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RESEARCH ARTICLE

STEM CELLS IN REGENERATIVE MEDICINE AND THERAPEUTIC POTENTIAL

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Abstract

Stem cells are a form of undifferentiated cell that has the potential to proliferate (self-renew), emerge from a single cell (clonal), and develop into different types of cells and tissues (potent). There are several sources of stem cells of varied potency.Although stem cell research has grown at an exponential rate, medicinal applications have moved considerably more slowly. The study is currently focused on understanding embryonic, adult, and inducible pluripotent stem cells. Adult stem cell research translation has demonstrated a decisive benefit that is larger than the present standard of care in the field of cardiovascular medicine. The future of stem cell research and therapy will continue to open up new diagnostic, therapeutic, and tissue regeneration pathways.In cellular treatment, stem cells can be employed to repair damaged cells or rebuild tissues. Furthermore, stem cells have advanced our understanding of development as well as disease causation. Cell lines that are particular to a disease can also be grown and employed in medication research.Despite considerable improvements in stem cell biology, ethical concerns about embryonic stem cells, tumour growth, and rejection restrict their applicability. However, several of these constraints are being overcome, which might lead to significant advancements in illness management. This article provides an introduction to the world of stem cells, including its definition, origin, and categorization, as well as their uses in regenerative medicine.

Introduction:-

Stem cells are undifferentiated cells found in the embryonic, foetal, and adult phases of life that give rise to differentiated cells that serve as the building blocks of tissue and organs. Tissue-specific stem cells are found in differentiated organs in the postnatal and adult phases of development and play an important role in organ repair after damage. The following are the primary properties of stem cells: (a) self-renewal (the ability to multiply widely), (b) clonality (typically emerging from a single cell), and (c) potency (the ability to differentiate into diverse cell types).These characteristics may differ amongst stem cells. For example, embryonic stem cells (ESCs) produced from the blastocyst have more self-renewal and potency, but adult tissue stem cells have restricted self-renewal since they do not multiply widely and can only develop into tissue-specific cells. The human body begins with the zygote and blastocyst, from which ESCs are produced to form the germ layers endoderm, mesoderm, and ectoderm. The germ layers give rise to certain organs. Some progenitor cells that have contributed to organ creation do not differentiate terminally and are preserved as tissue stem cells, which can be found in bone marrow, bone, blood, muscle, liver, brain, adipose tissue, skin, and the gastrointestinal system.Tissue stem cells are also referred to as

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progenitor cells since they give rise to terminally differentiated and specialised cells of the tissue or organ. These cells may be latent inside tissue, but they multiply upon damage and healing. The dynamics of tissue stem cells or progenitor cells vary by tissue; for example, stem cells regularly proliferate to supplement cells during normal turnover or injury in bone marrow, liver, lung, and gut, whereas they proliferate to replace damaged cells following injury in the pancreas, heart, or nervous system.

Stem cells have become a prominent focus for translational medicine during the last decade. These cell types have two characteristics that make them particularly appealing for regenerative therapy. A stem cell is a cell type that has the ability to self-renew while still retaining the ability to differentiate into several cell types. Stem cells are so distinct from progenitor cells, which may develop into mature cell types but are incapable of self-renewal, and somatic cells, which can proliferate but cannot differentiate. By combining the qualities of self-renewal and differentiation, stem cells may be able to produce an endless number of cell types of therapeutic significance.Stem cells are also becoming more appealing for fundamental research since they can be grown in vitro while retaining their natural characteristics, allowing basic investigations that would otherwise be difficult using primary tissue cultures or biopsy material. As a result, ESCs (embryonic stem cells) have become a reference model for studying essential molecular pathways that drive cell fate decision and organ development. Importantly, stem cells are currently present in clinics, particularly HSCs (haematopoietic stem cells), which have been effectively employed in bone marrow transplants for more than 40 years to treat various blood illnesses such as leukaemia. Future therapeutic uses of stem cells include a wide range of degenerative disorders (diseases in which one cell type or part of an organ fails) that might be addressed with stem-cell-based treatment. This includes major metabolic diseases such as T1D (Type 1 diabetes), caused by the destruction of insulin-secreting β-cells, diverse brain and myelin disorders in which specific neural cells are targeted such as MS (multiple sclerosis), PD (Parkinson's disease) or HD (Huntington's disease), heart disease, where some cardiac cells need to be replaced upon myocardial infarction, and genetic diseases like myopathy, where a specific subtype of cells are not functional. The range of ailments that stem cells have the potential to treat is enormous. We shall study the features of each stem cell type and evaluate their benefits for therapeutic use by giving pertinent instances in this review. Furthermore, we shall describe their disadvantages as well as the essential improvement for future clinical applications.

