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Hematopoietic Stem Cell Molecular Targets and Factors Essential for Hematopoiesis

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Abstract

Hematopoietic Stem Cells (HSCs) gained popularity in the area of medicine because of its remarkable potential to cure an enormous range of human diseases. These stem cells are used for therapeutic purposes for its regenerative capacity and possessed hematopoiesis. This process reflects characteristic properties, proliferation, and differentiation. These behaviors are a result of protein-mediated molecular interactions. However, these molecular interactions underlying are yet to be explored. Thus, the present review focuses on the molecular basis of hematopoiesis wherein, significant molecular interactions which regulate differentiation and proliferation has been discussed. Primarily, we have addressed the role of cytokines, transcription factors, proliferation, and pathways involved in hematopoiesis. Also, relationship with multiple cytokines, small molecules, nutrients, cell-cell contacts and the extracellular matrix which impel a cascade of signals that controls stem cell behavior and fate has been summarized in this review. A large number of datasets of hematopoiesis is publicly available to researchers around the world. This review also provides databases on hematopoiesis which will be very beneficial in facilitating common analysis, basic research and clinical diagnosis for the treatment of blood-related disorders.

Keywords: Stem cells; Proliferation; Differentiation; Hematopoiesis; Cytokines; Transcription factors

Abbreviations: HSCs: Hematopoietic Stem Cells; JAK: Janus Kinase; JM: Juxtamembrane; MAPK: Mitogen-Activated Protein Kinase; PI3K: Phosphoinositide 3-Kinase; PKC: Protein Kinase C; PLC-γ: Phospholipase C-γ; PTK: Protein Tyrosine Kinase; SCF: Stem Cell Factor; SH2: Src Homology 2; STAT: Signal Transducers and Activators of Transcription; HSCs: Hematopoietic Stem Cells; SHP-1: Src Homology 2 Domain Containing Phosphatase-1; SHP-2: Src Homology 2 Domain Containing Phosphatase-2; PTPs: Protein Tyrosine Phosphatases; ESCs: Embryonic Stem Cells; ASCs: Adult Stem Cells; PU.1: Purine rich box1; LT-HSCs: Long-Term reconstituting Hematopoietic Stem Cells; ST-HSCs: Short-Term repopulating Hematopoietic Stem Cells; CLP: Common Lymphoid Progenitor; CMP: Common Myeloid Progenitor; BMT: Bone Marrow Transplantation; MEP: Megakaryocytic Erythroid Progenitors; GMP: Granulcocyte Monocyte Progenitor; GATA-1: Erythroid Transcription factor of the GATA family; C/EBP: CCAAT/Enhancer Binding Proteins; FOG1: Friend of GATA-1; EGRS: Early Growth Response Protein-1; WBCs: White Blood Cells; RBCs: Red Blood Cells; AML1: Acute Myeloid Leukemia 1; NK: Natural Killer; MLL: Mixed Lineage Leukemia; SCL/TEL: T cell acute leukemia; bHLH: Basic Helix Loop Helix; ETS: E26 Transformation-Specific or E-Twenty-Six

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) [1,2]. 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) [3].

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 [4,5]. These quiescent cells are atypical cells and obtained from one in 10,000 bone marrow cells [6]. 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 [7]. HSCs produce Colony Forming Unit-Granulocytes, Erythrocytes, Megakaryocytes, and Macrophages (CFU-GEMM) [8]. 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., [10-12]. 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) [13]. 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.

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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 ST-HSCs 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 cytokines and their receptors in hematopoiesis

Cytokines interact with their respective receptors on both pluripotent and committed progenitor stem cells to regulate proliferation, and differentiation (Figure 1). This binding triggers the downstream signaling which results in the translocation of transcription factors from the cytoplasm to the nucleus. These transcription factors interact with other cell-specific transcription factors and regulate the self-renewal property of HSCs. Another level of competition and control is provided by chromatin-associated factors, such as MLL and BMI1 [22].

Cytokines manipulate the culture conditions by inducing selective gene expression in stem cells to proliferate, self-renew or differentiate into lineage-specific cell type [23]. The cytokines that play an essential role in hematopoiesis are listed in Table 2. The CSFs induce the multipotent hematopoietic progenitors and pluripotent HSC

S. No.	Database	Description/Link	PMID
1	BloodChIP	Explore transcription factor sites in human CD34+ and other healthy and leukemic cells based on ChIP-seq data. http://www.med.unsw.edu.au/CRCWeb.nsf/page/BloodChIP	24185696
2	BloodSpot	Provide gene expression profiles of healthy and malignant hematopoiesis in human or mice samples. http://www.bloodspot.eu	26507857
3	CODEX	A database specialized for grouping NGS data of human and mouse HSCs. http://codex.stemcells.cam.ac.uk	25270877
4	database R2	Genomics Analysis and Visualization Platform of hematopoietic factors. http://r2.amc.nl	29449653
5	DBA mutation database	Integrating information on Diamond-Blackfan Anemia (DBA) mutation and frequency at DNA, RNA, and protein level. http://www.dbagenes.unito.it	20960466
6	dbRBC	A database of human RBCs for DNA and clinical data. http://www.ncbi.nlm.nih.gov/projects/gv/rbc/main.fcgi?cmd= nit	22084196
7	ErythronDB	Providing the expression profile of murine erythroid cells. http://www.cbil.upenn.edu/ ErythronDB	23243273
8	European LeukemiaNet	Possessed physicians and patients information about diagnosis, treatment, and ongoing clinical trials. http://www.leukemia-net.org/content/home/index_eng. Html	23803709
9	ExAC	Exome Aggregation Consortium (ExAC), a database for clinical interpretation of genetic variants aggregate and harmonize exome sequencing. http://exac.broadinstitute.org/	28229513
10	Hembase	Integrating sequencing data of ESTs of human erythroid cells. http://hembase.niddk.nih.gov/	14681483
11	HemoPDB	Hematopoiesis promoter database, an information resource of transcriptional regulation in blood cell development. http://bioinformatics.med.ohio-state.edu/HemoPDB	14681365
12	HSC-Explorer	Contains hematopoiesis information. http://mips.helmholtz-muenchen.de/HSC/	23936191
13	JASPAR database	Transcription Factor binding profiles. http://jaspar.genered.net	30013175
14	KEGG database	KEGG (Kyoto Encyclopedia of Genes and Genomes), a database for biological interpretation of genome sequences and other high-throughput data. https://www.kegg.jp/	30321428
15	Leukemia Gene Atlas	Integrating microarray, DNA methylation, SNP, and high-throughput sequencing datasets of approximately 5800 leukemia and hematopoiesis samples. http://www.leukemia-gene-atlas. org/LGAtlas	22720055
16	LeukoStage Database	The qPCR data of gene expression in malignant and non-malignant cells of different lineages. http://camelot.lf2.cuni.cz/fiserkar/LSDat/ gens2/index.php	26674556
17	MicroRNA.org	Resource of microRNA target predictions and expression profiles. www.microrna.org	18158296
18	miRBase Targets	microRNA sequence repository of several species. http://microrna.sanger.ac.uk/targets/v3	24275495
19	NetPath	Reaction map of RANKL plays a role in hematopoiesis with bone remodeling. http://www.netpath.org/pathways?path_id=NetPath_21	21742767
20	Red Cell Membrane Disorder Mutations Database	Gene mutation data of the erythrocyte membrane associated with hemolytic anemia. http://research.nhgri.nih.gov/RBCmembrane	18341630
21	SBR-Blood	Hematopoietic systems biology repository contains datasets for array and sequencing-based platforms from mouse hematopoietic cells. http://sbrblood.nhgri.nih.gov	26590403
22	SCDb	Transcription factors stem cell database. http://stemcell.princeton.edu	12070015
23	StroCDB	Stromal Cell Database of biological and molecular studies of the surrogate niche. http://stromalcell.princeton.edu	15492413
24	TargetScan	miRNA target prediction data in mammals. www.targetscan.org	26267216

