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STEM CELL AND ITS TYPE

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Abstract

Stem cells are characterized by their extraordinary ability to self-renew and differentiate into various cell types, making them the leading candidates for regenerative medicine and biomedical research. This review thoroughly investigates the range of stem cells from totipotent, pluripotent (embryonic and induced pluripotent stem cells), multipotent (e.g., mesenchymal and hematopoietic stem cells), oligopotent, to unipotent types, explaining their origins and individual functional potential in tissue restoration, disease modeling, and therapeutic applications. Advances in stem cell biology have led to innovation in clinical applications, ranging from bone marrow transplantation to cardiac and liver tissue engineering, to emphasize their ever-increasing role in the treatment of hematological, neurological, and degenerative diseases. Combination of gene editing tools, like CRISPR-Cas9, with stem cell research offers new opportunities for personalized medicine, facilitating interventions specific to unique genetic profiles and reducing risks of immune rejection. In addition, stem cell tissue engineering and organoid development also hold the promise of transforming drug testing, disease modeling, and the construction of artificial organs. Although there are still ethical, technical, and regulatory issues, continued cooperative research efforts continue to broaden the applicability and safety of stem cell therapies. The future of stem cell science has the potential to revolutionize contemporary medicine, bringing hope for better, patient-specific therapies and new regenerative remedies for a range of chronic and heritable conditions.

Keywords: stem cell, totipotent, pluripotent, oligopotent,

1. Introduction

Stem cells are a distinct group of cells that exist at any stage of life with the mechanisms to self-renew and differentiate into a range of different cell lineages. Stem cells are important participants in the development of neonates and in the regeneration processes following injury or disease since they are the source from which specific cell types are derived in differentiated tissues and organs [1]. At the neonate stage of life, stem cells provide differentiation and proliferation into a variety of required cell types and cell lineages for continued development, whereas the primary role of stem cells in adults is regenerative and restorative [2]. Stem cells have properties that are unique to them compared to terminally differentiated cells providing

them with specific physiological functions. The potency of stem cells, or ability to differentiate into different cell types, is what makes stem cells classifiable by their potential for differentiation and classification by origin. Totipotent or omnipotent stem cells are capable of generating embryonic tissues and differentiating into all the requisite cell lineages for an adult. Pluripotent stem cells may differentiate into all three germ layers, whereas multipotent stem cells can differentiate into only one cell germ layer. Oligopotent and unipotent stem cells are the types associated with adult organ tissues which have "qualified" into that lineage of cells and can only diversify into types within that lineage [1].Embryonic stem cells originate from the inner cell mass of blastocysts and are totipotent. Their utility is usually limited by legal and ethical issues and therefore, mesenchymal stem cells are more commonly used. Mesenchymal stem cells can be isolated from a vast array of both neonate and adult human tissues and maintain their ability to differentiate into various types of cell types, and therefore can be utilized in a clinical and research context without the ethical implications associated with embryonic stem cells [3]. Another fundamental characteristic of stem cells is their innate capacity to self-renew and expand thereby providing a continuous supply of cells to replace aged or damaged cells. This expansion during the development phase creates the appropriate growth to develop into an adult organism. After the terminal development phase is finished, continued expansion allows for repairs and restoration on a cellular level, as in the case of damaged tissue to an organ [2]. These physiological and developmental characteristics are what make stem cells a large part of the field and practice of regenerative medicine since they are able to naturally produce entire tissues and organs from only a small number of precursor cells.

The function of stem cells in contemporary regenerative medicine began in the 1950's with the inaugural bone marrow transplantation in 1956, which provided potential to treat conditions in the future with further advancement and refinement of clinical techniques, ultimately beginning the process of clinical stem cell therapies that are now available [4,5]. Stem cell therapies are now offered to treat a variety of clinical issues that extend beyond the classic origins for genetic blood diseases, and have shown considerable success when other therapies have failed. One emerging advanced use for stem cells is treating pain states and neurodegenerative diseases like Parkinson's disease and Alzheimer's disease. In the context of neurodegeneration, stem cells offer hope to replace the neurons destroyed in the disease pathogenesis, which is not possible with current technologies and methods [6].

