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Proliferatic Potential of Hematopoietic Stem Cells (HSC) and its Application in Human Diseases

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A B S T R A C T

Plasticity is a newly recognized ability of stem cells to express their potential beyond the tissues from which they are derived. Organ generations have long been believed to be undertaken through organ specific and tissue specific stem cells. HSC's (Hematopoietic Stem Cells) are involved in replenishing apoptic and damaged cells. Currently, using Cell Lineage tracking stem cells of another organ by supplementing appropriate cytokines and growth factors that provide signal for differentiating into desired organ. As suggested by McCulloch(1963), during development and proliferation of HSC interaction of C Kit (as a ligand) with its receptor on stromal cells, in bone marrow, a hierarchy of stem cells and progenitor cells differentiate and produce different sub lineage of cells. Further, most important information need to be elicited, is to decode common molecular mechanism and genes involved in initiating stem cell taking lead in differentiation to a specific organ. Neurodegenerative cells in certain neuron related diseases may be advantageously generated through this technology.

Introduction

Stem Cells, also called biological cells, are found in all multicellular organisms, which can divide (via mitosis) and differentiate into diverse specialized cell types and can self-renew to produce more stem cells. In mammals, there are two broad types of stem cells: embryonic stem cells, which are

isolated from the inner cell mass of blastocysts, and adult stem cells, which are found in various tissues. In adult organisms, stem cells and progenitor cells act as a repair system for the body, replenishing adult tissues. Although in a developing embryo, stem cells can differentiate into all the

specialized cells (called pluripotent cells), yet they also maintain the normal turnover of regenerative organs, such as blood, skin, or intestinal tissues. The classical definition of a stem cell requires that it possess two properties, viz.

Self-renewal: The ability to go through numerous of cell divisions while maintaining the undifferentiated state.

Potency: The capacity to differentiate into specialized cell types. In the strictest sense, this requires stem cells to be either unipotent or pluripotent, so as to be able to give rise to any mature cell type, although multipotent or unipotent progenitor cells are sometimes referred to as 'stem cells'. Apart from this, it is said that stem cell function is regulated in a feedback mechanism.

Self-renewal

There are two known mechanisms to ensure that a stem cell population is maintained. These are:

Obligatory asymmetric replication: A stem cell divides into one 'Father Cell' that is identical to the original stem cell, and another 'Daughter cell that is differentiated.

Stochastic differentiation: When one stem cell develops into two differentiated daughter cells, another stem cell undergoes mitosis and produces two stem cells identical to the original.

Potency

Potency specifies the differentiation potential (the potential to differentiate into different cell types) of the stem cell.

Totipotent (omnipotent) stem cells can differentiate into embryonic and extra

embryonic and extra embryonic cell types. Such cells can construct a complete, viable organism. These cells are produced from the fusion of an egg and sperm cell. Cells produced by the first few divisions of the fertilized egg are also totipotent.

Pluripotent stem cells are the descendants to totipotent cells and can differentiate into nearly all cells, i.e. cells derived from any of the three germ layers.

Multipotent stem cells can differentiate into a number of cells, as for only those of a closely related family of cells.

Oligopotential stem cells can differentiate into only a few cells, such as lymphoid or myeloid stem cells.

Unipotent cells can produce only one cell type - their own, but have the property of self-renewal, which distinguishes them from non-stem cells (e.g., muscle stem cells).

Stem cell systems, thus, represent an effective and powerful approach for tissue development and regeneration of diverse tissue types. Common and defining features of these exceptional cells are the capacity for self-renewal and the potential for differentiation into multiple mature cell types. Recently, some new, surprising observations have indicated that stem cells isolated from one adult tissue can also give rise to mature cells of other cell lineages, irrespective of classical germ layer designations. This finding has taken quantum jump in both scientific knowledge and the potential applications of stem cells. Thus, the new findings contradict central dogmas of commitment and differentiation of stem and progenitor cells. Notwithstanding this, the true potential of somatic stem cells is just emerging and accordingly the new findings have to be

defined more fully and integrated into a unifying model of stem cell potential and behavior. As such, the emerging lines of evidence of the developmental plasticity of hematopoietic and other somatic stem cells can be potentially involved in treating many human diseases.