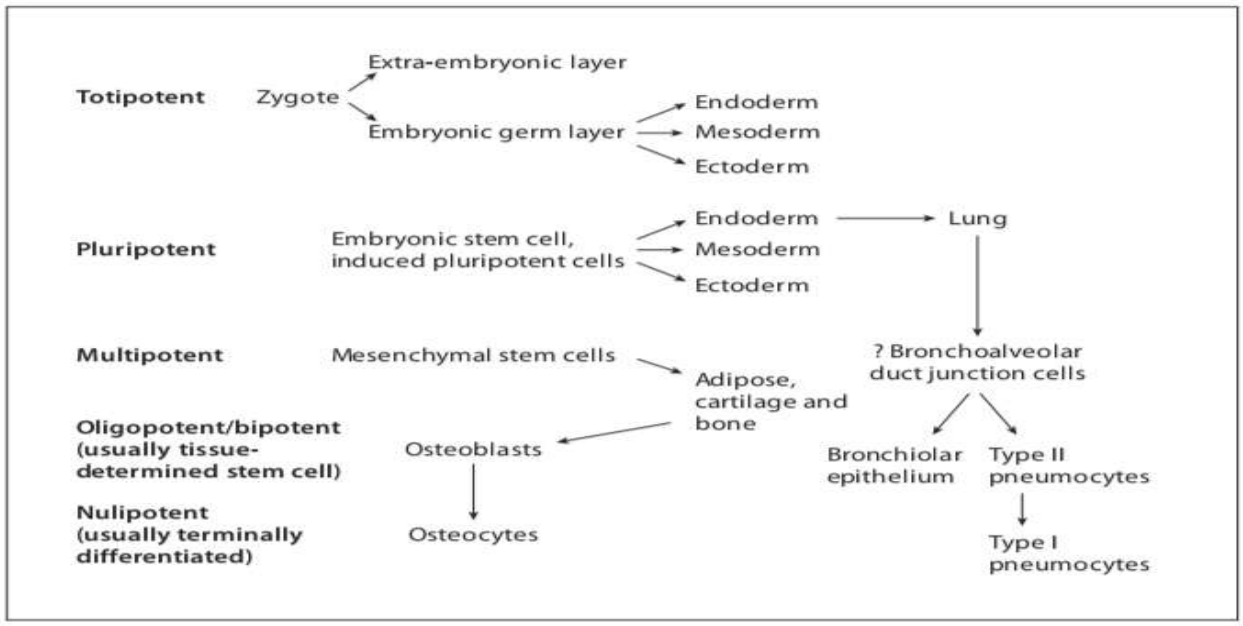

Figure 1:- The stem cell hierarchy.

Totipotent cells differentiate into embryonic and extra-embryonic tissue. Pluripotent cells develop cells from all three germ layers, whereas multipotent cells generate cells from only one germ layer. Bronchoalveolar duct junction cells in the lung have the potential to be multipotent, whereas type II pneumocytes are oligopotent and develop into type I alveolar pneumocytes.

Classification Of Stem Cells:
One of the two fundamental properties of stem cells is their ability to differentiate, which differs based on their origin and derivation. All stem cells are classified into five types based on their differentiation potential: totipotent or omnipotent, pluripotent, multipotent, oligopotent, and unipotent.

Totipotent Stem Cells:
Totipotent or omnipotent cells are the most undifferentiated cells observed in the early stages of development. A fertilised egg and the cells of the first two divisions are totipotent cells because they develop into embryonic and extraembryonic tissues, resulting in the formation of the embryo and the placenta.

Pluripotent Stem Cells:
Pluripotent stem cells can differentiate into cells from the three germ layers - ectoderm, endoderm, and mesoderm - from which all tissues and organs develop. Pluripotent stem cells, or ESCs, were originally formed from the blastocyst's inner cell mass.

Multipotent stem cells:
Most tissues include multipotent stem cells, which develop into cells from a single germ layer. The most well-known multipotent cell is mesenchymal stem cells (MSCs). They can be generated from bone marrow, adipose tissue, bone, Wharton's jelly, umbilical cord blood, and peripheral blood. MSCs attach to cell culture plates and are identified by surface cell markers. These cells have the ability to develop into mesoderm-derived tissue such adipose tissue, bone, cartilage, and muscle.

Oligopotent Stem Cells
Oligopotent stem cells have the ability to self-renew and produce two or more lineages within a given tissue; for example, oligopotent stem cells have been found on the pig's ocular surface, including the cornea, and have been shown to generate separate colonies of corneal and conjunctival cells. Because they may develop into both myeloid and lymphoid lineages, hematopoietic stem cells are an example of oligopotent stem cells. According to research, bronchoalveolar duct junction cells in the lung may give birth to bronchiolar epithelium and alveolar epithelium.

Unipotent stem cells:
Unipotent stem cells can only self-renew and develop into one kind of cell and create a single lineage, such as muscle stem cells, which give birth to adult muscle cells and no other cells. Type II pneumocytes of the alveoli of the lung give birth to type I pneumocytes.

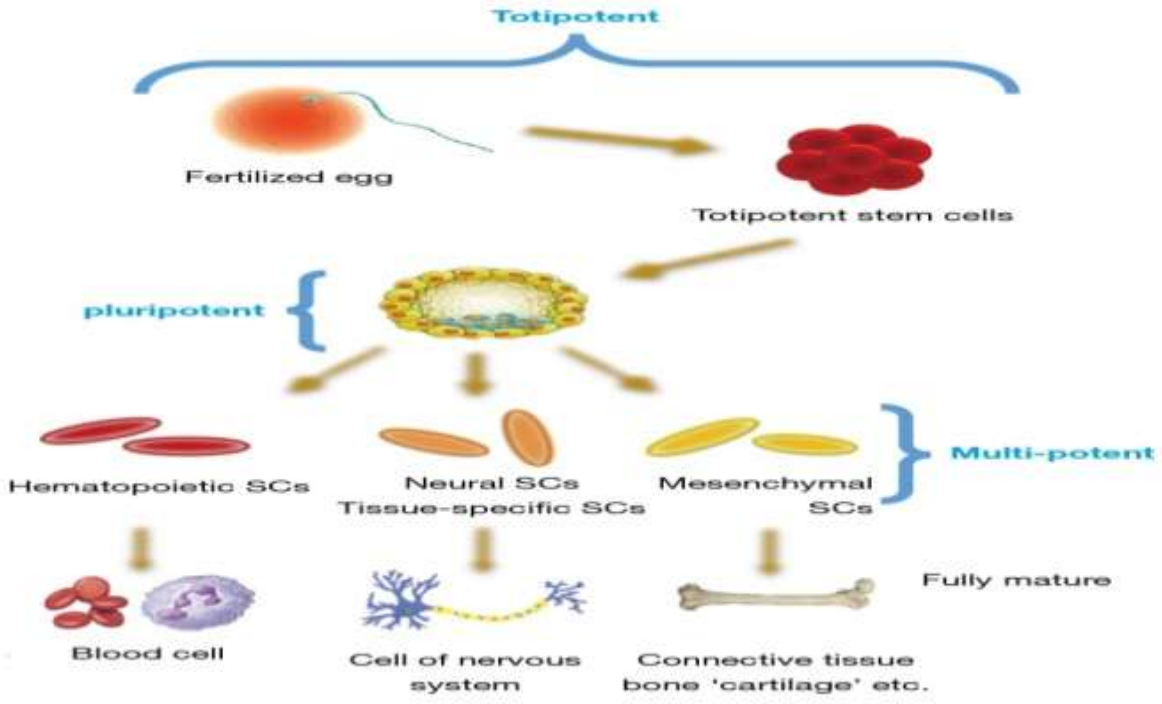

Figure 2:- A summary of stem cell taxonomy.