Organ bioengineering is yet another a quickly evolving and exciting application of stem cells with both clinical and research ramifications [7] With the potential of using a patient's own cells for organ manufacturing, organ transplants without immunosuppression is a possibility [8]. The idea of not needing to be placed on an organ donor list is certainly appealing, however there is still much technology to be developed before this combination can be clinically applied on a systematic level. This field has already significantly impacted research in that organ natured tissues can be grown in lab settings to attempt to model disease

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progression. This could allow transition into treatment development with the understanding of efficacy on a cellular level and the risk of affecting patients [9,10].

At present one of the most widespread clinical applications of stem cells in regenerative medicine is the treatment of inherited blood disorders. These blood disorders can encompass one or more genetic defects that impair the function of cells from the hematopoietic stem cell lineage. Treatment involves implanting genetically normal cells derived from a healthy donor to furnish a self-renewing source of normal functioning blood cells for life. These treatments can be limited by the availability of an appropriate donor [11].

Stem cells can be obtained from various sources including adult tissues and neonatal tissues such as umbilical cord blood or placental tissue. While embryonic stem cells have been used in research in the past, because of ethical concerns these have mostly been supplanted in use by stem cells from other sources [12]. Adult oligopotent and unipotent stem cells can be isolated from tissues such as bone marrow, adipose tissue, and trabecular bone [13].Bone marrow is often the most preferred source from which to obtain non-neonatal derived stem cells, however this source involves invasive and painful collection methods.

Peripheral blood progenitor cells have been employed in an effort to avoid collecting cells from the bone marrow. This method has its own problems and risks, as well as initially being a less effective source of stem cells. Furthermore, it has been shown that stem cells are all unique in their proliferative and differentiation potential based on their origin. Cells from umbilical Wharton's jelly and adipose tissue have proliferated significantly faster than cells from bone marrow and placental origins [14,15].

A rapidly emerging stem cell source, known as induced pluripotent stem cells (iPSC's), is now finding clinical uses as well.

Induced pluripotent stem cells (iPSCs) originate from somatic cells that have been reverted back to a pluripotent state through the use of reprogramming factors; this process generally requires less invasive procedures to obtain compared with traditional foundations [16,17]. After reverted to a pluripotent state, the cells are known to undergo directed differentiation to generate desired cell types. During directed differentiation, the cells are encouraged to differentiate into a cell type that is predictable by mimicking an appropriate microenvironment and/or extracellular signals in vitro [18]. In the future, on this basis, this will set the stage for a novel form of personalized gene therapy in which the oligopotent or unipotent cells might be obtained from tissue and reverted back to a less differentiated state before being delivered to an alternate location in that same patient. In addition to that, work is being developed to merge this approach with current forms of gene editing to develop a completely new continuum of therapies [19]. The benefit of a transplantation approach for

tissue repair would minimize the likelihood of donor rejection and does not necessitate the acquisition of a suitable donor as the cells are being obtained from that intended recipient [20,21].

2. Types of stem cell

2.1 Human embryonic stem cell

Human embryonic stem cells (hESCs) are pluripotential cells derived from the inner cell mass (ICM) of a human embryo at the blastocyst stage and they are capable of proliferating in culture for extended periods of time in an undifferentiated state. Human embryonic stem cells can become cells or tissues from all 3 primary germ layers (ectoderm, mesoderm, and endoderm). ESCs have a unique potential to cure, ameliorate or treat the vast majority of diseases or conditions, but their usage is limited or banned primarily due to ethical and religious concerns, immunological intolerance to this many-faceted source of stem cells, and risk of teratoma formation [22].

2.1.1 Stem cell classification based on potency

2.1.1.1 Totipotent

A stem cell is called totipotent when that stem cell can differentiate into allcell types. Zygote cell and morula that is formed after mitotic division in zygotecell are examples of totipotent stem cell.

2.1.1.2 Pluripotent

Pluripotent stem cells are classified as a type of stem cell that can differentiate into all cells except for every cell in the body. These cells are called embryonic stem cells and cells from the three germ layers of embryonic development: endoderm, mesoderm, and ectoderm.

2.1.1.3 Multipotent

A stem cell that can differentiate into a closely related group of cells. For example, hematopoietic adult stem cells can differentiate to become red blood cells, white blood cells, or platelets.

2.1.1.4 Oligopotent

A stem cell that has the potential to develop into several cell types is called oligopotent. An example is adult stem cells that can differentiate into lymphoid or myeloid cells.

2.1.1.5 Unipotent

A stem cell that can only generate cells like itself but has the ability to self-renew is required to be a stem cell. An example is adult muscle stem cells.