Table 1: Databases of hematopoiesis.

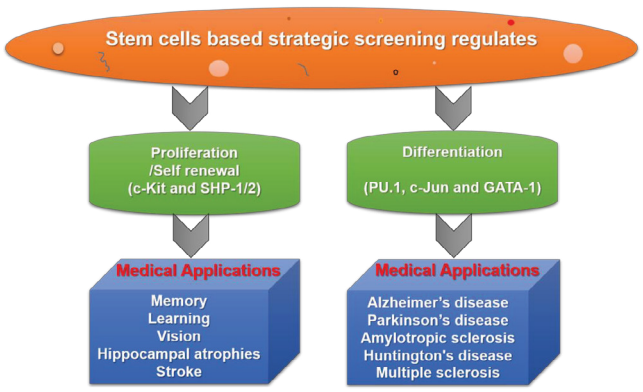

Figure 1: Essential properties of stem cells and their potential medical applications.

differentiation [24]. The CSFs are named depending on the fate of lineage formed which includes Erythropoietin (EPO), TPO, GM-CSF, G-CSF, and Macrophage-CSF (M-CSF). These cytokines have been grouped into four families, based on their signal transducing subunits:

1.) Homodimerizing

2.) Heterodimerizing

3.) Interferon family

4.) Tyrosine kinase receptors

The homodimerizing receptors belong to the same homodimeric type I subfamily of cytokine receptors, G-CSF-R, EPO-R, and TPO-R.

The heterodimerizing receptors have been classified into gp130 receptor family (IL6-Rα, LIF-Rβ, IL11-Rα, Oncostatin M-Rα, CNTF-Rα, and CLCF-R); common β receptor (βc) family (GM-CSFRα, IL3-

S. No.	Cytokines/ signaling	Role	PMID
1	Activin A	Production within bone marrow regulates of steady-state hematopoiesis.	1426103
2	bFGF or FGF-2	A potent hematopoietic growth factor, plays an important role in physiological and pathological hematopoiesis.	8714368
3	CXCL12/SDF-1	CXCL12 did not induce signaling through CXCR7, but formed functional heterodimers with CXCR4 and enhanced CXCL12-induced signaling in endothelial biology and valve development	17804806
4	EPO	Stimulates the proliferation and terminal maturation of CFU-E and BFU-E	7553874
5	FLT3	An angiogenic marker in multiple myeloma patients. Regulates proliferation and survival of MPP.	26521986, 26521986
6	G-CSF and GM-CSF	Both accelerate the recovery of normal granulopoiesis.	12069373
7	G-CSF and M-CSF	Act on more mature cells of the same lineage and are only required later during the differentiation of cell lineage.	7534912
8	GM-CSF	Induced proliferative stimulus to enhance platelet production, plays a role in megakaryocytopoiesis, and myelomonocytic lineage. Regulates cell metabolic activity, specifically by promoting glucose uptake.	1825794, 7534912, 27236376
9	IFNγ and myelosuppressive cytokine receptors	PKR (protein kinase R) plays essential roles in IFNγ signaling as a common mediator of signals for hematopoietic suppression.	21659535
10	IFN-γ, TNF-α, and IL-6	Contribute to the anemia in lymphoma, and elevated EPO and EPOR levels balanced negative regulatory effects on hematopoiesis to maintain normal hematopoiesis.	23628039, 25440916
11	IL 1, IL 6, and tumor necrosis factor (TNF)	Involved in the regulation of the immune response, hematopoiesis, and inflammation, etc.	2199284, 10851053, 9867112, 8630372, 19229053
12	IL-1α, IL-3, IL-6, and GM-CSF.	Role in erythropoiesis and megakaryopoiesis	7792269
13	IL-2 and TNF-α	Role in the control of normal hematopoiesis and leukemogenesis.	1999955
14	IL-27	Regulates immune responses as well as hematopoiesis and bone remodeling.	27677834
15	IL-2Rγc	The IL-2 receptor γ common chain is the shared subunit of the receptors for the IL-2 family of cytokines, which mediate signaling through JAK3 pathways to regulate lymphopoiesis and erythropoiesis.	26590317, 26404745
16	IL-3	Activates Jak2 signaling by c-Abl in 32D hematopoietic cells.	24923444
17	IL-3 and GM-CSF	Promotes a modest increase in Ca2+, plays a role in hematopoiesis, especially on certain cell subsets, basophil and mast cells, and alveolar macrophages.	22201962, 18775989, 9664156
18	IL-33	Triggers pathogenesis of myeloproliferative neoplasms and have a role in innate immunity.	26011644, 20643815
19	IL-5	Released from T lymphocytes of mammals infected with microorganisms or parasites, plays a role in hematopoiesis.	1365906
20	SCF	Increase the survival, self-renewal, and maintenance of HSCs	27365423, 11067877, 25100529
21	SDF-1/CXCR4	Signaling promotes restoration of hematopoiesis by regulating the homing and engraftment of MSCs and HSPCs.	17606439, 21186999
22	TGF-β and bFGF	Pathogenesis of idiopathic myelofibrosis. Also, regulates cell proliferation, differentiation, apoptosis, migration, and extracellular matrix production.	11317961, 9477133, 12428417
23	TNF-α	Induces extrinsic apoptosis and necroptosis of hematopoietic cells. A proinflammatory cytokine produced by macrophages plays an important role in inflammation and immune response.	26149913, 27358858, 23720862
24	TPO	Regulates the expansion and maturation of megakaryocytes. Also, contributes to the formation and the maintenance of hematopoietic cell clusters in the AGM (aorta-gonad-mesonephros) region.	10786657, 28235674
25	TPO and G-CSF receptors	In vivo role in hematopoietic cell fate decisions.	9892696

Table 2: Role of cytokines and their receptors in hematopoiesis.