Totipotency refers to the ability of embryonic stem cells (ESCs) to generate all three germ layers as well as extra-embryonic tissues or placental cells following fertilisation. Pluripotency: These more specialised blastocyst cells can self-renew and develop into the three germ layers and numerous lineages, but they do not create extra-embryonic tissues or placental cells. Adult stem cells, also known as somatic stem cells, are undifferentiated cells present in postnatal organs. These specialised cells are multipotent; they have a restricted ability to self-renew and are devoted.

Sources Of Stem Cells:

Stem cells are divided into four major categories based on their origin: embryonic stem cells, foetal stem cells, umbilical cord stem cells, and adult stem cells. Some researchers believe that adult and foetal stem cells evolved from embryonic stem cells, and that the few stem cells found in adult organs are the remnants of original embryonic stem cells that either gave up in the race to differentiate into developing organs or remained in cell niches in the organs that are called upon for repair during tissue injury.

Embryonic Stem Cells:

Embryonic stem cells are a kind of cell found in the inner cell mass of an embryo at a very early stage of development known as a blastocyst. The blastocyst stage of embryonic development occurs within 4-5 days following fertilisation, and the number of cells at that time is around 50-150. These cells are pluripotent, which means they can grow and differentiate into a variety of cell types (about 250 kinds) while proliferating. These, however, do not contribute to extraembryonic cells such as the placenta. Embryonic stem cells exist within the embryo, which splits and differentiates into germ layers as it matures. These cells are increasingly being grown because they can be intentionally cultured to generate cells of various sorts.Embryonic stem cell cultivation is essential because it provides a fresh source for in vitro regenerative medicine, genetic disorders, and toxicological testing. In mammals, embryonic germ cells in the gonadal area function similarly to embryonic stem cells. These cells, also known as primordial cells, subsequently differentiate and divide to generate male and female gametes.Pluripotent embryonic stem cells may differentiate into a variety of cell types in vitro, including endodermal cells. Understanding how ES cells develop should give solutions for reprogramming stem cells from adult organs.

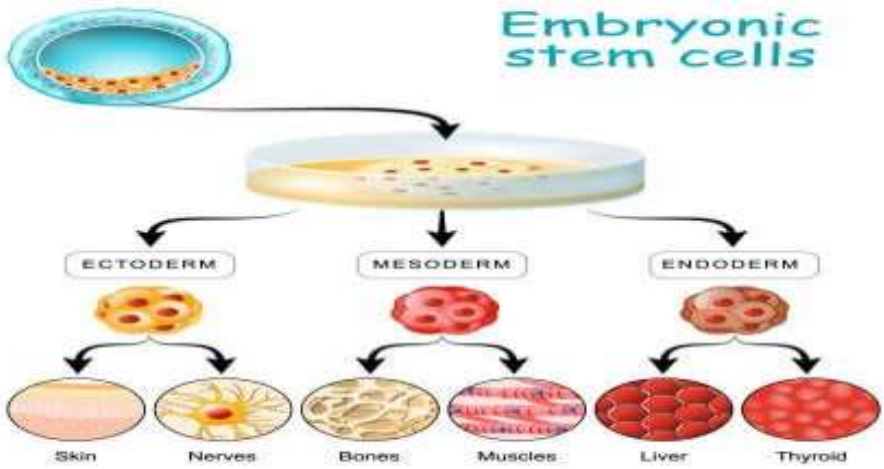

Figure 3:- Embryonic stem cells.

Fetal Stem Cells:
Foetal stem cells are basic cell types seen in foetal tissues. Abortuses have been shown to include neural crest stem cells, foetal hematopoietic stem cells, and pancreatic islet progenitors. Foetal neural stem cells present in the foetal brain have been demonstrated to develop into neurons as well as glial cells. Foetal blood, placenta, and umbilical cord have a high concentration of foetal hematopoietic stem cells.

Umbilical Cord Stem Cells:
Umbilical cord blood contains circulating stem cells, and its cellular components appear to be unique from those of bone marrow and adult peripheral blood. Recently, the properties of hematopoietic stem cells in umbilical cord blood have been defined. Umbilical cord blood hematopoietic stem cells have a frequency that equals or exceeds that of bone marrow, and they are known to create huge colonies in vitro, have variable growth factor needs, have long telomeres, and can be increased in long term culture. Cord blood has a lower graft versus host reaction than bone marrow, which might be related to increased interleukin-10 levels generated by the cells and/or less production of beta-2-microglobulin.

The ability of cord blood stem cells to develop into neurons and liver cells has demonstrated their multipotency. While much of the focus has been on cord blood stem cells and their preservation for eventual use, there have been indications that umbilical cord matrix cells contain potentially valuable stem cells. This matrix, known as Wharton's jelly, has been used to isolate mesenchymal stem cells. These cells have been propagated for extended population doubling times, display conventional stem cell markers including c-kit, and can be coaxed to develop in vitro into neurons.