2.2 Induced pluripotent stem cells

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Induced pluripotent stem cells (iPSCs) are pluripotent cells generated in the laboratory from adult somatic cells and have the biological properties of somatic cells for therapeutic uses and stem cells [23]. iPSCs are manufactured cells as they are generated through transduction and ectopic expression of the transcription factors, Oct3/4, Sox2, c-Myc, Nanog, and Klf4. With regards to unlimited proliferative capacity like ESCs and overcoming ethical and immunogenic challenges they could have a wide array of uses in many diseases (Fig. 1) [24]. iPSCs could be used widely for transplantation in individuals with various fulminating or degenerative diseases including neural diseases [25],,equivalent of retinal degeneration[26], hepatic diseases [27], producing diabetes [28], cardiovascular deficiency [29], pulmonary diseases [30],

skin diseases [31], graft-versus-host disease (GvHD) and tissue transplant [32], infertility [33], blood diseases [34], kidney defects [35], and gastro-intestinal tract disease [36], musculoskeletal system [37] along with COVID-19 [38].

2.3 Human amniotic epithelial cells

Human amniotic epithelial cells (hAECs) are a type of perinatal stem cell that can easily be obtained from the inner cell mass of the placenta. hAECs exhibit both pluripotent (capacity for differentiation into any cell type) and multi-potent (adult stem-cell-like immunomodulatory properties) behaviors with unique advantages such as simple isolation, large amounts, no ethical concerns and non-immunogenic and non-tumorigenic properties [39]. Similar to MSCs, hAECs contribute to protection and regeneration via direct cell-cell contact and paracrine mechanisms, and are being investigated for both cell based and cell-free therapeutic modalities [40]. There is a growing body of evidence to indicate hAECs have a high therapeutic potential in the area of tissue regeneration and for the treatment of immune-related and degenerative disease for example brain diseases and neurological illnesses (multiple sclerosis, Parkinson's disease, intracerebral hemorrhage, brain injury, spastic cerebral palsy), lung (COVID-19-related acute respiratory distress syndrome (ARDS), pulmonary fibrosis, bronchial fistula, bronchopulmonary dysplasia) and liver (liver fibrosis, steatohepatitis, cirrhosis) damage, corneal injury, diabetes, acute kidney injury, cardiovascular diseases, including myocardial infarction (MI) and stroke, inflammatory and autoimmune conditions (systemic inflammation, GVHD, autoimmune ovarian disease, thyroiditis; crohn's disease,systemic lupus erythematous), metabolic diseases (maple syrup urine disease), wound healing, healing of stage III pressure ulcers, delayed unions,Achilles tendon injury, and reproductive disorders (premature ovarian failure (POF), intrauterine adhesion and Asherman's syndrome) [41,42,43]. Lastly, the use of hAEC has been reported to obtain positive therapeutic outcomes before or after allogeneic transplantations [44,45].

2.4 Mesenchymal stem cells

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Mesenchymal stem cells (MSCs) are multi-potent stromal cells capable of self-renewal and differentiation into multiple cell types and have important functions in immunomodulation, tissue repair and regenerative medicine. In animal models and human clinical trials, MSCs have produced encouraging results for the repair of damaged tissue of a variety of degenerative and immune-mediated conditions [46]. MSCs can be isolated from many adult and perinatal tissues, including bone marrow, adipose, liver, spleen, synovial fluid, skin, dental pulp, gingiva, limbus, peripheral and menstrual blood, placenta, cord blood, amniotic fluid, chorion membrane, and Wharton's jelly [46,47]. MSCs are one of the most frequently utilized stem cell types and have exciting therapeutic potential in diseases and conditions due to benefits, including broad access and easy isolation, low chance of immunogenicity, high regenerative potential, and immunomodulatory capabilities. MSCs mediate their therapeutic effects through direct cell-to-cell contact, paracrine effect, and differentiation. MSCs have homing capabilities and migrate to damaged areas, and can differentiate into local components of damaged areas and secrete MSCS secretory factors that promote tissue repair such as extracellular vesicles, chemokine, cytokines, and growth factors [46,47]. Numerous clinical trials have been conducted on using MSCs to treat a variety of diseases including, those in the central nervous system (CNS)- (CNS-related injury, and CNS-related neurological disorders include: multiple sclerosis, spinal cord injury, stroke, cerebral palsy, autism spectrum disorders, amyotrophic lateral sclerosis, Parkinson's disease, Alzheimer's disease), diseases in the lung- (ARDS; acute respiratory distress syndrome, BPD; bronchopulmonary dysplasia, COPD; chronic obstructive pulmonary dysplasia, IPF, idiopathic pulmonary fibrosis, COVID 19), diabetes, skin disease (burns, wounds), premature ovarian insufficiency, cardiovascular diseases (heart failure, ischemic cardiomyopathy, non-ischemic dilated cardiomyopathy, severe ischemic heart failure, refractory angina), diseases of the digestive system, diseases of the liver, immune system diseases, (autoimmune refractory epilepsy, systemic lupus erythmatosus (SLE)), graft versus host diseases, musculoskeletal disorders, eye diseases, diseases of the kidneys etc[48,49,50,51,52,53].