Rα, and IL5-Rα); and IL2-R family (γ chain) (includes IL4-Rα, IL7-Rα, IL9-Rα, IL13-Rα, IL15-Rα, and IL21-Rα).

The interferon family comprises of IFN-α, IFNγ-R1/2, and IL10-R1/2 receptors whereas, tyrosine kinase receptors consist of FMS-like Tyrosine kinase 3 (FLT3) and c-Kit receptor [25].

These receptors are activated by three major pathways such as the JAK-STAT pathway, the p38 Mitogen-Activated Protein Kinase (MAPK) pathway, and the Phosphoinositide 3-Kinase (PI3K)/AKT pathway. Besides other pathways like NF-κB, TGF/SMAD, and Protein Kinase C (PKC) plays an essential role in regulating hematopoiesis and hematologic malignancies [26-29]. On the contrary, Tumor Growth Factor-beta (TGFβ), Tumor Necrosis Factor-alpha (TNFα), and Interferons (IFNs) are negative regulators of hematopoiesis and represent attractive drug targets [30]. Figure 2 shows the growth factors that play roles in the differentiation of HSCs. The SCF and FLT3 ligand bind with c-Kit and FLT-3 tyrosine kinase receptors, respectively which influence the proliferation individually and differentiation synergistically in CD34+ and CD38- progenitor cells [31]. Also, the synergistic effect of SCF with multiple cytokines in differentiation regulates BCL-2, BCL-XL, and perhaps other anti-apoptotic molecules, targeted to promote cell survival [32]. These receptors are essential targets for their down-regulation during normal differentiation.

Role of transcription factors in hematopoiesis

Transcription factors interact with the regulatory region of genes, either alone or in complex with co-activator to increase or decrease expression of genes [33]. The transcriptional network plays a crucial regulatory function in proliferation and differentiation in HSCs to become specialized into distinct blood cell lineage [34]. The Expression of lineage-affiliated transcription factors along with a simple hierarchy of hematopoiesis is shown in Figure 2. Several transcription factors, directly and indirectly, played a crucial role in regulating hematopoiesis (Table 3). Also, these transcription factors which regulate hematopoiesis have been discussed in single and multiple studies.

There are three key transcription factors, PU.1 and c-Jun, and GATA-1 which regulate myelopoiesis and erythropoiesis respectively (Figure 3) [35,36]. PU.1 also interacts synergistically or antagonistically with c-Jun, C/EBPδ, GATA-1, GATA-2, C/EBPα, c-Myb, CBP, AML-1B, AML-1/ETO, NF-EMS/Pip/IRF-4, and ICSBP/IRF-8, which governs most of the genes [37-47]. According to the classification of transcription factors, PU.1 (molecular weight 31 kDa) protein is encoded by SPI1 gene located on chromosome2 (mouse) or chromosome11 (human), related

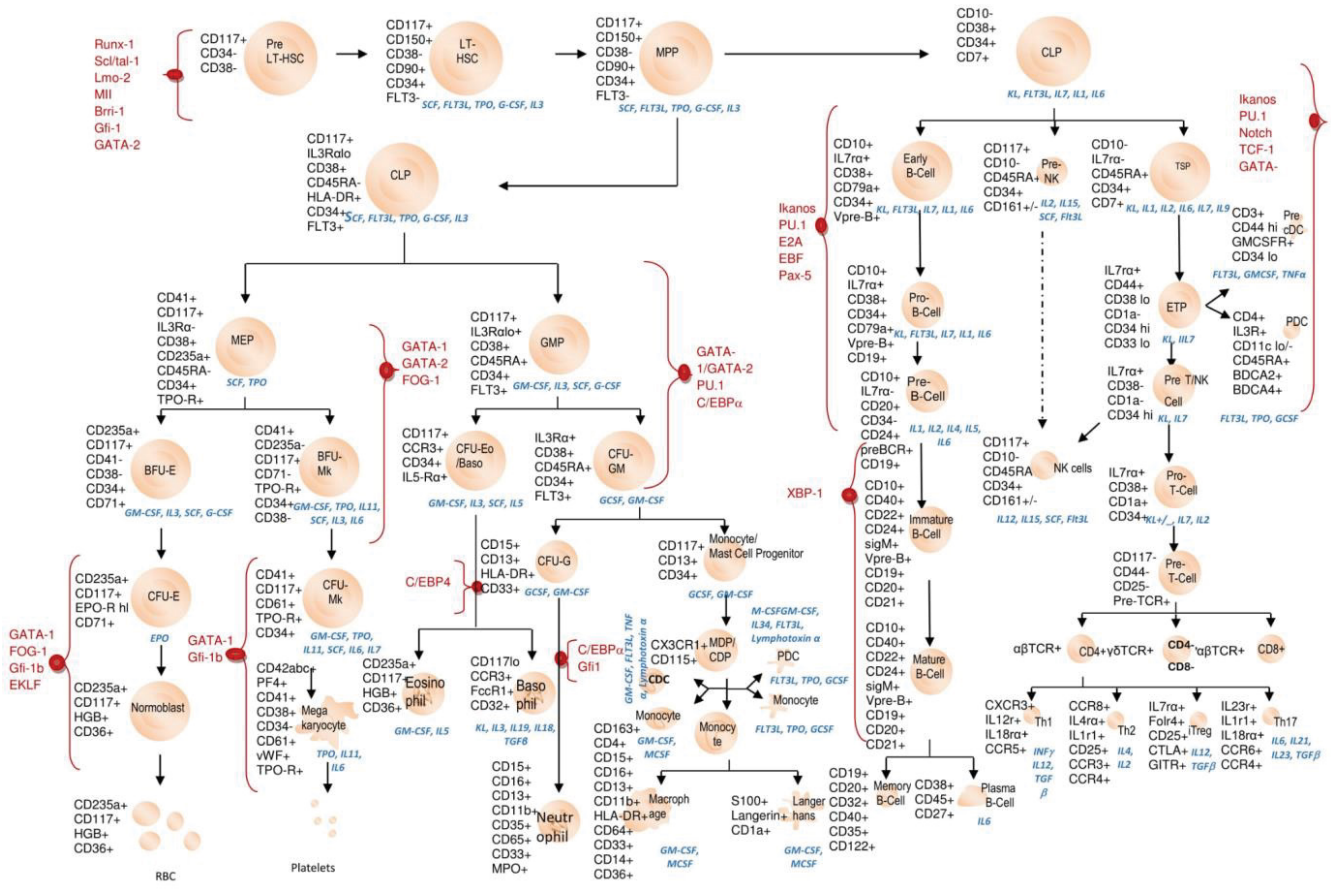

Figure 2: Hematopoiesis represents HSCs differentiation into erythrocytes, thrombocyte, basophils, eosinophils, neutrophils, monocyte, dendritic, NK cells, and B-lymphocytes and T-lymphocytes.
PDC: Plasma Dendritic Cells; CDC: Conventional Dendritic Cell; Monocyte 1: CD64+, CD14+, CD16+; Monocyte 2: CD64+, CD14+ CD16-; Monocyte 3: CD64-, CD14+, CD16+.