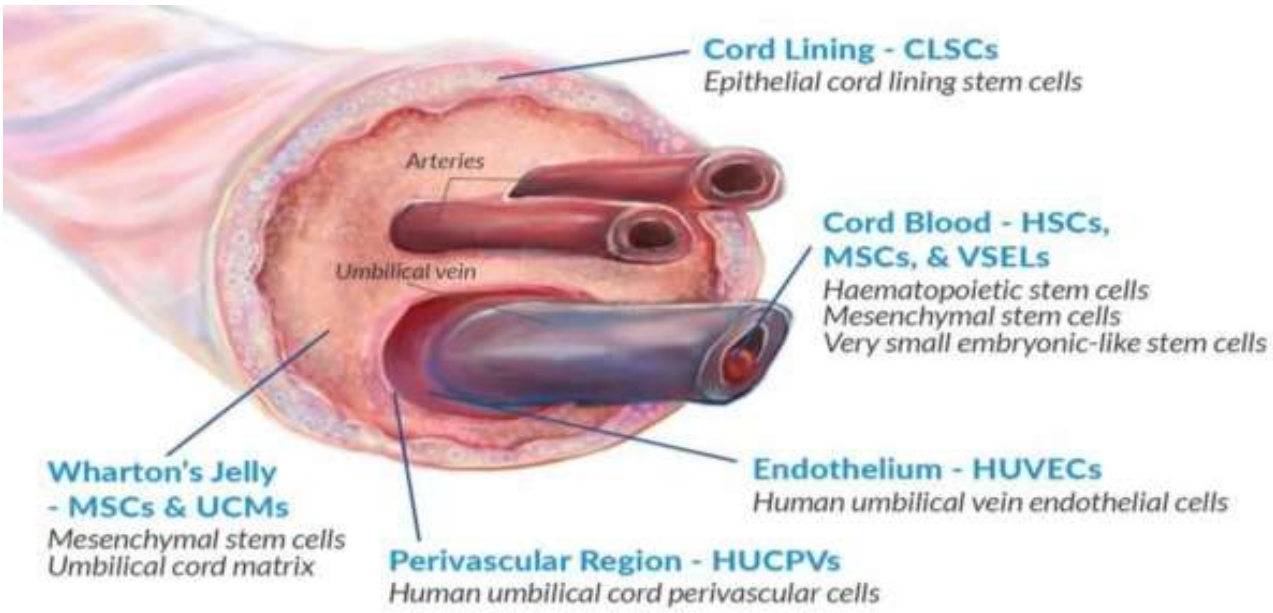

Figure 4:- Umbilical cord blood stem cells.

Adult Stem Cells:
Adult stem cells are undifferentiated cells that live in a tissue or organ alongside developed cells. They have the ability to regenerate and differentiate into multiple cell types. Adult stem cells, unlike embryonic stem cells, are confined to developing into discrete cell types of their tissue of origin, and are hence multipotent or unipotent stem cells. Adult stem cells' principal functions are to maintain and repair the tissue in which they dwell. Adult stem cells are uncommon and often tiny in quantity, although they can be discovered in a variety of adult organs.

Hematopoietic stem cells (Bone marrow cells and Peripheral blood):
Hematopoietic stem cells (HSCs) are uncommon cells of mesodermal origin seen in adult mammalian bone marrow that sit atop a hierarchy of progenitors that grow increasingly confined to multiple or single lineages. True HSCs stay primarily dormant in adult tissue and give birth to short-term HSCs with limited self-renewal potential (6-8 weeks). Short-term HSCs can become either common myeloid progenitor (CMP) or common lymphoid progenitor (CLP) when they exit the undifferentiated self-renewing condition. Erythrocytes, monocytes and macrophages, neutrophils, basophils, eosinophils, megakaryocytes/platelets, and dendritic cells are all derived from the myeloid lineage. Osteoclasts are also produced from monocyte/neutrophil hemopoietic cells. T- and B-lymphocytes, as well as Natural Killer cells, are produced by the lymphoid lineage.Because they are multipotent and can develop into several cell types both in vitro and in vivo, bone marrow stem cells may be more flexible and adaptable than previously thought.

