INTRODUCTION TO STEM CELLS

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Abstract

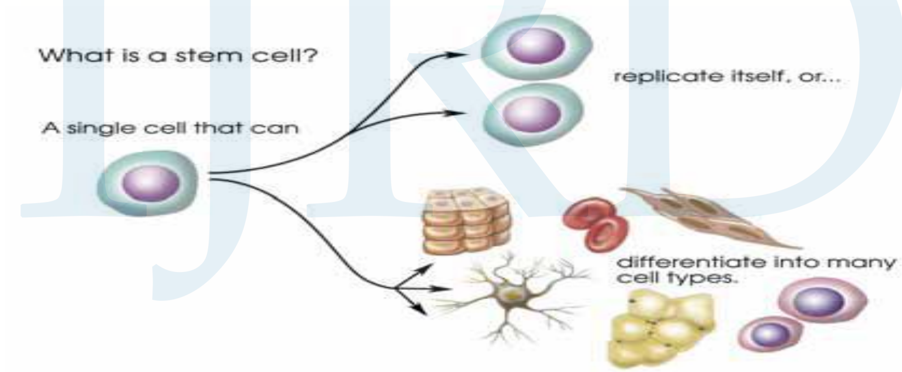
Stem cells are unspecialized cell. They are capable of continuous self-renewal. They can give rise to specialized cell types. Since the discovery of stem cells till now the totipotency is shown by very early embryonic stem cells. The adult stem cells possess multipotency and differential plasticity which can be exploited for future generation of therapeutic options. Mechanisms of stem cell maintenance are key to the regulation of homeostatis and likely contribute to aging. Stem cell therapy is useful in some of the disease. All said and done, stem cell research is still in the form of research and it's therapy form would take few decades more.

Keywords:

Introduction, Haematopoietic stem cells, Genesis of blood cells, Types of blood cells, Proprties of stem cells, Identifying stem cells, How are stem cells derived, Application of stem cells.

INTRODUCTION

Stem cells are unspecialized cells that have the ability to divide for indefinite period and give rise to specialized cells. In the context of human development, a zygote (fertilized ovum) is a stem cell. because it has the potential to form an entire organism, a zygote is known as a totipotent stem cell (to-TIP-o-tent;totus = whole;potential = power).inner cell mass cells, called pluripotent stem cells(ploo-RIP-o-tent;plur=several), can give rise to many (but not all) different types of cells. Later, pluripotent stem cells can undergo further specialization into multipotent stem cells (mul-TIP-o-tent),stem cells with a specific function. Examples includes keratinocytes that produce new skin cells and Spermatogonia that give rise to sperm. Pluripotent stem cells currently used in research are derived from the inner cell mass of embryos in the blastocyst stage that were destined to be used for infertility treatments but were not needed and from nonliving fetuses terminated during the three months of pregnancy. [1] Stem cell is a cell that has the ability todivide (self replicate) for indefinite periods-often throughout the life of the organism. Under the right condition, or given the right signals, stem cells can give rise (differentiate)to many different cell types that make up the organism. Stem cell have the potential to develop into mature cell that have the potential to develop into mature cells that have characteristic shapes and specialized functions such as heart cells, skin cells, or nerve cells. [2]