2.5 Hematopoietic stem cells

Hematopoietic stem cells (HSCs) are another type of multi-potent stem cells derived from bone marrow, peripheral blood and umbilical cord blood [54]. HSCs perform all the functions of other stem cells with the capacity of self-renewal and develop into all blood lineages and immune cells, red blood cells (RBCs), white blood cells (WBCs), and platelets. Hematopoiesis is continuously maintained for our whole life process, by either symmetric or asymmetric division of HSCs. It has been hypothesized that ultimately all hematological and immunological system disorders can be treated or cured by HSC based therapies or HSC transplantation (HSCT) [54,55]. HSCs are thought to be effective through (trans)differentiation, trophic factors production and lost or damaged cell population replacement. Both autologous and allogeneic HSC transplantations are practiced to treat and

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manage both malignant and non-malignant hematological, autoimmune and inherited metabolic disorders. HSCs have been reported as showing amazing potential to differentiate into many types of non-hematopoietic cells, including endothelial precursors, brain microglia and macroglia, hepatic cells, skeletal muscle, and cardiac muscle cells [45]. Hematologic malignancies such as Hodgkin lymphoma, non-Hodgkin lymphoma (NHL), acute and chronic lymphoid leukemia (ALL, CLL), multiple myeloma, acute and chronic myeloid leukemia (AML, CML), monocytic leukemia, and myelodysplasia, have been treated clinically with HSCT (NCT03613727) [56]. Additionally, HSCT use has been clinically investigated with solid tumors, including breast, neuroblastoma, renal cell carcinoma, Ewing, Wilms' tumor, retinoblastoma, osteosarcoma, germ cell tumors, and soft tissue sarcoma (rhabdomyosarcoma).The immune-mediated disorders that have been attempted to treat with autologous HSCT include: multiple sclerosis (MS), systemic sclerosis (SSc) (also known as scleroderma), Crohn's disease, type 1 diabetes mellitus (insulin-dependent), systemic lupus erythematosus (SLE), rheumatoid arthritis, and juvenile idiopathic arthritis [57].

2.6 Neural stem cells

Neural stem cells (NSCs) are multi-potent CNS stem cells with a distinct capacity for self-renewal and differentiation into the major CNS cell types (neurons, astrocytes, and oligodendrocytes) that have an important role in cell homeostasis by substituting for loss or deficiency of endogenous neurons and glial cells [58]. The NSC-dependent therapeutic strategy is considered a promising approach to treat untreatable neurological conditions such as neurodegeneration, stroke, and brain and spinal cord injury [59]. The neurodegenerative and neuroprotective properties of NSC are probably governed by different mechanisms such as producing neurotrophic factors, modulating immune/inflammation responses, neuronal plasticity, and cell replacement [60]. This application of NSCs in clinical use presents various hurdles, ranging from ethical issues, difficulties in sourcing human NSCs or limitations of low survival, differentiation, and proliferation. However, due to emerging technologies or advancements within the stem cell domain, sufficient numbers with quality of NSCs can be obtained via iPSCs or direct transdifferentiation of somatic cells; with no limitations [60]. To test their feasibility and effectiveness, numerous clinical trials have been conducted on neurological diseases and injuries, including stroke, amyotrophic lateral sclerosis (ALS), age-related macular degeneration (AMD), cerebral palsy (CP), hypoxic-ischemic encephalopathy (HIE), Parkinson’s disease (PD), progressive multiple sclerosis (P-MS), spinal cord injury (SCI) [61].

