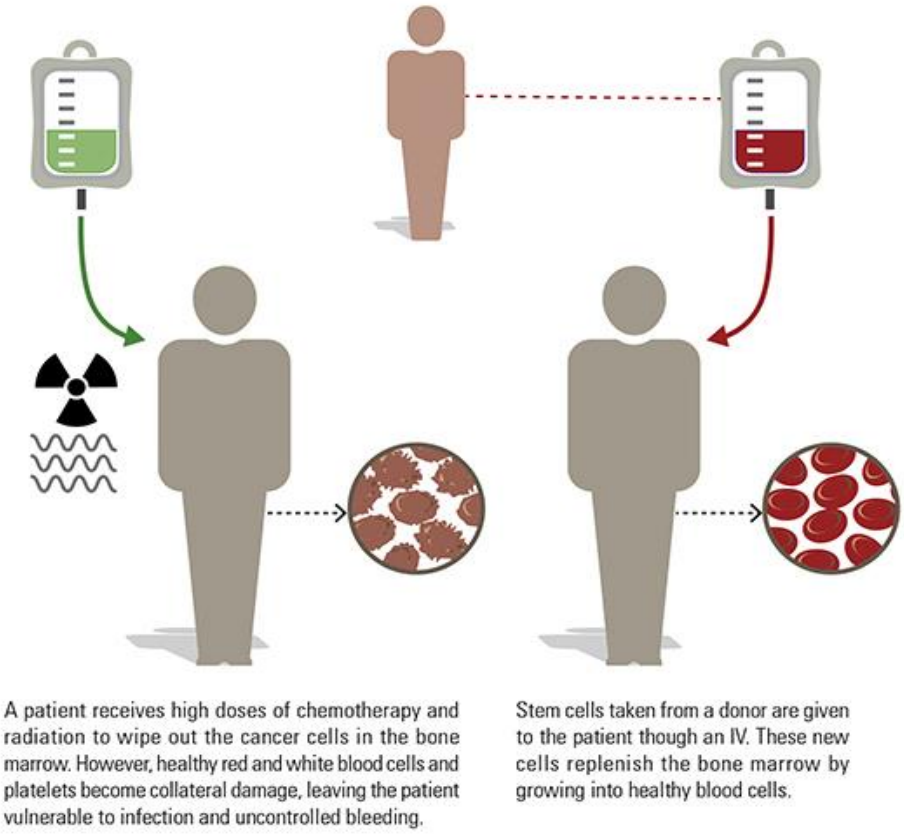

Fig. 3.2.2 Blood Stem cell therapy: Bone Marrow Transplant

- In summary, blood stem cells (HSCs) are essential for the **continuous production and replenishment of all blood cell types**, **maintaining the immune system**, and **enabling tissue homeostasis and repair** throughout an organism's lifespan.

- Their self-renewal and differentiation capabilities make them indispensable for the proper functioning of the hematopoietic system.

4. Induced Pluripotent Stem Cells (IPSCs)

Learning outcome (v):
Discuss the ethical implications of the application of stem cells in research and medical application and how human induced pluripotent stem cells (iPSCs) overcome some of these issues. (Procedural details of how iPSCs are formed are not required)

While stem cells offer great potential in treating many diseases and medical conditions, their use in research and therapy is often controversial.

4.1 Concerns about use of stem cells for research and therapeutic purpose

1. Human Embryonic Stem Cells (hESCs)

Destruction of Human Embryos

- hESCs for research is obtained from the inner mass cells of the blastocyst that inevitably leads to the destruction and killing of the embryo. Many view an embryo as a human life, thus its destruction is the **destruction of a life**, akin to murder.

- Although 'extra' embryos from IVF procedures in fertility clinics supply researchers with a source of hESCs, embryos are sometimes deliberately created for research or therapeutic purposes. This raises objections, as some who consider a blastocyst is a potential life, believe it has been created to be destroyed.

- Conversely, there are others with the strongly believe that hESCs hold the promise of sufficient benefit to human health to justify the use of human embryos for research purposes.

- Furthermore, there is currently ample embryos from infertility treatments donated for licensed stem cell research in many countries. Some hold the view that using these embryos for research are for greater good as these embryos are destined for destruction.

- There are also people who do not consider an embryo as 'a life' per se but a group of cells with the potential to develop into a life.

Informed Consent and Donor Rights

- Proper informed **consent procedures** must be followed when obtaining embryos or cells for ESC research, ensuring donors understand the potential uses and implications of their donation.

Commercialization and Commodification

- There are concerns about the **potential commercialization and commodification of human embryos and ESCs**, which could lead to exploitation or unethical practices.

2. Somatic Cell Nuclear Transfer (SCNT)

- In theory, the embryo generated using SCNT can be implanted into a uterus and allowed to continue development, potentially leading to the birth of a child. Thus, some parties are worried

about the use of nuclear transfer technologies for reproductive cloning (to reproduce humans). However, its actual feasibility has not been proven to date.

- Reproductive cloning is illegal in almost all countries. Despite this, some people fear that allowing nuclear transfer for therapeutic purposes will be the start of a ‘slippery slope’ into reproductive cloning.