HAEMATOPOIETIC STEM CELLS

It involves two stages; mitotic division or proliferation and differentiation or maturation. It is known for a few decades that blood Cells develops from a small population of common multipotent hematopoietic stem cells (HSC). HSC express a variety of cell surface proteins such as CD34 and adhesion proteins which help these cells to "Home" to the bone marrow when infused. HSC have the appearance of small or intermediate-sized lymphocytes and their presence in the marrow can be demonstrated by cell culture techniques by the growth of colony-forming units (CFU) pertaining to different cell lines. The bone marrow provides a suitable environment for growth and development of HSC. For instance, if HSC are infused intravenously into a suitably prepared recipient, they seed the marrow successfully but do not thrive at other sites. This principles forms the basis of bone marrow (or HSC) transplantation performed for various hematologic diseases. After a series of divisions, HSC differentiate into two types of progenitors-lymphoid (immune system)stem cells, and non-lymphoid or myeloid (Trilineage) stem cells. the former develops into T, B and NK cells while the latter differentiate into 3 types of cell lines-granulocytes-monocytes progenitors (producing neutrophils, eosinophils, basophils and monocytes), Erythroid progenitors (producing red cells), and megakaryocytic (as the source of platelets). Monocytes on entering the tissues form a variety of phagocytic macrophages, both of which together constitute mononuclear-phagocyte system. Lymphopoietic cells in the marrow undergoes differentiation to form B, T and natural killer (NK) cells of the immune system. Two cardinal functions of HSC are self renewal and differentiation of their progenitor cells to produce leucocytes, erythroid cells and platelets. Haematopoiesis or myelopoiesis is regulated by certain endogenous glycoproteins called haematopoietic growth factors, cytokines and hormones for examples:

1) Erythropoietin: for red cell formation
2) Granulocytes colony-stimulating factor (G-CSF): For production of granulocytes
3) Granulocytes-Macrophage Colony-Stimulating Factor (GM-CSF): for production of granulocytes and monocytes-macrophages
4) Thrombopoietin; for production of platelets .[3]

GENESIS OF BLOOD CELLS

As these cells produce, a small portion of them remains exactly like the original Pluripotential cells and is retained in the bone marrow to maintain a supply of these, although their numbers diminish with age. The intermediate stage cells are very much like the pluoripotential stem cells,even though they have already become committed to a particular line of cells and are called committed stem cells.

The different committed stem cells, when grown in culture, will produce colonies of specific types of blood cells. A Committed stem cells that produce erythrocytes is called a colony-forming unit-erythrocyteand the abbreviation CFU-E is used to designate this type of stem cell. likewise, colony-forming units that form granulocytes and monocytes have the designation CFU-GM, and so forth. [4]

TYPES OF STEM CELLS:

Stem cells are broadly classified into two categories:

Embryonic stem cells (ESC) and Adult stem cells (ASC).

Embryonic Stem Cells:

These cells are also known as early stem cells.Embryonic stem cells are derived from embryos at a developmental stage before the time of implantation would normally occur in the uterus. This developmental stage is the blastocyst stage – 32 cell stage from which these pleuripotent cells can be isolated.

Pleuripotency of embryonic stem cells:

Embryonic stem cells can give rise to cells from all three embryonic germ layers i.e. ectoderm, mesoderm and endoderm, even after being grown in culture for a long time. In other words they can develop into each of more than 220 cell types of the adult body when given the sufficient and necessary stimulation for a specific cell type. ES cells can be maintained in culture as undifferentiated cell lines or induced to differentiate into many different lineages. Pleuripotency distinguishes ES cells from multipotent cells found in adults, which can onlyform a limited number of different cell types**.**

Regulation of pleuripotency of ES cells:

Researchers at Genomic institute, Singapore in collaboration with colleagues from US, have cell type but have the property of self renewal which distinguishes them from nonstem cell discovered a gene that plays a crucial role in human embryonic stem cells. Scientists studying on mice identified a gene that encodes a transcription factor, sall4, a protein that switches gene on and off. Such transcription factors are crucial for the identity of the cell. Transcription factors also regulate the development of cells from the primitive cell stage to functional cell making up the tissue and entire development from the fertilized egg to grown individuals. some of these are:

Oct 4 protein: It has been used as a key marker for ES cells and for the pleuripotent cells of the intact embryo. Its expression must be maintained at a critical level for ES cells to remain undifferentiated.