With more than 50 years of experience of studying blood-forming stem cells - called hematopoietic stem cells, scientists have developed sufficient understanding to actually use them as a therapy. Currently, no other type of stem cell - adult, fetal or embryonic, has attained such status. Hematopoietic stem cells (HSCs) are the blood cells that give rise to all other blood cells and are derived from mesoderm. They are located in the red bone marrow, which are contained in the core of most bones. They give rise to the myeloid (monocytes and macrophages, neutrophils, basophils, eosinophils, erythrocytes, megakaryocytes/platelets, dendritic cells), and lymphoid lineages (T-cells, B-cells, NK cells). Hematopoietic stem cell transplants are now being routinely used to treat patients with cancers and other disorders of the blood and immune systems. Recently, researchers have observed in animal studies that hematopoietic stem cells appear to be able to form other kinds of cells, such as muscle, blood vessels, and bone. If this can be applied to human cells, it may eventually be possible to use hematopoietic stem cells to replace a wider array of cells and tissues than once was believed not possible.

Despite the vast experience with hematopoietic stem cells, scientists are still facing major roadblocks in expanding their use beyond the replacement of blood and immune cells. First, hematopoietic stem cells are unable to proliferate (replicate themselves) and differentiate (become specialized to other cell types) *in vitro* (in

the test tube or culture dish). Second, scientists do not yet have an accurate method to distinguish stem cells from other cells recovered from the blood or bone marrow. Therefore, it will be only prudent that until scientists overcome these technical barriers, it would be unlikely that hematopoietic stem cells will be applied as cell replacement therapy in diseases such as Diabetes, Parkinson's Disease, spinal cord injury, and many others. Since blood cells are responsible for constant maintenance and immune protection of every cell type of the body, their relentless and brutal work requires that blood cells, along with skin cells, must have the greatest powers of self-renewal of any adult tissue.

Blood and immune cell forming stem cells are known as hematopoietic stem cells (HSCs) and they are ultimately responsible for the constant renewal of blood which is responsible for the production of billions of new blood cells each day. Physicians and basic researchers have known and capitalized on this fact for more than 50 years in treating many diseases. The first evidence and definition of blood-forming stem cells came from studies of people exposed to lethal doses of radiation in 1945. Taking a cue from this, basic research soon followed. After duplicating radiation sickness in mice, scientists found they could rescue the mice from death with bone marrow transplants from healthy donor animals. In the early 1960s, Till and McCulloch began analyzing the bone marrow to find out which components were responsible for regenerating blood. They defined what the two hallmarks of an HSC remain: it can renew itself, and it can produce cells that give rise to all the different types of blood cells. This is shown in Fig I which depicts the sources of HSCs.

Sources of Hematopoietic Stem Cells

1. Bone Marrow
2. Peripheral Blood
3. Umbilical Cord Blood
4. Fetal Hematopoietic System
5. Embryonic Stem Cells and Embryonic Germ Cells

HSC in the bone marrow has four actions in its repertoire: 1) it can renew itself, 2) it can differentiate, 3) it can mobilize out of the bone marrow into circulation (or the reverse), or 4) it can undergo programmed

cell death, or apoptosis. Understanding the how, when, where, which, and why of this simple repertoire will allow researchers to manipulate and use for tissue and organ repair is still not very clear and in-depth research on this aspect needs to be carried out.