2.7 Vascular stem/progenitor cells

Vascular stem/progenitor cells (VSPCs) such as endothelial progenitor cells, smooth muscle progenitor cells, pericytes, and MSCs, reside in blood vessels, and make diverse vascular cells needed for vascular construction, maintenance, repair, and remodeling [62]. [63]] describe the

four primary VSPC types include endothelial progenitor cells (EPCs), smooth muscle progenitor cells (SMPCs), pericytes, and MSCs, whose cells are involved in vasculogenesis and angiogenesis) EPCs are identified as a population of stem cells that have the capacity to proliferate through typical clonal proliferation and differentiate into mature endothelial cells (ECs) residing in a variety of tissues including bone marrow, spleen, blood vessel wall, lipid, and placenta [64].

EPCs show vascular regeneration function via direct and indirect paracrine actions that involve normal angiogenesis, arteriogenesis (collateral growth), and neovasculogenesis (growth of new capillaries [65]. There have been several clinical trials assessing the therapeutic potential of EPCs targeting a variety of disease processes namely; peripheral artery disease, coronary artery disease, dilated cardiomyopathy, ischemic stroke, refractory angina, atherosclerosis, critical limb ischemia, pulmonary arterial hypertension, diabetic foot, liver cirrhosis, lymphedema, erectile dysfunction, and bone defects [66].

SMPCs can undergo differentiation into mature vascular smooth muscle cells (SMCs), which are important to contract the blood vessels and regulate angiotasis and blood pressure [64]. The predominant sources of SMPCs are the bone marrow, blood, vessel walls, skeletal muscle, kidney and extravascular matrix [67]. SMPCs can exhibit multiple phenotypes induced by different conditions, mechanical forces, and growth factor stimulations such as synthetic or proliferative, inflammatory, osteogenic, endocytic, and phenotypes [68].

Pericytes are multi-functional perivascular cells found in the basement membrane that exhibit stem cell characteristics due to their ability to differentiate into a number of different cell types [69]. They have been shown to function in a number of ways, including differentiate into different cell types, contribute to angiogenesis, maintain blood vessel structural integrity, play a role in the inflammatory response (cytokines and chemokines release) and debris phagocytosis [69,70]. Pericytes have been proposed as an ideal therapeutic cell type, notably for use in ischemic and vascular dysfunction-based diseases, because of their versatile and multi-potent abilities [69].

2.8 Epidermal stem cells

Epidermal stem cells (EpiSCs) are primarily located in the epidermis, which has a rich blood supply in both the basal layer and the hair follicle bulge [71]. As a cell population with infinite proliferative potential, EpiSCs are constantly producing functional cells to heal damaged or dead cells for skin regeneration, metabolism, and wound healing. EpiSCs possessing potential anti-aging [72] properties were developed to treat burns, congenital skin damage, chronic wounds, epidermolysis bullosa, vitiligo, limbal stem cell deficiency, alopecia, and urethra regeneration.

Table 1: Advantages and disadvantages of different types of stem cell therapy applications

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Types of stem cells	Advantages	Disadvantages	References
Human embryonic stem cell	Development within cells of all three germ layers.	Concerns regarding ethics, possibility of immune rejection, Risk of developing teratomas.	22
Induced pluripotent stem cells	There will be ability to directly obtain from the patients own cells, for the reduction of the risk of rejection, ideal for disease modeling and drug discovery.	Possibility of genetic mutation, risk of teratomas.	23
Mesenchymal stem cells	Isolated from virtually all tissues, Easy to isolate, Capacity to differentiate into numerous cell types, Immunomodulatory effect.	Challenging to cultivate for long durations in culture.	29
Hematopoietic stem cells	Broad range of contexts, ability to differentiate to all blood cells, potential for autologous and allogeneic transplantation.	Limited access, donor limitations, difficulties in collection techniques.	56
Neural stem cells	Development into glial cells and neurons.	Limited accessibility, risk for tumor development.	39
Vascular stem/progenitor cells	Differentiation into smooth muscle and endothelial cells, which holds promise for addressing the difficulties in vascular regeneration and repair.	Difficult to isolate and grow in vitro, limited potential for differentiation.	62
Epidermal stem cells	Development into additional epidermal cells and keratinocytes.	Limited availability,tumor development risk, and restricted replication capacity.	71