Nanong protein: It is essential for maintenance of the undifferentiated state of the mouse cells. The expression of Nanong decreased rapidly as mouse ES cells differentiated and when its expression level was maintained by a constitutive promoter, mouse ES cells could remain undifferentiated and proliferate in the absence of either LIF or BMP in serum free medium. Nanong is also expressed in human ES cells, though at a much lower levels. compared to that of Oct4 and its function in human ES cells was yet to be examined. Recent studies also implicate the Wnt-catenin signaling in maintaining pleuripotency.

Adult Stem Cells:

Adult stem cells are undifferentiated cells found throughout the body that divide to replenish dying cells and regenerate damaged tissue. They are also known as somatic stem cells which can be found in children as well as adults.

Properties: The rigorous definition of stem cell require that it possesses two properties: Self renewal- the ability to go through numerous cycles of cell division while maintaining the undifferentiated state and multipotency- the ability to generate progeny of several distinct cell type e.g. both glial cells and neurons, opposed to unipotency restriction to a single cell type. To ensure self renewal, stem cell undergoes two types of cell division: symmetric division give rise to two identical daughter cells both endured with stem cell properties and asymmetricdivision which produces only one stem cell and a progenitor cell with limited self renewal potential. Progenitor can go through several round of cell division before terminally differentiating into a mature cell. It is believed that molecular distinction between symmetric and asymmetric division lies in differential segregation of cell membrane proteins (such as receptors) between the daughter cells.

Regulation of differentiations of Adult Stem

Cells: Adult stem cell researches have been focused on uncovering the general molecule mechanism that control their self renewal and differentiation.

Bmi-1: The transcriptional repressor Bmi-1 is one of the polycamb-group proteins, which was discovered as a common oncogene activated in lymphoma and later shown to specially regulate hemato-poietic stem cells. The role of Bmi-1 has also been illustrated in neural stem cells.

Notch: The Notch pathway has been known to developmental biologists for decades. Its role in control of stem cell proliferation has now been demonstrated for several cell types including hematopoietic, neural and mammary stem cells.

Sonic hedgehog and Wnt: These developmental pathways are also strongly implicated as stem cell regulators.

Plasticity: A change in stem cell differentiation from one cell types to another is called trans-differentiation, and the multiplicity of stem cell differentiation options is known as developmental plasticity.

Type of Adult Stem Cells: Stem cells with broad differentiation potential appear to exist in adult bone marrow and perhaps in other tissues well. stem cells located outside of the bone marrow are generally referred to as tissue stem cells. Such stem cells are located in sites called niches (niche- a specialized cellular environment that provides stem cells with the support needed for self-renewal. Straddling and Xie characterized the niche cells that govern the production of drosophila embryonic germline stem cells- those cells in the ovary that are the earliest precursors to eggs. According to the scientists,their findings offer a potentially valuable model to explore how stem cells are regulated in vivo). For instance in the gastrointestinal tract they are located at isthmus of stomach glands and at the base of crypts of the colon. Niches have been identified in other tissuessuch as the bulge area of hair follicles and the limbus of corneal.

Bone marrow stem cells: Bone marrow is the major source of adult stem cells. There aremainly two types of marrow stem cells:

1. Bone marrow hematopoietic stem cells: Hematopoietic stem cells are stem cells andthe early precursor cells which give rise to all the blood cell types that includes both the myeloid (monocytesand macrophages, neutrophils, basophils, eosinophils, erythrocytes, megakaryocytes/platelets and some dendritic cells) and lymphoid lineages (T-cells, B-cells, NK cells, some dendritic cells). Hematopoietic stem cells generate all the blood cells and can reconstitute the bone marrow after depletion caused by disease or irradiation.