3. General Ethical Considerations

Access and Equity

- As stem cell therapies become available, there are concerns about ensuring **equitable access** and preventing disparities based on socioeconomic status or other factors.

Long-term Monitoring and Support

- Clinical trials involving stem cell therapies may require long-term monitoring and support for participants, particularly if irreversible effects or complications arise, raising questions about the **responsibilities of researchers and sponsors**.

Regulatory Oversight and Guidelines

- There is a need for **robust regulatory oversight and guidelines** to ensure the ethical and responsible conduct of stem cell research and clinical applications, addressing issues such as informed consent, safety, and equitable access.

4.2 Induced pluripotent stem cells (iPSCs)

4.2.1 What are iPSCs

- iPSCs are somatic cells which are reprogrammed by altering their chemical environment (e.g. using different transcription factors, DNA methyl transferases, miRNAs etc.) to become stem cells.

- iPSCs possess unlimited self-renewal capacity and are pluripotent, thus can differentiate into many types of cell lineage. Hence, iPSCs can replace the use of ESCs and may overcome the ethical issues regarding its use in research and medical applications.

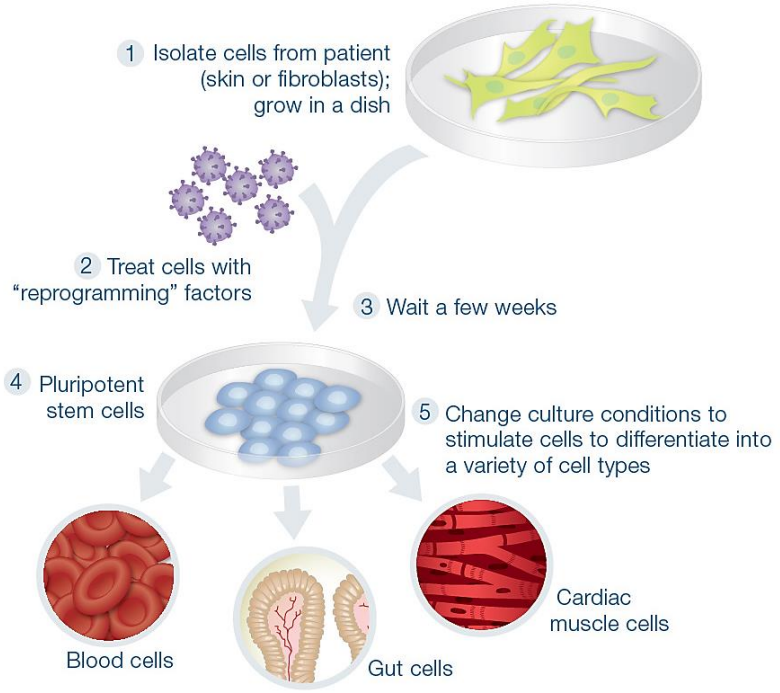

Fig. 4.2.1 Creation of iPSCs

4.2.2 Applications of iPSCs

- **Regenerative medicine**

  iPSCs can be used to produce patient-specific cells by **reprogramming patient's own somatic cells** to become stem cells. The resultant iPSCs can then be transplanted to the targeted site to replace damaged or diseased cells.

- **Disease modelling**

  IPSCs can be used to **study molecular mechanism of diseases**. The diseases can be modelled using iPSCs to better understand of their causes. This knowledge may be further utilized for developing treatments for these diseases.

- **Drug discovery**

  Effects of many toxic compounds like hazardous chemicals or environmental conditions encountered by humans can be **tested on iPSCs**. Newly designed pharmaceutical drugs can also be evaluated for toxicity and effects by using iPSCs.

- **Advantages**

  1. Reduce risk of immune rejection

  As iPSCs can be produced using patient's own somatic cells, the cells used for therapy are **genetically identical to the patient's cells**. Thus, there is **no need for patients to take immunosuppressant** to prevent immune cells from destroying the transplanted stem cells or tissue.

  2. Almost unlimited supply

  As iPSCs can be **created from somatic cells donated from a donor** unlike hESCs which must be derived from embryos discarded after IVF.

  Furthermore, the tissue donation process for iPSC production is **safer** and **less invasive** than egg donation for IVF.

  3. Circumventing ethical concerns

  Use of iPSCs **avoids the ethical controversies of embryo destruction**. iPSC technology provides a potentially viable alternative to hESCs without invoking sharp dispute about whether we are wrongfully 'destroying human beings'.

- **Disadvantages**

  1. Low efficiency and partial reprogramming of cells

  The rate of successful reprogramming of cells is variable. Although some iPSCs have successfully exhibited some aspects of pluripotency, studies on iPSCs long term viability and stability is lacking.

  2. Risk of tumorigenesis

  Formation of tumour from transplanted iPSCs due to insertional mutagenesis is a potential problem. iPSCs can later undergo abnormal growth due to introduction of transcription factor genes into its genome during the reprogramming process using viral vectors. Thus, producing safe and highly purified iPSCs will remain a challenge for future medical application.