S. No.	TF	Role	PMID
1	AF10	AF10 is important for proper hematopoietic differentiation. AF10 plays a key role in the maintenance of multipotent hematopoietic cells.	23284727
2	AHR	Aryl Hydrocarbon Receptor (AHR) known to regulate cellular responses to oxidative stress and inflammation through transcriptional regulation of molecules involved in the signaling of nuclear factor-erythroid 2-related factor-2 (Nrf2), p53 (TRP53), retinoblastoma (RB1), and NFκB.	22628113, 18983985, 19896476
3	AML1	AML1 transcription factor is a critical regulator of normal hematopoiesis.	11368373, 11721960, 12946863, 19813271, 19151769, 10200536, 12643014, 9778047
4	AML1, C/EBPα, HOX, and GATA family	All these transcription factors play an important role in hematopoiesis	18766960, 10557039
5	AML1, C/EBPα, RARα, MOZ, p300/CBP, and MLL	All of which are important in the regulation of hematopoiesis.	21823042
6	AML1/PEBP2αB/CBFa2 gene or PEBP2β/CBFb	PEBP2/CBF plays an important role in angiogenesis.	10644985
7	AP-1	Activator protein-1 (AP-1) regulates a wide range of cellular processes including proliferation, differentiation, and apoptosis.	22822070
8	BATF	TF BATF is essential for an initial commitment of naive CD8(+) T cells to effector development.	25548173
9	Biklf	A krüppel-like transcription factor is preferentially required for erythroid cell differentiation in zebrafish.	11553329
10	C/EBPα	CCAAT/enhancer binding protein α (C/EBPα) is involved in the myeloid development and indispensable for the formation of granulocytes.	20807890, 26511037, 24561082, 17217039
11	C/EBPβ	CCAAT/enhancer-binding protein β (C/EBPβ) transcription factor is required for stress-induced granulopoiesis, whereas C/EBPα plays a critical role in maintaining steady-state granulopoiesis.	25940801, 9637691, 9637691, 29973462, 25448741
12	CBFβ	Core Binding Factor β (CBFβ) is complexed with the RUNX family of transcription factors in the nucleus to support activation or repression of genes related to bone (RUNX2), hematopoiesis (RUNX1) and gastrointestinal (RUNX3) development.	24648201, 20195544
13	Cdx	Cdx genes (Cdx1, Cdx2, and Cdx4) is involved during embryonic hematopoiesis in the mouse.	18511567
14	Cf-ETS	cDNA encoding a putative ETS transcription factor, play indispensable roles in blood cell differentiation and linage commitment during hematopoiesis. CF-ETS is a potential biomarker for hematopoiesis studies in sea scallop Chlamys farreri.	19446578
15	c-fos	c-fos or GATA-1, which could pay the role in the Ginsenosides (GS) induced up-regulation correlated with proliferation and differentiation of hematopoiesis.	12577377
16	c-Maf	c-Maf is one of the large Maf (musculoaponeurotic fibrosarcoma) is crucial for definitive erythropoiesis in the fetal liver.	21628412
17	c-Myb	Regulating hematopoietic cell proliferation and cytokines synthesis by bone marrow fibroblasts.	20823231, 8643572, 7688794, 19955420, 18585056, 16597594, 8643572, 21960247, 11290610, 8084617, 18187733, 24257756
18	CREB	Cyclic-AMP response element binding protein (CREB) functions in glucose homeostasis, growth-factor-dependent cell survival, proliferation, and memory. CREB acts as a proto-oncogene to regulate hematopoiesis and contributes to the leukemia phenotype.	16096372, 15837624, 19960054, 16196046, 17975014, 16819137
19	CUX1	Homeodomain-containing transcription factor knockdown promotes PI3K signaling, drives HSC exit from quiescence and proliferation, and results in HSC exhaustion	29592892
20	Ebf2	Early B cell factor 2 (Ebf2), acts as a transcriptional determinant of an osteoblastic niche that regulates the maintenance of hematopoietic progenitors, in part by modulating Wnt signaling.	20887955, 20887955
21	EKLF	Eklf expression defines a novel role for Eklf as a regulator of lineage fate decisions during hematopoiesis.	17715392, 18448565, 18448565
22	ERG	ETS factor, ERG, has emerged as a key player in normal hematopoiesis. Critical regulator of adult HSCs, essential for maintaining self-renewal during HSC cycling.	21664289, 19487285, 23719302, 29050203, 21673349
23	ESE-1	ETS family of transcription factors regulates cell proliferation, cell differentiation, embryonic development, neoplasia, hematopoiesis, angiogenesis, and inflammation.	22157719
24	Etv2	ETS domain transcription factor is an essential regulator of vasculogenesis and hematopoiesis.	22406820
25	Evi1	Ecotropic viral integration site-1 is an oncogenic transcription factor in murine and human myeloid leukemia. Evi1 targets the GATA-2 for the transcription factors which regulates the HSC pool hierarchically.	15889140, 15889140, 20842122, 19385966
26	Fli-1	Regulates hematopoiesis and hemostasis.	10891501, 17688409, 28586009
27	Fli-3	Fli-3 encoding mir-17-92 involved in the development of erythroleukemia and its important role in hematopoiesis.	17586726
28	Foggy/Spt5	Negatively and positively regulates transcription elongation. Plays an important role in GATA-1 gene expression and erythropoiesis through its transcriptional activation domain.	21205096
29	FOXM1	Forkhead box M1belongs to the forkhead/winged-helix family of transcription factors and regulates a network of proliferation-associated genes.	28154085
30	FOXO3	Forkhead transcription factor 3 plays role in development, aging, and, in longevity.	24747665, 26084022, 18371339

