Hematopoietic Stem Cells

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Abstract: Haematopoiesis is the formation of blood cellular components. All cellular blood components are derived from haematopoietic stem cells. Hematopoietic stem cells give rise to all lineages of blood cells. Because HSCs must persist for a lifetime, the balance between their proliferation and quiescence is suitably regulated to ensure blood homeostasis while limiting cellular damage. Cell cycle regulation therefore plays a important role to control the HSC function during both fetal life and in the adult.
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Hematopoietic stem cells (HSCs) are the blood cells that divide to all the other blood cells and are derived from mesoderm. They are located in the red bone marrow, which is contained in the core of most bones. They give rise to the myeloid (monocytes, macrophage, neutrophils, basophils, eosinophils, erythrocytes, megakaryocytes, platelets, dendritic cells, etc) and lymphoid lineages (T-cells, B-cells, NK-cells, etc). Hematopoietic tissue contains cells with long-term and short-term regeneration capacitiesand committed multipotent, oligopotent, and unipotent progenitors. HSCs are a heterogeneous. HSCs are found in the bone marrow of adults, specially in the pelvis, femur, sternum, umbilical cord blood and peripheral blood. Stem and progenitor cells can be taken from the pelvis at the iliac crest using a needle and syringe. The cells can be removed as liquid or they can be removed via a core biopsy. In order to harvest stem cells from the circulating peripheral, blood donors are injected with a cytokine, such as granulocyte-colony stimulating factor (G-CSF), that induce cells to leave the bone marrow and circulate in the blood vessels. HSCs can replenish all blood cell types and self-renew. A small number of HSCs can expand to generate a very large number of daughter HSCs. This can be used in bone marrow transplantation when a small number of HSCs reconstitute the hematopoietic system. HSCs have a higher potential than other immature blood cells to pass the bone marrow barrier and travel in the blood from the bone marrow in one bone to another bone. When settle in the thymus they may develop into T cells. In the case of fetuses and other extramedullary hematopoiesis, HSCs can settle in the liver or spleen and develop. This ability is the reason why HSCs may be harvested directly from the blood.With regard to morphology, hematopoietic stem cells resemble lymphocytes. They are non-adherent, and rounded, with a rounded nucleus and low cytoplasm-to-nucleus ratio. Since PHSC cannot be isolated as a pure population, it is not possible to identify them in a microscope. The above description is based on the morphological characteristics of a heterogeneous population, of which PHSC are a component. Many of these markers belong to the cluster of differentiation series, such as CD34, CD38, CD45, CD90, CD105, CD133 and c-kit, etc. There are many differences between the human and mice hematopoietic cell markers for the commonly accepted type of hematopoietic stem cells. HSC cannot be easily observed directly, and, therefore, their behaviors need to be inferred indirectly. Clonal studies are likely the closest technique for single cell in vivo studies of HSC. Here, sophisticated experimental and statistical methods are used to ascertain that, with a high probability, a single HSC is contained in a transplant administered to a lethally irradiated host. The clonal expansion of this stem cell can then be observed over time by monitoring the percent donor-type cells in blood as the host is reconstituted. The resulting time series is defined as the repopulation kinetic of the HSC (Wikipedia, 2015).

Mesoderm is one of the three primary *germ layers* in the early *embryo*. The other two layers are the *ectoderm* (outside layer) and *endoderm* (inside layer), with the mesoderm as the *middle* layer between them. The mesoderm forms mesenchyme, mesothelium, non-epithelial blood cells and coelomocytes. Blood cells are responsible for maintenance and immune protection of every cell type of the body.

HSCs reside in the bone marrow and have the unique ability to give rise to all of the different mature blood cell types and tissues. HSCs are self-renewing cells: when they proliferate, at least some of their daughter cells remain as HSCs, so the pool of stem cells does not become depleted. This phenomenon is

called asymmetric division. All blood cells are divided into three lineages.

Hematopoiesis is the lifelong process by which all the cells of the blood system are produced in a hierarchical manner from a small population of hematopoietic stem cells, which reside in the bone marrow cavity in adult mammals.

Bone marrow is a flexible tissue in the interior of bones. Red blood cells are produced by cores of bone marrow in the heads of long bones in a process. Bone marrow is a key component of the lymphatic system, producing the lymphocytes that support the animal's immune system.

Lymphatic system is part of the circulatory system, comprising a network of lymphatic vessels that carry lymph directionally towards the heart. Lymph is similar to blood plasma but contains lymphocytes and other white blood cells.