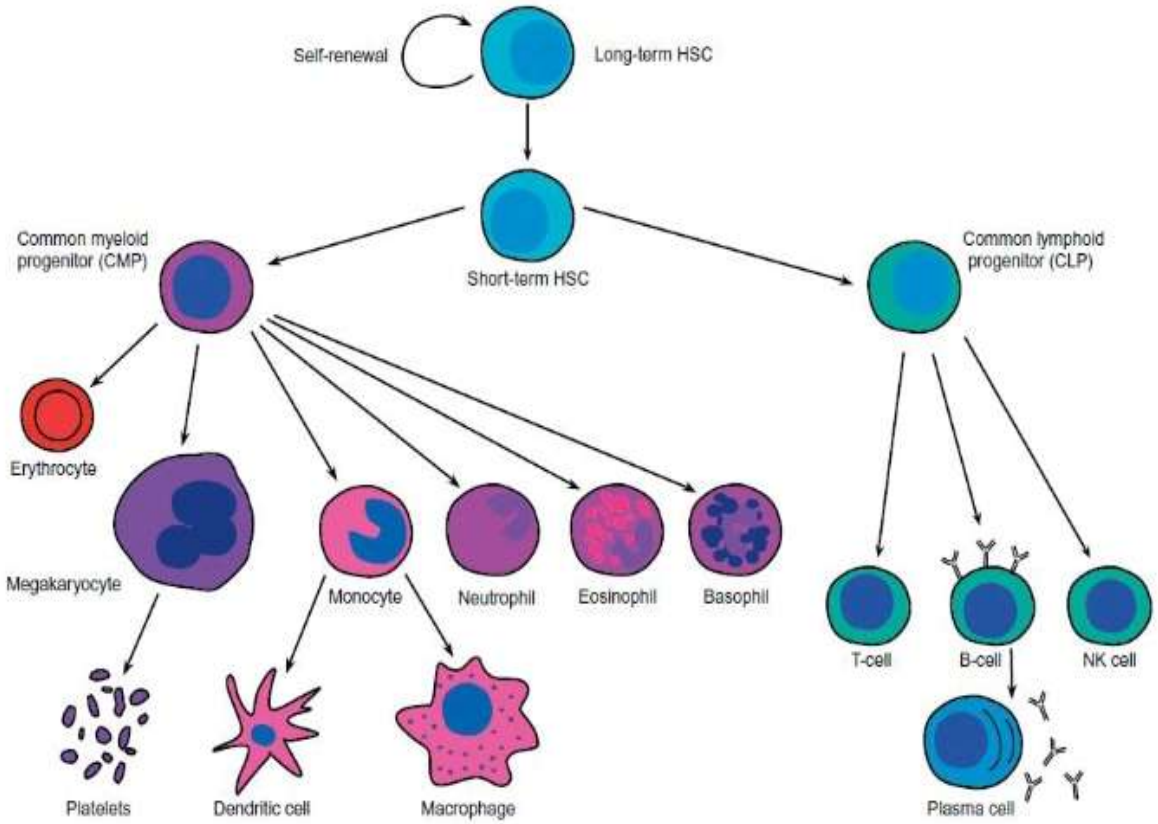

Figure 5:- Differentiation of hematopoietic stem cell.

Mesenchymal stem cells:
Mesenchymal stem cells (MSCs) are discovered in the nonhematopoietic bone marrow stroma postnatally. The stromal tissue of bone marrow is made up of a diverse population of cells, including reticular cells, adipocytes, osteogenic cells, smooth muscle cells, endothelial cells, and macrophages. In a stable state or in reaction to damage, stromal tissue turnover and repair occur with the participation of a population of stem cells located in the stroma. MSCs can be produced from periosteum, fat, and skin in addition to bone marrow stroma. MSCs are multipotent cells that can develop into cartilage, bone, muscle, tendon, ligament, and fat.Recent research suggests that there is a rare pluripotent cell among MSC cells that can give birth to both mesodermal and endodermal tissues. The authors refer to this as a Multipotent Adult Progenitor Cell.

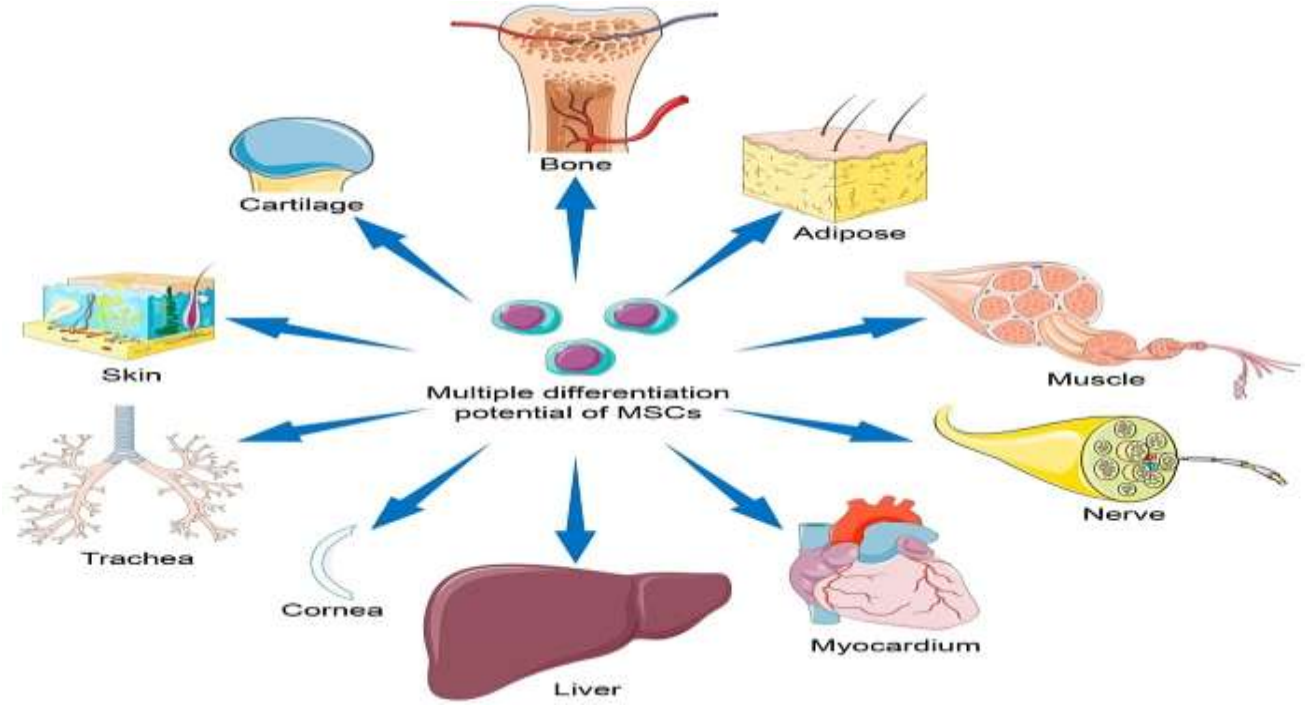

Figure 6:- Differentiation of Mesenchymal stem cell.

Neuronal stem cells:

The neural stem cells, also known as neural progenitor cells, are found in two separate regions of the brain. In lateral ventricles, one population is found in the ventricular-subventricular zone. According to the mouse model, this population is primarily responsible for the regeneration of neurons in the olfactory bulb. The second population is located near the hippocampus's interface between the hilus and dentate gyrus.Endogenous NSCs appear to be able to create virtually exclusively neurons in vivo, although a single NSC can generate neurons, astrocytes, and oligodendrocytes in vitro. NSCs are multipotent progenitor cells that can self-renew.Although the subventricular zone B cells appear to be the only genuine NSCs at the moment, research is still being done to identify other self-renewing, multipotent NSCs, and there is contradicting information in the literature. While some studies have shown that the SVZ astrocyte is the NSC, others have suggested that the SVZ NSC is an ependymal cell. It was also shown that SVZ astrocytes were able to form multipotent neurospheres that produced both neurons and glia, in contrast to ependymal cells, which were unipotent and gave birth to just glial cells. A stem cell niche has been proposed for the adult mammalian brain, and the ultimate fate of the NSC is tightly regulated by external factors.