31	GABP	Necessary for stem/progenitor cell maintenance and myeloid differentiation in human hematopoiesis and chronic myeloid leukemia.	27100840
32	GATA	Essential for the development of endoderm during embryogenesis and the renewal of the differentiated epithelium in the mature gut. GATA-1, one of the hematopoietically expressed members, is required for normal erythroid and megakaryocytic differentiation. GATA-2 crucial for the proliferation and maintenance of hematopoietic stem cells and multipotential progenitors. GATA-4/5/6 functions in a common pathway, at the time of cardiac crescent formation, for regulating early embryonic cardiac morphogenesis.	24436352, 9657742, 26445707, 23371459, 21605981, 22492510, 8643572, 11146164, 8643572, 16158817, 9657742, 15659348, 16144799, 12577377, 17688409, 23241114, 7738198, 9621433, 8045339, 21788913
33	Gfi1 and Gfi1b	DNA-binding zinc finger transcription factors Gfi1 and Gfi1b, regulators of both early hematopoiesis.	26447191, 20190815, 12351384, 12351384, 20190815, 17646546, 18504458, 19164764, 20453161, 25398765
34	Hhex	Key regulator of early lymphoid development, functioning, at least in part, via regulation of the cell cycle.	25472970, 25472970, 29263042
35	HIF-1 and HIF-2	Hypoxic signaling plays an essential role in maintaining oxygen homeostasis and cell survival. Role in the regulation of skeletal development, bone formation, and regeneration, as well as joint formation and homeostasis.	21360287, 17998056, 19662436, 15899860, 23324380, 16427735
36	HLA-G	HLA-G transcription indicated a contribution to the tumoral progression by blocking natural killing reaction.	8988550, 8795141
37	HLF	Transcription factor hepatic leukemia factor, HLF as a critical regulator of HSC quiescence and as an essential factor for maintaining the HSC pool during regeneration.	29262330
38	Hmga2	Hmga2 as a transcriptional target of RUNX1 and a critical regulator of myeloid progenitor expansion.	25150295
39	HOXA9	HOXA9 plays a critical role in both normal hematopoiesis and leukemogenesis, particularly in the development and maintenance of mixed lineage leukemia (MLL)-rearranged leukemia.	22633751, 14604967
40	HOXB10	Regulation of HOXA10 expression in megakaryocytic differentiation.	17688409
41	Hoxb4	Overexpression promotes the dramatic expansion of bone marrow HSCs without leukemic transformation and induces development of definitive HSCs from the early embryonic yolk sac.	21278354, 14962901, 15854307, 17761289
42	HOXB6	In vitro, HOXB6 immortalized a factor-dependent myelomonocytic precursor capable of granulocytic and monocytic differentiation.	15522959, 10996827
43	HOXB7	HOX family of homeobox transcription factors plays a role in the proliferation and differentiation of primary hematopoietic cells.	11290787
44	HPIP	Hematopoietic pre-B-cell leukemia transcription factor-interacting protein (HPIP) is a corepressor of pre-B-cell leukemia homeobox (PBX) 1 and is known to play a role in hematopoiesis.	25060351
45	ICSBP	Interferon consensus sequence binding protein (ICSBP), novel role in regulating the proliferation and differentiation of hematopoietic progenitor cells.	8861914
46	Ikaros	Ikaros family of proteins- comprising Ikaros, Aiolos, Helios, Eos, and Pegasus - are zinc finger transcription factors regulate important cell-fate decisions during hematopoiesis, particularly in the development of the adaptive immune system.	21477865
47	Jumu	Jumeau (Jumu), controls the hemocyte differentiation of lymph gland through multiple regulatory mechanisms.	28350299
48	KLF4	Krüppel-like factor 4 is a zinc finger protein with dual functions that can act as a transcriptional activator and repressor of genes involved in cell proliferation, differentiation, and apoptosis and regulates the development and function of the myeloid and lymphoid blood lineages.	26908828, 26908828, 22170051
49	Klf6	Krüppel-like factor 6 (Klf6; copeb in zebrafish), copeb/Klf6 is essential for the development of endoderm-derived organs.	20430021
50	LEF1	Lymphoid enhancer-binding factor 1 plays a crucial role in the maintenance, proliferation, and differentiation of normal hematopoietic stem/progenitor cells.	26117056
51	LMO2	LIM domain only 2 regulates hematopoiesis and vascular development, endothelial proliferation and angiogenesis.	27792641, 27779255
52	MEF	Myeloid Elf-1 like factor plays a critical role in NK and NK-T cell development and the constitutive expression of perforin by NK cells.	14636650
53	MEF2C	Myocyte enhancer factor 2C identified as an essential regulator of muscle development and hematopoiesis.	23435431
54	meis1	Meis1, jointly with pbx1, regulates primitive hematopoiesis as well as vascular development in zebrafish	21048033
55	MLF1	Myeloid Leukemia Factor plays an important role in hematopoiesis and leukemia, notably by regulating the stability of RUNX transcription factors.	22885977, 22411814
56	Monocytic Leukemia zinc finger (MOZ)	Role of MOZ-driven acetylation in controlling a desirable balance between proliferation and differentiation during hematopoiesis.	19264921
57	Mxd4	Regulates proliferation of blood progenitor.	21782766, 21782766
58	Myc, USF, TFII-I, and Tal11/SCL	Function sequentially, cooperatively, or antagonistically in regulating expression programs during the differentiation of erythroid cells.	21282467, 21779460
59	MYCN (N-Myc)	MYCN reprograms hematopoietic cell fate by regulating NDRG1 and several lineage-specific hematopoietic transcription factors.	23554972, 23554972
60	Myeloid zinc finger 1 (MZF1)	MZF1 expression interfered with the ability of embryonic stem cells to undergo hematopoietic commitment and erythromyeloid colony formation and prevented the induced expression of CD34 and c-Myb mRNAs during differentiation	25436607
61	NANOG, OCT4, and SOX2	Pluripotent factors expression in and pluripotency of hESCs is maintained by Tip110.	22132941