Clinical Uses of Hematopoietic Stem Cells using cord blood stem cells are described in Table-1 below:

Table.1 Depicts the Diseases that can be Cured by Haematopoietic Stem Cells

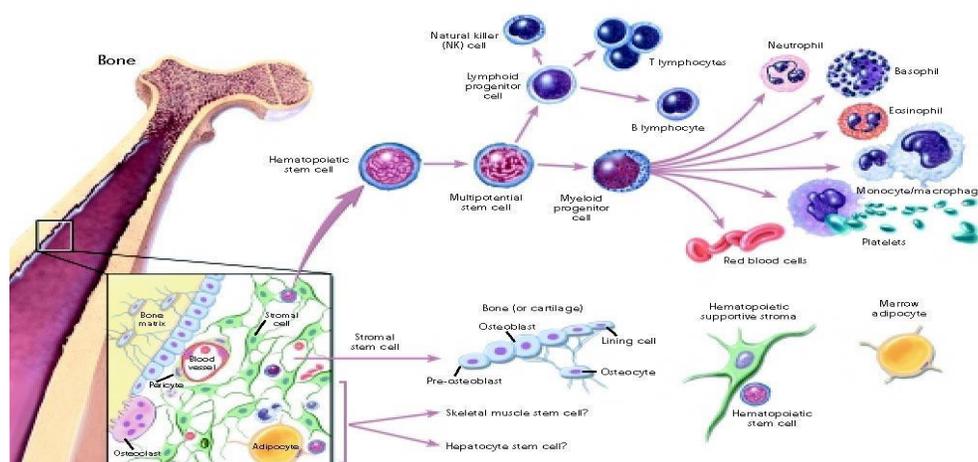
Myelodysplastic Syndromes are also called pre-leukemia Leukemia is a cancer of the blood immune system, where the cells are called leukocytes or white
1. Acute Lymphoblastic Leukemia (ALL)
2. Acute Myelogenous Leukemia (AML)
3. Acute Biphentotypic Leukemia
4. Acute Undifferentiated Leukemia
5. Chronic Lymphocytic Leukemia (CLL)
6. Chronic Myelogenous Leukemia (CML)
7. Juvenile Chronic Myelogenous Leukemia (JCML)
8. Juvenile Myelomonocytic Leukemia (JMML)
1. Refractory Anemia
2. Refractory Anemia with Ringed Sideroblasts
3. Refractory Anemia with Excess Blasts
4. Refractory Anemia with Excess Blasts in Transformation
5. Chronic Myelomonocytic Leukemia
Lymphoma is a cancer of the leukocytes that circulate in the blood and lymph vessels
1. Hodgkin's Lymphoma
2. Non-Hodgkin's Lymphoma
Other Disorders of Blood Cell Proliferation
1. Anemias
2. Aplastic Anemia
3. Fanconi Anemia
4. Congenital Dyserythropoietic Anemia
5. Paroxysmal Nocturnal Hemoglobinuria
6. Inherited Red Cell Abnormalities
7. Sickle Cell Disease
8. Beta Thalassemia Major
9. Diamond-Blackfan Anemia
10. Pure Red Cell Aplasia
11. Inherited Platelet Abnormalities
12. Amegakaryocytosis / Congenital Thrombocytopenia
13. Glanzmann Thrombasthenia