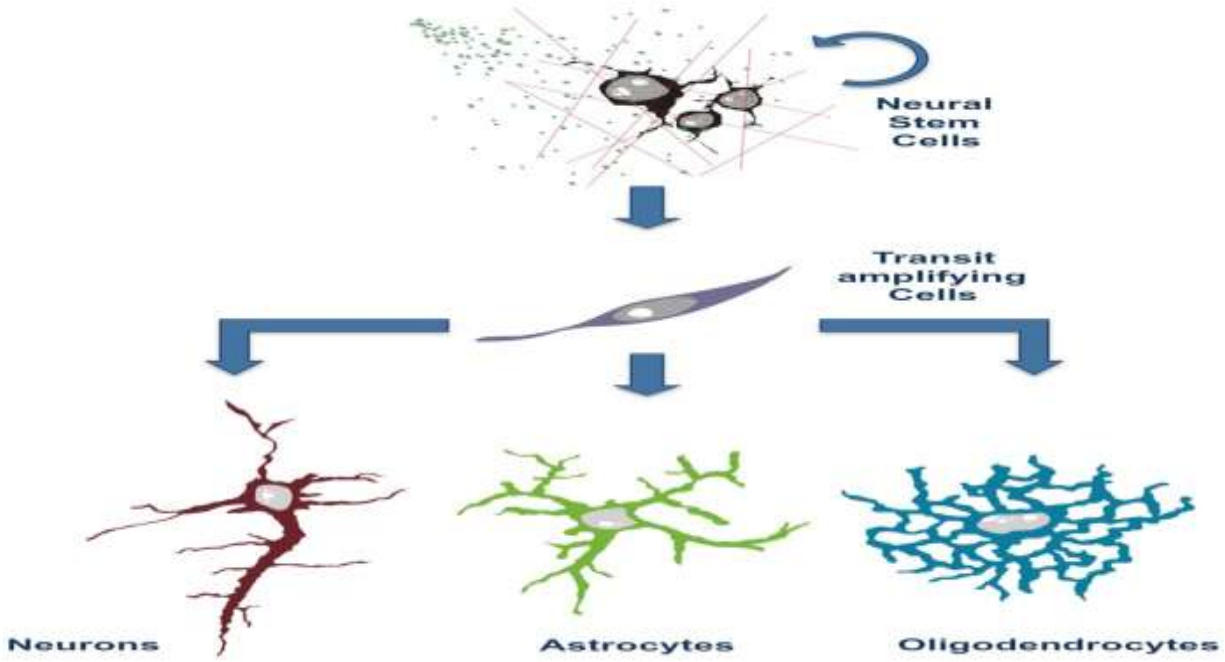

Figure 7:- Neuronal stem cell.

Skin and hair epidermal stem cells

The outer epidermis and underlying dermis make up the human skin.The epidermis is also made up of sebum and hair glands. The keratinocyte, an epithelial cell that divides and is found in the basal layer of the epidermis, is the most significant kind of cell in the epidermis. Once these cells have left the basal layer, they go through terminal differentiation, resulting in a highly specialised cell known as a squame. This squame then either forms the hair shaft or the lipid-filled sebocyte, which together form the outer skin layer that protects the underlying living skin cells from the harsh environment. The epidermis contains stem cells near the base of the hair follicle, and these cells' capacity for self-renewal enables the regrowth of skin and hair cells.Throughout adulthood, fresh keratinocytes are continually created to replace lost hairs and squames from the outer skin layers. The "transient amplifying cell" is an intermediary cell formed during the differentiation of stem cells that gives rise to more differentiated cell types including keratinocytes and sebocytes.

Induced Pluripotent Stem Cells:

Due to the limits of adult stem cells, new pluripotent cells known as induced pluripotent cells were produced from adult cells through the process of gene reprogramming. When adult cells and embryonic stem cells are cultivated together, new cells with characteristics of stem cells are created. These new cells are known as induced pluripotent stem cells. Other somatic cells can occasionally also be reprogrammed to develop pluripotency. Similar to embryonic stem cells, induced pluripotent stem cells have the ability to be encouraged to develop into several cell types. They differ from embryonic stem cells, nevertheless, in terms of the degree of gene expression and the state of the cells' chromatin.

These cells are very important because they may be employed in therapeutic treatment, which will allow doctors to create cells for almost every organ in the body specifically for each patient. Additionally, they stop the use of additional embryonic stem cells, which might raise ethical concerns. By creating induced pluripotent stem cells from the disease's adult or somatic cells, it also aids in the investigation of novel genetic illnesses. In order to transplant cells during severe heart and eye disorders, induced stem cells from the heart and eyes can be utilised.