62	NFATc2	Plays a role in the maintenance of steady-state hematopoiesis and bone remodeling in adult organisms.	21750088
63	NF-E2	Role in Megakaryocyte Maturation and Platelet Production	10355135, 16860008
64	NF-E2	NF-E2 plays role in differentiation of megakaryocytes and erythrocytes.	10556187
65	Nfil3	Functions in immune cells as key regulator of CD8α(+) dendritic cell and natural killer cell development in mice. Enriched in the myeloid compartment of adult zebrafish including eosinophils.	22561072
66	Nfix	Early B lymphopoiesis and myelopoiesis.	25780920
67	NFIX	Nuclear Factor One X (NFIX)	30287093
68	NF-Ya	NF-Ya is a potent cellular regulator of HSC self-renewal.	16081537
69	NRF2	Appropriate control of NRF2 activity by KEAP1 is essential for maintaining HSCs and guarantees their stress-induced regenerative response.	28674188, 22039262
70	Oct-04	Oct-4 is required for the initial specification of mesoderm and subsequently is required for the development of hematopoietic cells from uncommitted mesoderm.	19321862
71	Otx1	Plays a pivotal role in brain development and expressed in hematopoietic pluripotent and erythroid progenitor cells.	12934017, 21050313
72	p400/mDomino	p400/mDomino plays a critical role in embryonic hematopoiesis.	17535249
73	Pax5 and PU.1	EDAG was a transcriptional regulator which had transactivation activity and regulated the expression of several key transcription factors such as PU.1 and Pax5 in transgenic hematopoietic stem cells.	17690693
74	PcG	Polycomb group proteins are major negative regulators of gene expression in mammals and plays a role in normal and malignant hematopoiesis.	30341152
75	PEBP2/CBF	Plays an important role in angiogenesis.	10644985
76	PITX2	Paired-like homeodomain transcription factor 2 (PITX2) gene plays a critical role in cell proliferation, differentiation, hematopoiesis, and organogenesis.	24076438, 24076438, 16195330
77	Prep1	Pre-B-cell leukemia homeobox (Pbx)-regulating protein-1 (Prep1) involved in early development, genomic stability, insulin sensitivity, and hematopoiesis.	25157139, 25157139
78	PSC	Posterior Signaling Centre (PSC) is dispensable for blood cell progenitor maintenance.	26150488
79	PU.1	Purine-rich box1 has a key role in the development of most hematopoietic cell lineages but also in the suppression of leukemia. PU.1 is developmentally upregulated during normal human myelopoiesis.	25205721, 16978063, 9474745, 18463231, 17361223, 15914556, 20520638, 7520173, 22674382, 26622774
80	RARs and PLZF	Retinoic acid receptors (RARs) plays role in hematopoiesis.	14521715
81	RUNX1/2/3	Runt-related transcription factor 1 hematopoietic master regulator plays role in hematopoiesis and represses the erythroid gene expression program during megakaryocytic differentiation. Runx1, Runx2, or Runx3 subunit, along with a non-DNA binding CBF β subunit required at one or more stages of hematopoiesis.	25749719, 23613270, 25847244, 25911237, 27020276, 26060100, 27137656, 25263451, 11756550, 20711992, 16890157, 26060100, 16674921, 28926098, 26590920, 22024923, 24561082, 25802202, 25847244, 22411814, 28012022, 15156179, 16390320
82	SALL4	Role in developmental events as well as embryonic stem cell pluripotency maintenance.	22555391, 24163373
83	SCL	Transcription factor stem cell leukemia (SCL), also known as the T-cell acute lymphocytic leukemia 1 (TAL1), plays a key role in the regulation of hematopoiesis by modulating the phosphorylation level of the key proteins in MEK/ERK pathway.	24405580, 23974202
84	SNAI2 and SNAI3	Snail family of transcription factors, both SNAI2 and SNAI3 deletion was required to fully impact the generation of mature T and B cells.	24674754
85	SOX11	SRY (sex determining region Y)-box 11 involved in tissue remodeling during embryogenesis and is crucial for neurogenesis.	21124928
86	Sox17	SOX17 plays a key role in priming hemogenic potential in endothelial cells, thereby regulating hematopoietic development from hESCs/iPSCs.	23169777
87	Sp3	Zinc-finger transcription factor specificity protein 3 (Sp3) has been implicated in the regulation of many hematopoietic-specific genes and showed their role in the erythroid and myeloid cell lineages.	12676787
88	Spi-1	Role in zebrafish myeloid cell differentiation	19131555, 24850855
89	SPI1, GATA3, TCF-7, Etv5, c-maf, and TBX21	Differentially methylated in specific cell lineages and stages of the hematopoietic cascade.	17433759
90	Srf	Serum response factor (Srf) is a MADS-box transcription factor, critical for muscle differentiation. Srf is required for normal megakaryocyte maturation and platelet production.	20525922
91	STAT	Signal transducer and activator of transcription proteins play a key role in the production of mature hematopoietic cells. Signal transducer and activator of transcription 3 is a key transcriptional mediator for many cytokines and is essential for normal embryonic development, development, and regulation of innate immunity. Deletion of STAT3 during hematopoiesis results in abnormalities in myeloid cells and causes Crohn's disease-like pathogenesis. STAT5 does not play a significant role in the regulation of proliferation of normal hematopoietic cells derived from cord blood. STAT5 activated by SHP2 in GF-mediated proliferation, survival, and differentiation of human progenitor cells.	23797472, 12571365, 18234692, 29914167, 21085192, 21670473, 11287618, 23565285, 25550197, 20508164, 17630355, 12393407, 12813566
92	STAT3, GATA1, and ZBP-89 (ZNF148)	PTPN9 plays an important role in erythropoiesis by disrupting an inhibitory complex of phosphorylated STAT3, GATA1, and ZBP-89.	24727614

93	STG I	Shrimp crustin Pm4 and STG I as novel RNA binding proteins that play an important role in down-regulating astakine expression at the post-transcriptional level and are crucial for the maintenance of hematopoiesis.	24013515
94	SWI/SNF	Genomic instability linked to helicase-like transcription factor deregulation, and strongly suggests a tumor suppressor function of the SWI/SNF protein in acute myeloid leukemia.	26802049
95	SZF1/ZNF589	Stem cell zinc finger 1 (SZF1)/ZNF589 epigenetically repress transcription by recruiting chromatin-modifying complexes to the promoter regions of their respective target genes.	26738774
96	TEAD	The TEAD family transcription factor Scalloped regulates blood progenitor maintenance and proliferation in Drosophila through PDGF/VEGFR receptor (Pvr) signaling.	28322737
97	TEL	TEL (translocation-ETS-leukemia or ETV6) locus, is frequently rearranged in human leukemias of myeloid or lymphoid origin and required specifically for hematopoiesis within the bone marrow.	9694803
98	Tfe3	Transcription Factor for Immunoglobulin Heavy-Chain Enhancer 3 (Tfe3), regulates the expression of MAFB during macrophage differentiation.	19332055
99	TIF1γ	Plays essential roles in multiple murine blood lineages and that its function in transcription elongation is evolutionally conserved.	23159334
100	TRF3	TATA-box-binding protein (TBP)-related factor 3, is required for early development and initiation of hematopoiesis in zebrafish.	19777587
101	VDR	Vitamin D receptor mediates the actions of its ligand, 1,25-dihydroxy vitamin D(3) [1,25(OH)(2)D(3)], which can promote monocyte/macrophage differentiation and inhibit proliferation and cytokine production by activated T lymphocytes.	11956247, 28635660
102	WT1	The Wilms tumor gene 1 (WT1) affects proliferation and differentiation in erythroid and myeloid cells.	15907324, 11237525
103	XBP-1	Essential for hepatocyte growth.	10652269
104	YBX1	Y-box protein is involved in erythroid cell development	21369783, 21369783
105	ZBP-89	ZBP-89 (Zfp148) plays a critical role in erythroid lineage development, with its loss at the embryonic stage causing lethal anemia and thrombocytopenia. Also, a direct repressor of PU.1 and activator of SCL/Tal1 and GATA-1.	24549639, 23936136, 25319994
106	ZFP191	ZFP191 played an essential role in aggressive proliferation and migration of VSMCs, which in turn facilitated intimal hyperplasia.	23755975
107	ZNF191	Human zinc finger protein 191 (ZNF191) interact with the widespread TCAT motif which constitutes the HUMTH01 microsatellite in the tyrosine hydroxylase (TH) gene.	18096443
108	ZNF24	Zinc finger transcription factor 24 is involved in negative regulation of vascular endothelial growth factor (VEGF) and PDGFR-β and may represent a novel repressor of VEGF and PDGFR-β transcription respectively. Implicated in transcriptional regulation of genes associated with hematopoiesis, brain development, and cancers, oncogenesis.	20510677, 22678762

Table 3: Role of a transcription factor in hematopoiesis.