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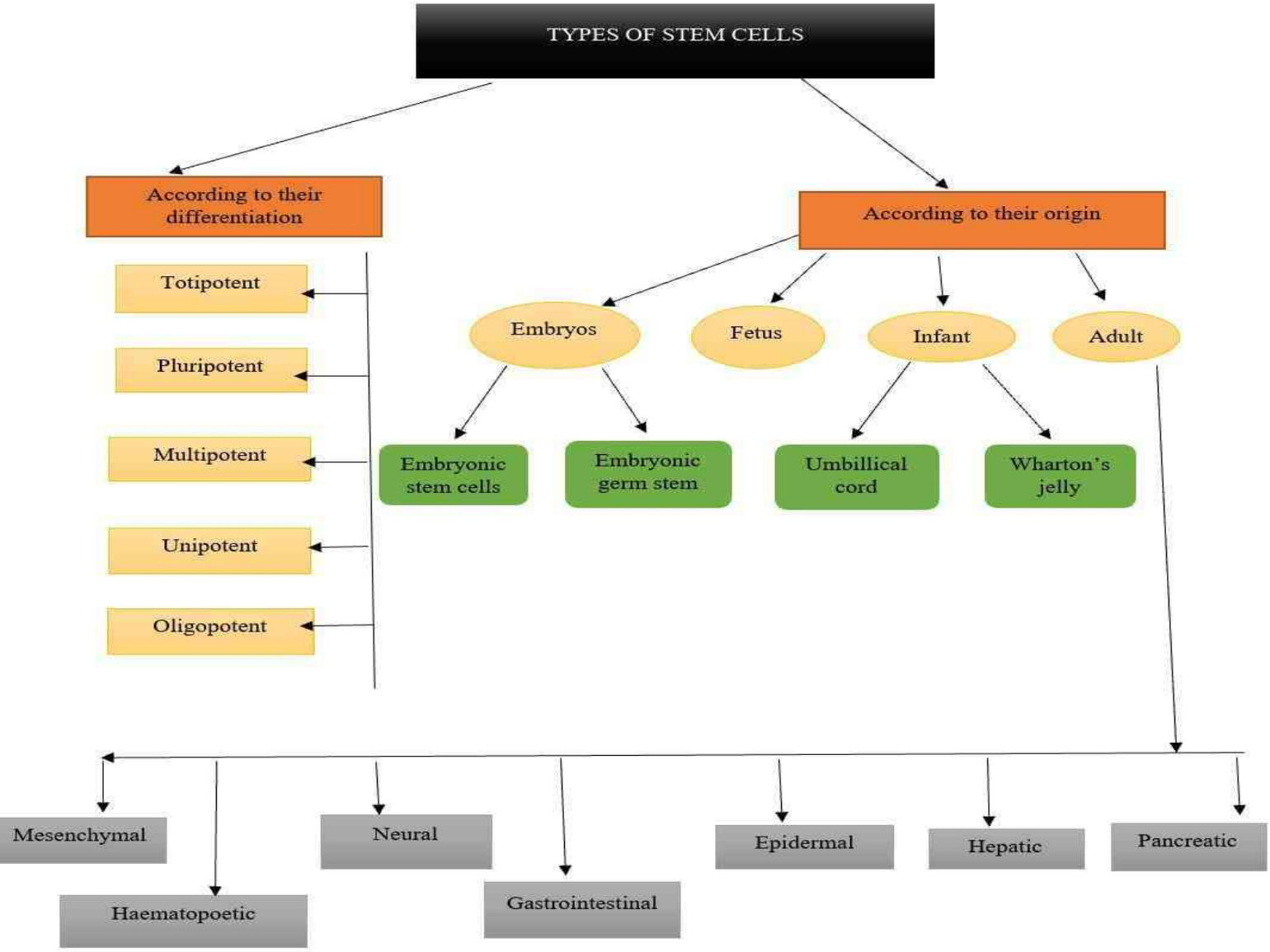

Fig. 1 : Stem cell classification and their clinical applications

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Future prospective:

Stem cell research continues to carry tremendous implications and opportunities for regenerative medicine, tissue engineering, and personalized therapy. As we progress through the capabilities of biotechnology and genetic engineering, stem cells should open vast potential for the treatment of degenerative diseases, such as Parkinson, diabetes, spinal cord injury, or cardiac disorders.