Bone marrow stromal cells, also known as mesenchymal stem cells or fibroblastic colony-forming units, are multipotent non-hematopoietic stem cells adhering to culture plates (Abdallah and Kassem 2009). Mesenchymal stem cells of the bone marrow have the ability to renew and differentiate themselves into multiple lineages of conjunctive tissues, including bone, cartilage, adipose tissue, tendons, muscle, and bone marrow stroma. Those cells have been first described by Friedenstein et al., who found that mesenchymal stem cells adhere to culture plates, look like in vitro fibroblasts, and build up colonies (Friedenstein et al. 1987). The cell cycle activity of HSCs is carefully modulated by a complex interplay between cell-intrinsic mechanisms and cell-extrinsic factors produced by the microenvironment. This fine-tuned regulatory network may become altered with age, leading to aberrant HSC cell cycle regulation, degraded HSC function, and hematological malignancy.

Bone marrow is the site of hematopoiesis and bone marrow transplant has been successfully used for decades as a means of treating various hematological malignancies in which the recipient hematopoietic compartment is replaced by donor-derived stem cells. Progenitor cells in bone marrow are capable to differentiate into other tissues, such as cardiac tissue. Clinical trials have been conducted demonstrating beneficial effects of bone marrow infusion in cardiac patients. It is believed that injured tissue, whether neural tissue after a stroke, or injured cardiac tissue, has the ability to selectively attract bone marrow stem cells, perhaps to induce regeneration. Bone marrow has therapeutic effect in conditions ranging from liver failure, to peripheral artery disease, and the possibility of using bone marrow stem cells in kidney failure has been relatively understudied (Ma et al. 2009).

Mesenchymal stem cells have been brought to the attention of many researchers, because these cells are of great interest for treating various human diseases. Many studies have isolated mesenchymal stem cells and controlled, in vitro, its differentiation into cartilaginous tissue and bone using specific growth factors, with the objective of using this technology for repairing injured tissues of mesenchymal origin (Xian and Foster 2006; Kurdi and Booz 2007).

The umbilical cord is a conduit between the developing embryo or fetus and the placenta. During prenatal development, the umbilical cord is physiologically and genetically part of the fetus and normally contains two arteries and one vein. The umbilical vein supplies the fetus with oxygenated, nutrient-rich blood from the placenta. The blood within the umbilical cord, known as cord blood, is a rich and readily available source of primitive, undifferentiated stem cells. These cord blood cells can be used for bone marrow transplant.

Macrophages are a type of white blood cell that engulfs and digests cellular debris, foreign substances, microbes, and cancer cells in a process called phagocytosis. They play a critical role in non-specific defense (innate immunity), and also help initiate specific defense mechanisms (adaptive immunity) by recruiting other immune cells such as lymphocytes. In humans, dysfunctional macrophages cause severe diseases such as chronic granulomatous disease that result in frequent infections.

Basophils contain large cytoplasmic granules which obscure the cell nucleus under the microscope when stained. However, when unstained, the nucleus is visible and it usually has two lobes. The mast cell, another granulocyte, is similar in appearance and function. Both cell types store histamine, a chemical that is secreted by the cells when stimulated. However, they arise from different cell lines, and mast cells usually do not circulate in the blood stream, but instead are located in connective tissue. Like all circulating granulocytes, basophils can be recruited out of the blood into a tissue when needed.

Hematopoietic stem cell transplants can be used to treat patients with cancers and other diseases of the blood and immune systems. Hematopoietic stem cells are able to form other kinds of cells, such as muscle, blood vessels, and bone, and hematopoietic stem cells can replace a wider array of cells and tissues. The stem cells that form blood and immune cells are known as hematopoietic stem cells, which are responsible for the constant renewal of blood—the production of billions of new blood cells every day. The hematopoietic stem cell is the cell isolated from the blood or bone marrow that can renew itself, differentiate to a variety of specialized cells, mobilize

out of the bone marrow into circulating blood and undergo programmed cell apoptosis.

If bone marrow cells from the transplanted animal are transplanted to another lethally irradiated animal and restore its hematopoietic system over some months, they are the long-term stem cells that are capable of self-renewal. Other cells from bone marrow can immediately regenerate all the different types of blood cells, but under normal condition they cannot renew themselves over the long term that are considered as the short-term progenitor or precursor cells. Progenitor or precursor cells are relatively immature cells that are precursors to a fully differentiated cell of the same tissue type, which can proliferate but only have a limited capacity to differentiate into more than one cell.

The classic source of hematopoietic stem cells is bone marrow. Although quiescence is essential for the self-renewal of adult HSCs, they must nonetheless retain the capacity to proliferate rapidly, albeit transiently, in response to extrinsic cues that signal injury or infection.