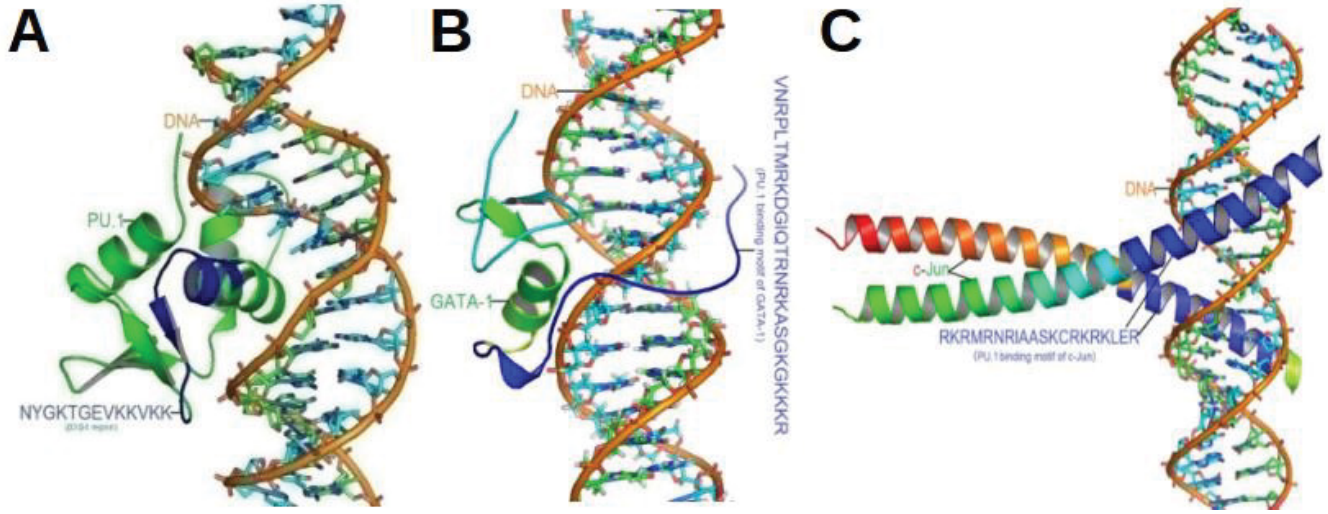

Figure 3: Transcription factors with DNA binding domain **(A)** binding site of PU.1 for GATA-1 and c-Jun **(B)** binding site of GATA-1 for PU.1, and **(C)** binding site of c-Jun for PU.1 shown as ligand pocket represented by binding sequence (blue color).

to SpiB (43%) and SpiC (40%) family. Spi subfamily of PU.1 belongs to the family of ETS associated factors underneath the class of tryptophan cluster, further classified under Helix turn helix domains superclass [48]. PU.1 protein is the target of phosphorylation events, noticeable on serine 148 [49]. PU.1 possesses three domains, an activation domain (10-13 amino acids), a PEST domain (118-170 amino acids), and an ETS DNA-binding domain (100 amino acids). In the PEST domain, residues 41 and 45 are essential for the enhancement of macrophage proliferation [50].

The PU.1, a master regulator of hematopoiesis, promotes lineage-specific differentiation of HSC in granulopoiesis and myelopoiesis [51,52]. In contrast, GATA-1 is involved in erythroid or megakaryocytic or eosinophil, and lymphopoiesis differentiation. The GATA-1 comes

under the two-zinc finger GATA factors subfamily of GATA-type zinc fingers family which further comes under other C4 zinc finger-type factors class, originated from Zinc coordinating DNA binding domains superclass. Importantly, acetylation sites, lys312, lys314, and lys315 of GATA-1 were found blocked after binding with PU.1 [53]. Table 4 shows the intermolecular hydrogen bonding of PU.1 and GATA-1 complex [53,54].

The PU.1, GATA-1, and GATA-2 are recognized as lineage-specific transcription factors that are expressed in MPP cells [55]. Yeast two-hybrid screen, in vitro Glutathione S-Transferase (GST) pull-down, and in vivo immunoprecipitation assays reported that the DNA-binding domain of PU.1 interacts with the zinc finger region of GATA-2 similar to GATA-1 [56]. Nevertheless, dysregulation of either PU.1 or GATA-1 activity leads to leukemogenesis [57-60]. However, manipulating the relative expression levels, by inhibiting GATA-1 or activating PU.1 or vice versa, led to differentiation of leukemic blasts cell differentiation into erythroleukemia [61,62]. Evaluation of the PU.1 and GATA-1 expressions is very important for the determination of MPP cell fate otherwise it can block cell differentiation and expansion of a clonal population of leukemic cells.

Besides, GATA-1 expresses in Megakaryocytic or Erythroid Progenitors (MEPs) that result in megakaryocyte and red blood cell precursors, whereas C/EBPα is present in GMPs [63]. However, according to Transfac database, c-Jun comes under the Jun factors subfamily of Jun related factors family under the bZIP class of Basic domain superclass (http://genexplain.com/transfac/). Likewise, C/EBPα falls under the C/EBP related factors family, Basic Domains class and Leucine zipper factors (bZIP) superfamily [43].

Direct antagonism between C/EBP and FOG1, EKLF and Fli-1, GATA-3 and T-bet, and Gfi1 and PU.1 shows a relationship among cell fate for eosinophil and multipotential, erythroid and megakaryocytic, TH1 and TH2, and neutrophil and monocyte cells, respectively. Nevertheless, without Gfi1 in mice, neutrophil precursors fail to mature and incompletely silence monocyte or macrophage gene expression [63]. Myeloid cells contained a high expression of PU.1 and C/EBP. These altogether with more widely expressed factors, AML1, ETS1, and c-Myb, activates myeloid specific promoters, such as the murine neutrophil elastase, G-CSF, M-CSF, and GM-CSF promoters [51]. The transcription regulators, Early growth response-1/2 (Egr-1/2) and NGFI-a binding protein 2 (Nab2), induces macrophage differentiation that needs a high-level of PU.1 expression [53].