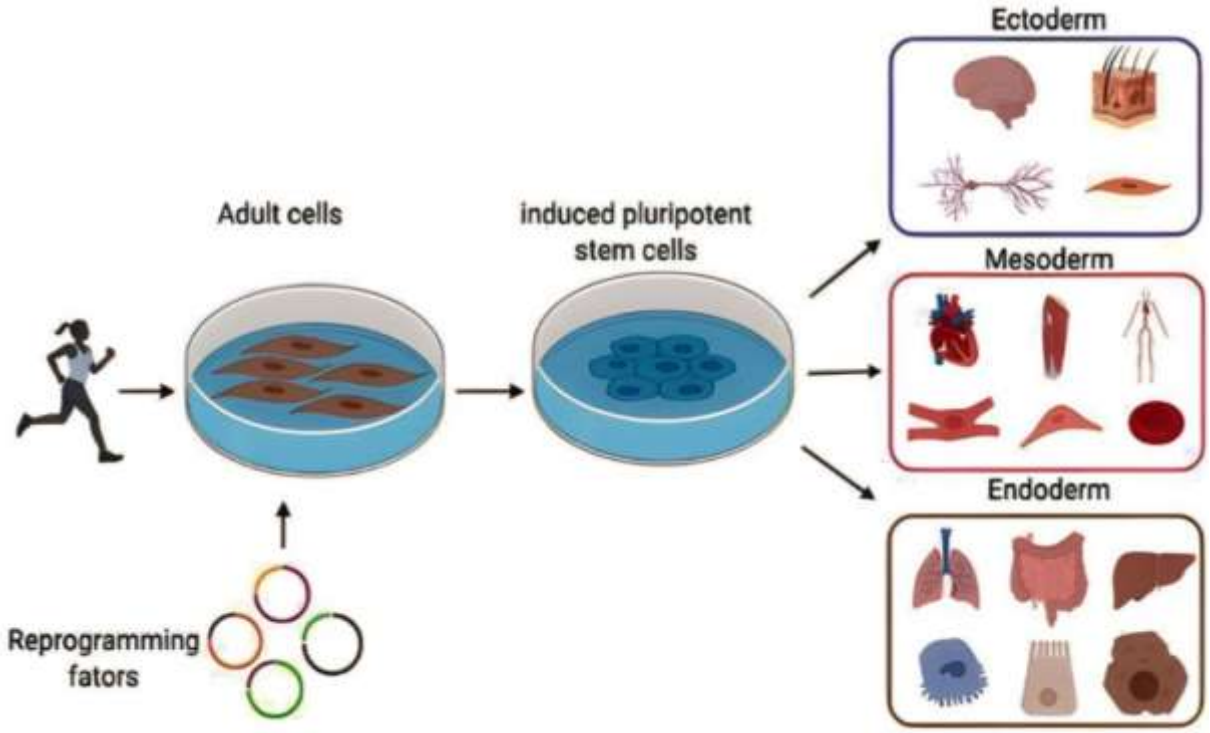

Figure 8:- Induced Pluripotent stem cells.

Clinical Use Of Stem Cells And Regenerative Medicine:

Due to their extensive usage in fundamental research and the prospects they present for the creation of novel treatment approaches in clinical practise, stem cells have a significant impact on modern medicine. They are useful in a variety of biological and medicinal applications due to their properties. For instance, ESCs are superb instruments for comprehending organogenesis and human development. It will be crucial to use stem cells, such iPSCs, in the search for innovative, secure treatments.Additionally, stem cells may be able to restore organs or even replace damaged tissue. With the use of iPSCs, it is possible to create disease-specific human models that will help researchers better understand the pathogenetic pathways underlying human diseases and enable advancements in cell-based therapies for degenerative diseases.

Nearly every degenerative condition has been the subject of cell therapy research. Preclinical research and clinical trials have shown promising results in a number of illnesses, including diabetes, chronic myeloid leukaemia, cirrhosis, pulmonary fibrosis, Crohn's disease, heart failure, and neurological disorders. The immunomodulatory properties of stem cells have also been found to be useful in a number of conditions where inflammation is the predominant symptom.Regenerative medicine and cell treatment both present challenges. Although MSCs, placental tissue, and iPSCs get around the issue, immune rejection is still a concern. It is still unclear how stem cells, in particular iPSCs, maintain their genetic stability. The development of tumours can be caused by genetic instability. While naturally occurring teratomas and associated tumours may form through the use of ESCs or iPSCs in therapeutic cell transplantation, the flexibility and self-renewal that characterise stem cells may promote carcinogenesis in the host tissue. Finally, a number of ethical issues have been brought forward, mostly in relation to the usage of ESCs. These include the moral dilemmas surrounding the destruction of an embryo to produce ESCs. Now, iPSCs may be able to get around this.

Stem Cell Therapy Potential And Application:

One use for stem cells that encourages the repair of damaged and dysfunctional tissues and their derivatives is stem cell therapy, sometimes referred to as regenerative medicine. Because some of these cells may unintentionally lead to the production of uncommon solid tumours known as teratomas, pluripotent stem cells are not frequently employed therapeutically in people. However, it has been applied to cure spinal wounds and blindness in animals.

On the other hand, multipotent stem cells taken from bone marrow have been employed to treat leukaemia, myeloma, and lymphoma since the 1960s. The potential of mesenchymal stem cells to regenerate whole joints may also help treat other illnesses.

Pluripotent cells should not be used in place of multipotent stem cells as the latter would result in the immune system of the recipient's body rejecting the transplant. Therefore, stem cell therapy is a great way to enhance the facilities and methods for treating a variety of chronic illnesses. Before their full therapeutic promise can be realised, however, much more research on their biology, manipulation, and safety is still required.

Tissue regeneration:
The use of stem cells for tissue regeneration is perhaps the most significant. A person in need of a new kidney, for instance, formerly had to wait for a donor before having a transplant.

There is a lack of organ donors, but scientists may be able to generate a certain tissue type or organ using stem cells by guiding them to develop in a particular way. As an illustration, physicians have previously created new skin tissue using stem cells that are found just below the skin's surface. By grafting this tissue onto the injured skin, they may then treat a serious burn or other lesion and new skin will regrow.

Treatment for cardiovascular disease:
A group of scientists from Massachusetts General Hospital revealed in PNAS Early Edition in 2013 that they have used human stem cells to produce blood arteries in laboratory animals. Networks of blood-perfused arteries had developed two weeks after the stem cells had been implanted. These generated blood arteries had the same high calibre as the surrounding natural ones. The scientists believed that this kind of approach will someday aid in the treatment of vascular and cardiovascular problems in humans.

Brain disease treatment:
In the future, doctors may be able to cure brain disorders like Parkinson's and Alzheimer's using replacement cells and tissues. For instance, Parkinson's disease causes uncontrollable muscular movements as a result of brain cell destruction. Stem cells might be used by scientists to repair the damaged brain tissue. The specialised brain cells that inhibit the uncontrolled muscular movements may return as a result. Treatments are hopeful since embryonic stem cells have already been tested to be differentiated into these sorts of cells.