In addition to the established stem cell model, the development of induced pluripotent stem cells (iPSCs) will offer new and diverse possibilities of obtaining patient-specific cells for treating diseases while improving immune acceptance and ethical validity. In addition, incorporating stem cell technology into the CRISPR gene editing platform should result in safer and more precise therapies by allowing us to correct genetic defects prior to transplanting corrected stem cells into patients.

Future possibilities of 3D bioprinting and organ regeneration using stem cells would allow for the production of functional tissues or whole organs for transplant. Stem cells will also continue to provide vital contributions toward drug testing, disease modeling, and personalized medicine development to create safer and more effective methods for patients to traditionally administered medications.

Conclusion:

Stem cells are among the most exciting fields of modern biological and medical research because of their remarkable capacity for self-renewal and for differentiation into specialized cell types. Stem cells play an essential role in growth, development and repair of tissue. In terms of origin and potential, stem cells can be classified broadly into four types: embryonic stem cells, adult (somatic) stem cells, induced pluripotent stem cells (iPSCs), and perinatal stem cells. While all types have their own strengths and weaknesses — embryonic stem cells are pluripotent, and can potentially form almost any cell type, adult stem cells are generally multipotent, and can contribute to the maintenance and repair of specific tissues. iPSCs address some of the ethical and practical challenges associated with embryonic stem cells, as iPSCs are generated by reprogramming adult cells into a 'stem' like state, which opens a new and personalized chapter for therapeutic applications.

Acknowledgement

The authors would like to express their sincere gratitude to Rapture Biotech, Dehradun, and the entire team for their invaluable support and guidance throughout the preparation of this review. We also gratefully acknowledge the financial assistance provided by Rapture Biotech, Dehradun, which made this work possible.

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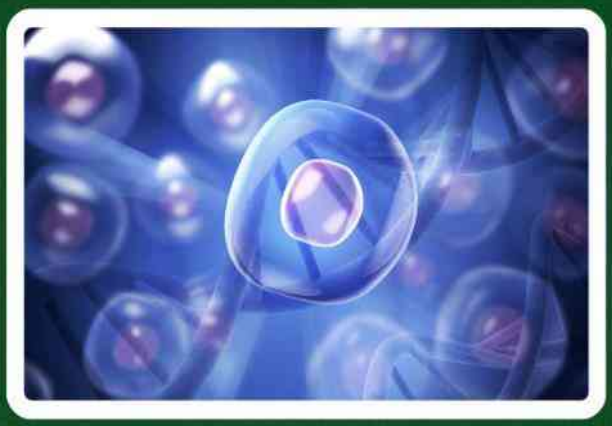

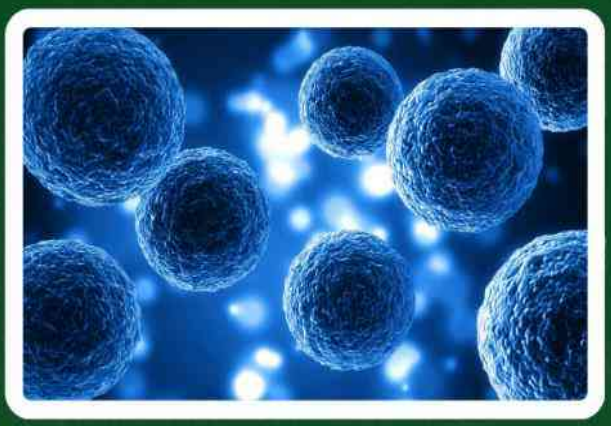

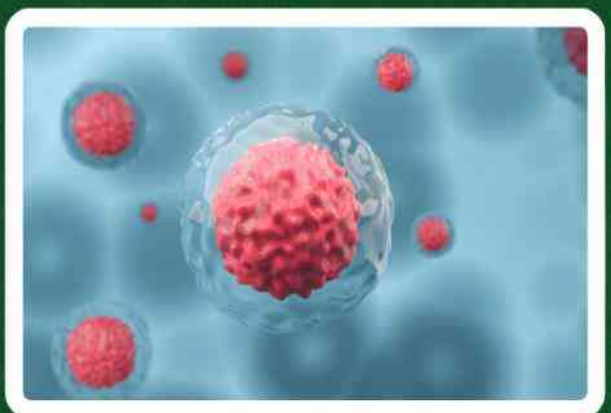

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