2. Bone marrow stromal stem cells: Mammary stem cells provide the source of cells forgrowth of mammary gland during puberty and gestation and play an important role in carcinogenesis of breast. A single such cell can give rise to both luminal and myoepithelial cell types of the gland and has been shown to regenerate the entire organ in mouse. Mesenchymal stem cells are multipotent stem cells that can differentiate into variety of cell types in vitro or vivo include osteoblasts, chandrocytes, myocytes, adipocytes, neuronal cells, and described lately, into beta pancreatic ielet cells. These cells have been classically obtained from the bone marrow, and mesenchymal stem cells.[5] Stem cells are impacting drug discovery as they potentially provide a source of human cells that can be used for screening and safety testing. Stem cell therapy is a reality in the form of bone marrow transplants but in other areas is still at a very early stage.however,the promise is of regenerative treatments based either on stem cell replacement or chemical stimulation of endogenous stem cells.[6]

PROPERTIES OF STEM CELLS

Stem cells in the bone marrow have two important properties: self renewal and differentiation.

Self renewal: This is the property of duplicating themselves that means they renew themselves and therefore physiologically they do not die and at the same time they proliferate into different lineage of cells. Due to self renewal, the bone marrow never goes out of stock for stem cells stem cells reserve in bone marrow remains always adequate.

Differentiation: This is the property of developing into specific lineage of cells. Due to the property of differentiation, stem cells differentiate into progenitor cells of various cell lines. Thus, different cell lineages are formed from stem cells that give rise to specific blood cells.

Types

There are two different stem cells: myeloid stem cells and lymphoid stem cells.

Myeloid stem cells: Myeloid stem cells are pluripotent in nature that give rise to three types of different progenitor cells. These are erythroid progenitors that form erythroid series, the granulocytic progenitors that forms granulocytes (neutrophil, eosinophil, and basophil), monocyticprogentitors form monocytes, lymphocytic progenitors that form lymphocytes and megakaryocytic progenitors that forms platelets.

Lymphoid stem cells: Lymphoid stem cells are unipotent stem cells (UPSC) that produce only cells of lymphocytes series.[7] Stem cells are emerging as one of the fundamental underpinnings of tissue biology. they allow blood, bone, gametes, epithelia, nervous system,muscle and myriad other tissues to be replenished by fresh cells throughout life.These potent agents are controlled within restricted tissues to be replenished by fresh cells throught life. These potent agents are controlled within restricted tissues microenvironments known as "niches".

IDENTIFYING STEM CELLS:

Accurately identifying stem cells in vivo remains the biggest obstacle to progress in understanding stem biology. Normal stem cells and their neighbouring cells within tissues can rarely be pinpointed by histological methods. Properties that have been widely assumed to mark stem cells,such as preferential bromodeoxyuridine (Brdu) label retention (caused by an expected tendency of stem cells to divide more slowly than many of their progency). It has been possible to genetically tag individual stem cells and to document their ability to self-renew for a prolonged period.

Stem cell markers

Two types of useful markers have been identified. First, stem cells sometimes contains distinctive structures related to their early state of differentiation, such as an aggregate of endoplasmic reticulum like vesicles(called the spectrosome) in drosophila germline stem cells (GSCs). Second, components of the signaling pathways involved in stem cell maintenance and daughter cell programming, for instance the proteins Dad (kai and Spradling,2003) or Socs36E (Bach et al.,2007) in male and female GSCs, respectively, allow stem cell identification if combined with anatomical information.

Identification of stem cells through lineage analysis

Recent advances in the application of Cre-recombinase fate mapping in mice have begun to provide insights into the nature of mammalian stem cells. The recent identification of instenstinal stem cells by Cleavers and colleagues illustrates the power of both single-cell resolution and lineage markings for the identification of a mammalian stem cell niche in vivo.

