Insights in Stem Cells

Extended Abstract
Vol. 6, Iss. 1
2020

Stem Cell Congress 2019-Hematopoietic Stem Cell Molecular Targets and Factors Essential for Hematopoiesis- Pawan Kumar Raghav- Institute of Nuclear Medicine and Allied Sciences

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Introduction

Based on origin, stem cells are broadly classified into Embryonic Stem cells (ESCs); Umbilical Cord Blood Stem Cells (UCBSCs); and Adult Stem cells (ASCs). ASCs have been identified in umbilical cord blood and the placenta which can lead to various types of blood cells. Bone marrow cells are the secondary source of ASCs, which consist of HSCs and Mesenchymal Stem Cells (MSCs). HSCs contain the potential of self-renewal and differentiation into specialized blood cells. HSCs reside in a niche within the bone marrow and are mainly present in the G0 phase of the cell cycle. These quiescent cells are atypical cells and obtained from one in 10,000 bone marrow cells . These cells are present in an endosteal and vascular niche composed of crosstalk network between HSCs, osteoblasts, endothelial and perivascular reticular cell. The receptors present on these cells interact with cytokines, chemokines, integrins, and morphogens which lead to committed progenitor cells. HSCs produce Colony Forming Unit-Granulocytes, Erythrocytes, Megakaryocytes, and Macrophages (CFU-GEMM). The cytokine, Granulocyte Macrophage-Colony Stimulating Factors (GM-CSF) or Granulocyte-Colony Stimulating Factors (G-CSF) triggers the differentiation of human myeloid cells [9]. Stem cell proliferation is maintained by factors c-Kit ligand, Stem Cell Factor (SCF), Thrombopoietin (TPO) and morphogens (Notch ligands, Wnt, Hedgehog, TGFβ, and BMP), etc.,. These factors provide signals that control their fate decision through differentiation into multiple lineages regulating their self-renewal. The SCF mediated proliferation in stem cells is regulated by their interaction with its receptor, c-Kit. This interaction activates the intracellular signaling which is negatively regulated by SHP-1/SHP-2 (Src (v-src avian sarcoma [Schmidt-Ruppin A-2] viral oncogene homolog) homology 2 (SH2) domain-containing phosphatase-1/2). Transcription factors, PU.1, c-Jun, GATA-1, and CCAAT/Enhancer Binding Proteins α (C/EBPα) regulates the myeloid differentiation [4]. The critical role of molecules which control these properties is an important aspect that must be considered while identifying potential target for designing a drug. Therefore, for successful application of HSCs for therapeutic purposes, it is essential to determine the targets and factors to understand the mechanisms that govern its fate. Hence, this review focuses on understanding the molecular targets and factors, their interactions that are involved in controlling hematopoiesis.

Hematopoiesis HSCs are capable of hematopoiesis and further subdivided into Short-Term HSCs (ST-HSCs) and Long-Term HSCs (LT-HSCs) [14]. These cells are different from other CFU or Multipotent Progenitors (MPPs) as they possess the distinct repopulating ability. LT-HSCs are renowned for their extensive self-renewal capacity, whereas the STHSCs have less self-renewal capacity but possess higher differentiation potential. In hematopoiesis, HSCs produce every lineage including red blood cells, platelets, and various lymphoid and myeloid cells. The lymphoid cells further differentiate into Natural Killer (NK) cells, T-cells, and B-cells, while myeloid cells differentiate into granulocytes, monocytes, macrophages, microglial cells, and dendritic cells [15]. The hematopoietic hierarchy begins with HSCs that differentiate into lineage-restricted progenitors and terminally differentiated cells [16-21]. The differentiation and proliferation of HSCs are regulated by cytokines and their respective receptors, and transcription factors. Besides, we collect the freely available databases/datasets providing information of transcriptomic, genomic data, and clinical resources in the area of hematopoiesis (Table 1). The 76 articles were obtained from PUBMED by using the search term “databases of hematopoiesis” from title or abstract.

Role of proliferation in hematopoiesis

This work is partly presented at 2nd International Conference on Stem Cells and Regenerative Medicine May 20-21, 2019 held in Rome, Italy

HSCs play a crucial role in homeostasis, immune response, and in transplantation to treat numerous diseases. The maintenance, self-renewal, and proliferation of HSCs are necessary for advanced HSC expansion. Hematopoiesis has an essential role in improving the efficiency of expansion for the transplantation. Transplantation of stem cells into irradiated recipients, reconstitute hematopoiesis with resultant average life spans. Transplantation requires two essential properties, proliferation to renew the stem cell compartment (self-renewal) and lifelong production of blood cells. These characteristics are regulated by ligands, macromolecules, and drugs. Binding of SCF to c-Kit causes receptor dimerization that maintains self-renewal and proliferation of HSCs. SCF acts synergistically with CSF such as GM-CSF, IL-3, and EPO, which in turn activates c-Kit intrinsic tyrosine kinase activity. Dimerization occurs due to simultaneous binding of a dimeric SCF molecule with two c-Kit monomers. Afterward, autophosphorylation of tyrosine residues of activated c-Kit occurs mainly outside the kinase domain. These residues serve as docking sites for STATs, signal transduction molecules containing SH2 or phosphotyrosine (pY) binding domains, Shc, Grb2, IRS1/2 and PI3K molecules [79]. The critical residues that undergo autophosphorylation, which is in the Juxtamembrane (JM) domain, include Y568 and Y570. The primary function of c-Kit is the progression of proliferation in HSCs, regulated by the PI3K and the MAPK pathway. The c-Kit has the potential to be involved in multiple signal transduction pathways via interaction with several enzymes and adaptor proteins. The adaptor proteins, APS, Src Family Kinases (SFK), and SHP-2, binds with phosphorylated Y568 (pY568) whereas, SHP-1 and adaptor protein Shc binds with phosphorylated Y570 (pY570). However, C-terminal Src homologous kinase (Chk) and the adaptor Shc binds in the JM domain at pY568 and pY570 of c-Kit. Also, Growth factor receptor-bound protein-2 (Grb2), PI3K, and phospholipase C bind at pY703, pY721, and pY730 respectively, in the Kinase Insert Domain (KID) of c-Kit. The pY900 in Distal Kinase Domain (DKD) binds to PI3K which further activates the adaptor protein Crk. The pY936 in the DKD binds with the adaptor proteins APS, Grb2, and Grb7. These c-Kit interactions result in the activation of several signal transduction pathways as shown in Figure 4. Besides, phosphorylated STATs, generated as homodimers and heterodimers of STAT, later translocate to the nucleus to influence transcription that leads to proliferation, survival, and differentiation.

Conclusion

Stem cells are identified as pluripotent and multipotent cells found in bone marrow which can differentiate into any tissue in the body. Though pluripotent ESCs are more efficient than multipotent adult stem cells in producing any cell type, many ethical issues have been raised towards the use of ES cells. Therefore, current investigative approaches are looking at using pluripotent stem cells in replacement therapies as they regenerate functional tissues for multiple injuries, spinal cord injury, and can cure Alzheimer's and diabetes. Pluripotent stem cells possess their characteristic properties, self-renewal, and differentiation, regulated by factors like mitogens, cytokines, small molecules, nutrients, cell-cell contacts and extracellular matrix. Thus, designing a drug for stem cells requires a deep understanding of its elemental properties and factors which regulate these properties. Besides, Infectious diseases (typhoid, hepatitis, tuberculosis, diphtheria, whooping cough, polio, and pneumonia) caused by fecal matter, contaminated water, and poor living conditions would likely be solved by inducing stem cells to differentiates selectively into myeloid cells.

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