14. Inherited Immune System Disorders
15. SCID with Adenosine Deaminase Deficiency
16. SCID with Adenosine Deaminase Deficiency
17. SCID which is X-linked
18. SCID with absence of T & B Cells
19. SCID with absence of T Cells, Normal B Cells
20. Omenn Syndrome
21. Inherited Immune System Disorders: Neutropenias
22. Infantile Genetic Agranulocytosis
23. Myelokathexis
24. Inherited Immune System Disorders: Other
25. Ataxia-Telangiectasia
26. Bare Lymphocyte Syndrome
27. Common Variable Immunodeficiency
28. DiGeorge Syndrome
29. Hemophagocytic Lymphohistiocytosis
30. Leukocyte Adhesion Deficiency
31. Lymphoproliferative Disorders
32. Lymphoproliferative Disorder, X-linked
33. Wiskott-Aldrich Syndrome
34. Myeloproliferative Disorders
35. Acute Myelofibrosis
36. Agnogenic Myeloid Metaplasia
37. Polycythemia Vera
38. Essential Thrombocythemia
39. Phagocyte Disorders
40. Chediak-Higashi Syndrome
41. Chronic Granulomatous Disease
42. Neutrophil Actin Deficiency
43. Reticular Dysgenesis
44. Bone Marrow Cancers
45. Multiple Myeloma
46. Plasma Cell Leukemia
47. Waldenstrom's Macroglobulinemia
Transplants for Inherited Disorders of the Immune System & Other Organs
1. Cartilage-Hair Hypoplasia
2. Erythropoietic Porphyria
3. Hermansky-Pudlak Syndrome
4. Pearson's Syndrome
5. Shwachman-Diamond Syndrome
6. Systemic Mastocytosis
Transplants for Inherited Metabolic Disorders
1. Mucopolysaccharidosis (MPS) Storage Diseases
2. Hurler Syndrome (MPS-IH)
3. Scheie Syndrome (MPS-IS)
4. Hunter Syndrome (MPS-II)
5. Sanfilippo Syndrome (MPS-III)
6. Morquio Syndrome (MPS-IV)
7. Maroteaux-Lamy Syndrome (MPS-VI)
8. Sly Syndrome (MPS-VII) (beta-glucuronidase deficiency)
9. Mucopolipidosis II (I-cell Disease)

10. Leukodystrophy Disorders
11. Adrenoleukodystrophy (ALD)
12. Krabbe Disease(Globoid Cell Leukodystrophy)
13. Metachromatic Leukodystrophy
14. Pelizaeus-Merzbacher Disease
15. Lysosomal Storage Diseases
16. Niemann-Pick Disease
17. Sandhoff Disease
18. Wolman Disease
19. Other Inherited Metabolic Disorders
20. Lesch-Nyhan Syndrome
21. Osteopetrosis
Solid tumors not originating in the blood or immune system
1. Neuroblastoma
2. Medulloblastoma
3. Retinoblastoma
Neurologic Disorders
1. Autism
2. Cerebral Palsy
3. Hearing Loss
4. Hypoxic Ischemic Encephalopathy
5. Spinal Cord Injury
Autoimmune Disorders
1. Amyotrophic Lateral Sclerosis
2. Crohn's Disease
3. Diabetes, Type 1
4. Graft-versus-Host Disease
5. Kidney plus stem cell transplant
6. Lupus
7. Multiple Sclerosis
8. Rheumatoid Arthritis
9. Scleroderma
Cardiovascular Disorders
1. Congenital Defects
2. Support for Misc. Open Cardiac Surgery
3. Hypoplastic Left Heart Syndrome (HLHS)
4. Grow Vascular Graft
5. Ischemia
6. Critical Limb Ischemia
7. Compartment Syndrome (Battlefield Trauma)
8. Ischemic Stroke
9. Ischemic Heart Disease
10. Cardiac Repair
11. Myocardial Infarction
12. Cardiomyopathy
Gene Therapy for Inherited Disorders
1. Adrenoleukodystrophy
2. Chronic Granulomatous Disease (X-linked)
3. Fanconi Anemia

4. HIV
5. Metachromatic Leukodystrophy
6. Severe Combined Immunodeficiency
7. Sickle Cell
8. Thalassemia
9. Wiskott-Aldrich Syndrome
Orthopadaeic disorders
1. Alveolar Cleft Palate Repair
2. Knee Cartilage Repair
Miscellaneous
1. Bronchopulmonary Dysplasia (BPD)
2. Epidermolysis Bullosa
3. HIV aka "AIDS"
4. Lysosomal Storage Diseases
Source: Parents guide to cord blood
Treatments using cord tissue stem cells
Over 30 clinical trials around the world are researching the capability of these stem cells in treating:
1. Stroke
2. Spinal cord injury
3. Liver disease
4. Diabetes
5. Cartilage injury

Fig.1 Sources of Haematopoietic Stem Cells



The Stem Cell Database

Ihor Lemishka and colleagues at Princeton University and the Computational Biology and Informatics Laboratory at the University of Pennsylvania have collaborated to record all the findings about hematopoietic stem

cells (HSC) genes and markers in the Stem Cell Database.