Cell culture assays

Central nervous system stem cells have generally been identified based on their abilityto self-renew and to form multilineage colonies in culture.Culture environments sometimes alter the patterning of cells ways that modify their fates and even their developmental potentials. similar concerns apply to other mammalian stem cells that have been identified and studied primarily based upon their behavior in cultures or after expansion in cultures. This problem has been addressed in neural crest stem cells that give rise to the peripheral nervous system in the developing embryo by using flow cytometry to prospectively identify and isolate the neural crest stem cells that are capable of forming multilineage colonies in culture. [8]

Stem cells secretions protects retinal ganglion cells in glaucoma*:*

A new study in rats shows that stem cells secretions called exosomes, appears to protect cells in the retina, the light-sensitive tissue in the back of the eye, the findings published in stem cells translational medicine, point topotential therapies for glaucoma, a leading cause of blindness in the United states. The study was conducted by researchers at the National Eye Instiute (NEI) part of the NIH. Exosomes are tiny membrane-enclosed packages that form inside of cells before getting expelled. Long thought of as part of a cellular disposal system, scientists have more recently discovered that exosomes are packed with proteins, lipids and gene-regulating RNA. Studies have shown that exosomes from one cell can be taken up by another by fusing with the target cell's membrane, spurring it to make new proteins. The role of stem cells exosomes on ganglion cells, a type of retinal cell that forms the optic nerve that carries visual information from the eye to brain. The death of retinal ganglion cells leads to vision loss in glaucomas . [9]

HOW ARE STEM CELLS DERIVED?

"Cloning is defined as beginning when an embyo is implanted in a woman's womb" for the purpose of initiating a pregnancy that could result in the creation of a human fetus or the birth of a human being.[Reproductive cloning]There is another definition also cloning is "defined as beginning when an embryo is created with DNA that matches that of an existing person.[Therapeutic purpose]Any stem cells or cell types derived from them, that are transplanted into an unrelated recipient run the risk of causing a serious immune reaction and may be rejected.

The process of cell nuclear replacement, or 'therapeutic cloning', has been suggested as a way of avoiding this problem by making it possible to derive ES cells that are genetically (and therefore immunologically) identical to the recipient. Cell nuclear replacement involves injecting the nucleus from a normal body cell into an oocyte (egg) from which the nucleus has been removed, creating a construct that can be induced to behave as if it were a fertilized egg, dividing and developing into an embryo. This is the same process that was used to create the first cloned mammal, Dolly the sheep. The difference is that in 'therapeutic cloning' the aim is to use the cloned embryo to derive ES cells, not to implant it in a woman's uterus with the purpose of producing a cloned human being. [10]

APPLICATION OF STEM CELLS:

Knowledge about stem cell science and their potential applications has been accumulating for more than 30 years. Limited types of stem cell therapies are already in use. The most well known therapy is the stem cell transplant (a form of a bone marrow transplant) for cancer patients. But it has been only recently that scientists have understood stem cells well enough to consider the possibilities of growing them outside the body for long periods of time. Today stem cells have found applications in varying area of medicine ranging from therapeutics to replacement of lost tissues. [11-18]

Some of the Medical conditions where stem cells have found their use are as follows:

- Type 1 Diabetes in Children
- Nervous system disease and Alzheimer's disease
- Immunological disease like severe combined immunodeficiency disease(the "bubble boy" disease), Wiskott-Alrich syndrome, and the autoimmune disease lupus
- Diseases of bone and cartilage like Osteogenesis imperfect and chondrodysplasias
- Cancer, Cardiac diseases, Spinal cord injury
- Blindness

- Treatment of urological disorders like complicated bowel resection and possible complications, such as adhesions, mucus secretion, metabolic derangements and even malignant transformation
- Age related functional defects
- Lung diseases like Pulmonary idiopathic arterial hypertension, chronic obstructive pulmonary disease
- Chronic live injuries
- Digestive disorders like Crohn's disease
- Arthritis, inflammatory skin diseases and Muscular diseases

Stem cells also used in the field of medical research:

- Study of Human developmental biology
- Models of Human disease that are constrained by current animal and cell culture models
- Transplantation and Gene therapy
- Forensic DNA profiling and Correlation and collection of Ante-mortem data and Post-mortem data [11-18]

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