Cell deficiency therapy:
One day, researchers hope to be able to create healthy heart cells in a lab that they can then implant into patients with heart conditions. By repopulating the heart with healthy tissue, these new cells could be able to treat heart damage.

Similar to this, type I diabetics may get pancreatic cells to replace any lost or damaged insulin-producing cells caused by their own immune systems. The only viable treatment at this time is a pancreatic transplant, although there are not many pancreases available for transplant.

Treatments for blood diseases:
Adult hematopoietic stem cells are now often used by physicians to treat illnesses including leukaemia, sickle cell disease, and other immunodeficiency issues.

All blood cell types, including the oxygen-carrying red blood cells and the disease-fighting white blood cells, can be produced by hematopoietic stem cells, which are found in bone marrow and blood.

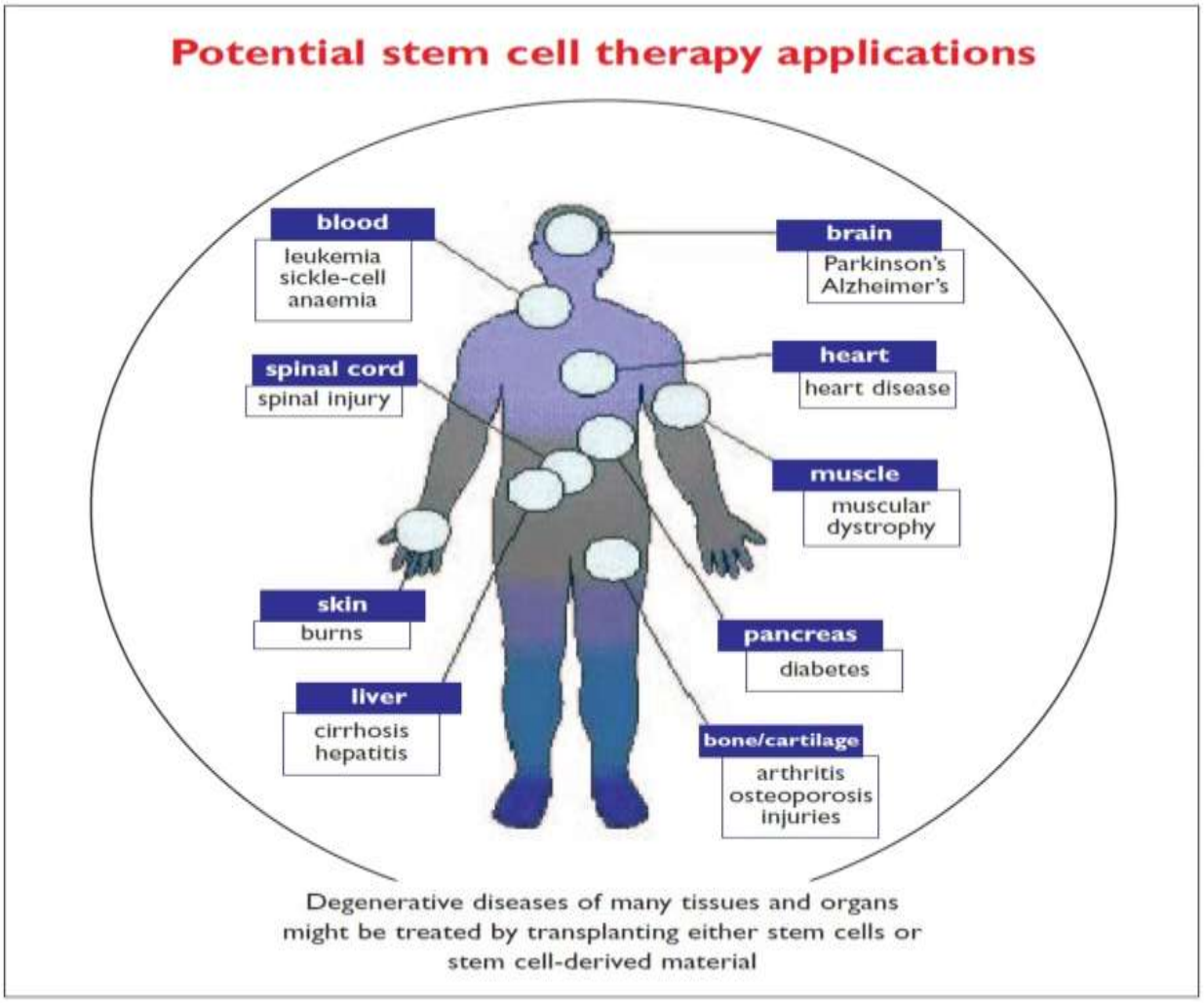

Figure 9:- Stem cell therapy application.

Conclusion:-

Understanding organogenesis and the body's ongoing ability for regeneration via stem cells is crucial. They could serve as a model for the investigation of pathogenetic pathways and help scientists better comprehend the pathophysiology of various diseases. They also provide the chance to create biological models for the investigation of novel pharmacological substances. The ability of these cells to repair damaged tissue and potentially regenerate organs, however, is their most significant promise. There have been many published research procedures, preclinical investigations, and clinical trials up to this point. There are a variety of dangers and challenges, even if some clinical trials have already revealed encouraging findings for the development of novel treatment strategies in cell-based medicine.Despite this, we have a lot of hope for the future of regenerative medicine because of continuing research and development.In order to replace or protect cells in degenerative, traumatic, and ischemic illnesses, stem-cell-based regenerative medicine has created novel therapeutic paths. The utilisation of multipotent and pluripotent cells from various sources in vivo, as well as their inclusion in the first preclinical and clinical trials, has given patients fresh hope and, as a short-term objective, aspires to bring cell-based treatment to the clinic.

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