In the late 1980s and early 1990s, it was known that blood from the human umbilical cord and placenta was a rich source of stem cells. The umbilical cord and placenta support the development of fetus during pregnancy and they are delivered along with the baby, and are usually discarded after the birth. Since the first successful umbilical cord blood transplants in children, the collection and therapeutic use of these cells has grown quickly. The New York Blood Center's Placental Blood Program in Manhattan of New York City is the largest U.S. public umbilical cord blood bank and has more that ten thousand donated samples for the transplantation purpose. Since it began to collect umbilical cord blood in 1992, New York Blood Center has provided thousands of cord blood units to patients. A lot of umbilical cord blood recipients have lived over eight years, relying on the stem cells from an umbilical cord blood transplant. Now, many countries have umbilical cord blood banks.

The number of blood cells in the bone marrow and blood is regulated by genetic and molecular mechanisms. Apoptosis is the process of programmed cell death that leads cells to self-destruct. If there are too few stem cells in the body, more cells divide and boost the numbers. If excess stem cells are injected into an animal, they simply wouldn't divide or would undergo apoptosis and be eliminated. Excess numbers of stem cells in the transplant will improve the engraftment. Stem cells transplantation can treat cancers (NIH, 2014). Hematopoietic stem cells are the paradigm for understanding the fundamental properties of adult stem cells, and for clinical stem cell therapy. Bone marrow transplantation is the standard of care treatment for a variety of malignant and benign hematological diseases.

T cells are a heterogeneous cell population comprising different subsets that exert distinct roles in cell-mediated immunity. Granulocytes are released from the bone marrow and make up the major group of leukocytes in the blood.

According to Symonds's opinions, CAL-USA-11 is a Phase I/II human study designed to assess the safety, feasibility, and tolerability of the Cal-1 product in HIV-infected individuals who have previously been on ART but are not currently taking any antiretroviral agent. Symonds gives an objective of the Cal-1 therapy is to increase the number of protected cells in the body of an individual infected with HIV to the point where the virus is incapable of causing harm. This would potentially reduce or eliminate the need for a lifetime of antiretroviral therapy. Symonds's study has three arms. All participants will receive the Cal-1 product. Participants in two of the three study arms will also receive different doses of a drug known as busulfan prior to the infusion, which has the potential to make the therapy more effective. Laboratory assessments performed throughout the course of the study will monitor: • the participants' general health and level of HIV infection; • the participants' level of CD4+ T cells; • the presence of Cal-1 modified cells in various cell types in the blood and lymphoid tissue; and • the safety of the approach. The primary objectives of the study are to evaluate: • The safety, feasibility, and tolerability of Cal-1 gene-transduced hematopoietic cell populations. • The safety and tolerability of low- and moderate-dose busulfan as a non-myeloablative conditioning agent as a means to improve engraftment of transduced HSPC. The study is open to men and women ages 18 to 65 who are HIV-infected but do not have any other serious medical conditions. Participants must have been well-controlled on ART in the past, but must not be taking ART currently. Treating stem cells along with T cells, it can create the potential for the progeny of the stem cells and exhibit genetic resistance to HIV, and therefore repopulate the participant's immune system (Symonds, 2015).

The first isolation of hematopoietic stem cells (HSC) required quantitative clonal assays for every blood cell progenitor type and methods to sort cells based on their unique expression profiles, as determined by cell surface markers. All HSC activity in adult mouse bone marrow (BM) was shown to be contained in a population marked by the composite phenotype of c-Kit+, Thy-1.1lo, lineage marker-, and Sca-1+. In humans, the isolation of a lCD34+CD90+ progenitor cell resulted in the purification of a homogeneous HSC population. The test for HSCs is in their ability to rescue myelo-ablated hosts from

hematopoietic failure, and establish long-term multi-hematopoietic lineage reconstitution. Clinical implantation of HSCs into cancer patients has led to stable grafts depleted of contaminating hematopoietic cells and resident or metastasized malignant cells. The continued identification of novel hematopoietic stem cell markers will enable improved efficiency in the purification of HSCs for the treatment of disease (eBioscience, 2014).

Turritopsis nutricula is capable of rejuvenating itself due to a process called transdifferentiation. Transdifferentiation occurs when a non-stem cell turns itself into another type of cell. But, it is not clear if stem cells are involved in this immortality or not. As my opinion, the transdifferentiation in *Turritopsis nutricula* has related mechanism to stem cell when the life cycle reverted. It is important to reveal the relationship of this *Turritopsis nutricula* transdifferentiation and stem cell (Ma and Yang, 2010).

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