These collaborators have diligently prepared the database five years ago, its goal being listing and annotating all the genes that are differentially expressed in mouse liver HSCs from different blood sources, and a related

database, constructed in collaboration with Kateri A. Moore - also at Princeton University. Based on this data bank it will be possible to document all genes active in stromal cells, which provide the microenvironment in which stem cells are maintained. The combined power of the two databases, along with new tools and methods for studying molecular biology, will help researchers put together a complete portrait of the hematopoietic stem cell and how it works. Further, these databases will continue to grow and take advantage of other efforts, such as those to complete the gene sequences of mammals. So as to take gainful advantage of these data banks, they are proposed to be publicly available to researchers around the world to carry forward further researches to fill the existing void in the research already done till now.

The National Marrow Donor Program

Launched in 1987, the National Marrow Donor Program (NMDP) was created to connect patients who need blood-forming stem cells or bone marrow with potential nonrelated donors. Ironically, about 70 percent of patients who need a life-saving HSC transplant cannot find a match in their own family.

The NMDP is made up of an international network of centres and banks that collect cord blood, bone marrow, and peripherally harvested stem cells and that recruit potential donors. As of February 28, 2001, NMDP listed 4,291,434 potential donors. Since its start, the Minneapolis-based group has facilitated almost 12,000 transplants-75 percent of them for leukemia. As per the recent data, the total no of more than 1 million blood stem cell transplants has been made upto 11.3.2015 in USA. In India too, although successful stem cell transplants are being made, the data for exact number of transplants made is not available.

Barriers to the Development of New and Improved Treatments Using Hematopoietic Stem Cells

Notwithstanding the advances made till now in stem cell research, there are many barriers in the development of new and improvised treatment methods and skills using HSCs. They are mentioned below:

Boosting the Numbers of Hematopoietic Stem Cells

Outfoxing the Immune System in Host, Graft, and Pathogen Attacks

Understanding the Differentiating Environment and Developmental Plasticity

Research 30 November, 2015

The growth factor independence-1(GFI1) proteins orchestrate the emergence of haematopoietic stem cells through recruitment of Lysine specific demethylase-1 (LSD1)

Research | 16 November 2015

A perisinusoidal niche for extramedullary haematopoiesis in the spleen

Haematopoietic stem cells normally reside in a bone marrow niche but they are recruited to the spleen after physiological stresses; here, endothelial cells and stromal cells around sinusoidal blood vessels of the spleen are shown to secrete key niche factors to support this process

Reviews | 07 December 2015

Childhood to adult transition and long-term follow-up after blood and marrow transplantation

Amelioration of murine sickle cell disease by nonablative conditioning and γ -globin gene-corrected bone marrow cells

Conclusion

Grounded in half a century of research, the study of hematopoietic stem cells is one of the most exciting and rapidly advancing disciplines in biomedicine today. Breakthrough discoveries in both the laboratory and clinic have sharply expanded the use and supply of life-saving stem cells. Yet; even more promising applications are on the horizon and scientist's current inability to grow HSCs outside the body could delay or thwart progress with these new therapies.

New treatments include graft-versus-tumors therapy for currently incurable cancers, autologous transplants for autoimmune diseases, and gene therapy and tissue repair for a host to other problems. The techniques, cells, and knowledge that researchers have now are found to be inadequate to realize the full promise of HSC-based therapy.

Thus, in conclusion, some key issues for tapping the potential of hematopoietic stem cells will be finding ways to safely and efficiently expand the numbers of transplantable human HSCs *in vitro* or *in vivo*. Moreover, it will also be important to gain a better understanding of the fundamentals of how immune cells work in fighting infections, in causing transplant rejection, and in graft-versus-host disease as well as master the basics of HSC differentiation. Concomitant advances in the gene therapy techniques and the understanding of cellular plasticity are also likely to make HSCs one of the most powerful tools for healing.

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