Among these transcription factors, Mixed Lineage Leukemia (MLL), Runx1, TEL/ETV6, SCL/tal1, and LMO2 genes, contributes to the most known leukemia-associated translocations in patients [64]. The transcription factor, SCL encourages myeloid differentiation, whereas, E2A (a helix-loop-helix protein) is needed for lymphoid development [65,66]. PU.1 with low expression level leads to lymphoid commitment whereas, a high expression expedites myeloid cells development [67]. Runx1 increases the PU.1 expression and contributes to cell commitment to the CMP lineage [68]. The basic-Helix-Loop-Helix (bHLH), SCL/tal-1 and associated protein partner, and the Lim-domain containing LMO2 are essential to developing both primitive and definitive (adult) hematopoietic systems. Similarly, in the absence of Runx1, no hematopoietic clusters are formed in the dorsal aorta in mice. In zebrafish, Runx1 lies downstream of Notch signaling, required to induce hematopoiesis [63].

Reported PU.1 interacting residues		Reported GATA-1 interacting residues	
In paper	In PDB (1PUE)	In paper	In PDB (1GAT)
L172	L174	H289	H38
Y173	Y175	R293	R42
W213	W215	Q290	Q39
N219	N221	L288	L37
M228	M230	L284	L33
K227	K229	G283	G32
Y225	Y227	S310	S59
E207	E209		
K245	K247		
H205	H207		

Table 4: PU.1 interacting residue with GATA-1.

Role of proliferation in hematopoiesis

HSCs play a crucial role in homeostasis, immune response, and in transplantation to treat numerous diseases [69]. 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 [70]. 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 [71]. These characteristics are regulated by ligands, macromolecules, and drugs (Table 5) [22,70,72-75].

S. No.	Molecules/ genes/ drugs	Function	PUBMED ID
1	Wnt3A/5	Increases self-renewal 3- fold in culture. Induce proliferation of B- cell precursors in a LEF-1 dependent manner. Suppresses tissue recovery.	27077077, 27698112, 18957545, 21693582, 19365403
2	Bmi-1	Deficiency results in decreased self-renewal but overexpression increases self-renewal. Represses the gene encoding cell cycle regulator INK4A	16778178, 26028528
3	Retinoic acid	Alterations in Hox gene expression and also modifies Wnt-mediated signaling pathway. Maintains HSCs in culture and can increase self- renewal in serial transplantation experiments.	17846663
4	DNMT3A and DNMT3B	Required for DNA methylation in HSCs	17420264
5	p21	Lack results in higher rate of HSC proliferation and differentiation, lower self- renewal capacity. Hence required for maintaining HSC quiescence	12795424, 22039255
6	Axin	Abnormal/aberrant expression inhibits HSC proliferation, increased cell death of HSCs in vitro and reduced reconstitution in vivo	11689955,
7	Valproic acid	Increases both proliferation and self- renewal, accelerates cell cycle progression, down-regulates p21cip1/waf1, inhibits GSK3β thereby activating Wnt signaling pathway, up-regulates Hoxb4, induces differentiation or apoptosis in leukemic blasts, increases the replating capacity of murine HSC	15805245
8	Laq824	Properties similar to valproic acid on HSC	15805245
9	Stem Regenin (SR-1)	Increases ex vivo expansion of peripheral blood-derived CD34+ cells by 50 fold	26669897

Table 5: Molecules, genes or drugs that regulate HSC proliferation and their self-renewal characteristic.

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 [76]. Dimerization occurs due to simultaneous binding of a dimeric SCF molecule with two c-Kit monomers [77,78]. 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 (Figure 4) [80]. 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 [80]. 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 [27-29].

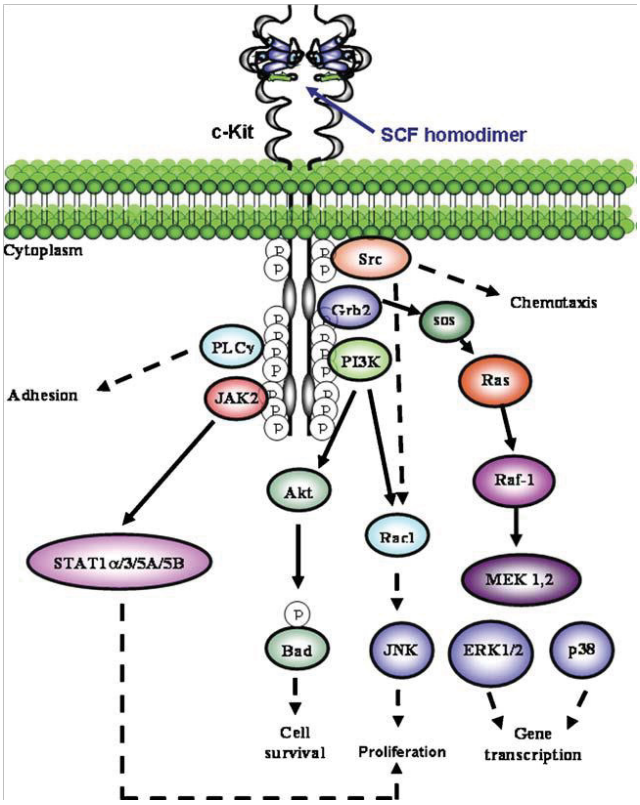

Figure 4: c-Kit signal transduction and its function [80].

Grb2 is an adaptor protein that plays a critical role in MAPK pathway by binding to pY703 and pY936 of c-Kit [81]. The complex of Grb2 with son-of-sevenless (sos) protein interacts with G-protein Ras and initiates activation of Raf-1 and finally the MAPK p38, ERK1/2, and c-Jun N-terminal Kinase (JNK). This evident that MAPK acts on transcription factors activity, and thereby on gene transcription. Reportedly, the Ras/Erk pathway is crucial in cell division and survival [82]. Even though Ras can activate some signal transduction molecules such as Rac or PI3K, its role in the Ras/Erk cascade is the most well characterized [83,84].

PI3K Pathway promotes proliferation by PI3K interaction with pY721 of c-Kit [85]. SCF-induced PI3K recruitment leads to Akt activation that subsequently phosphorylates the pro-apoptotic protein, bad. This indispensable mechanism of phosphorylation inhibits the activity of Bad, thereby promoting cell survival [86]. PI3K is also known to mediate SCF-induced proliferation of Bone Marrow-derived Mast Cells (BMMC) by activating the small Guanosine Triphosphate (GTP) binding protein Rac1 and JNK pathways [87,88].

Phospholipase C-γ (PLC-γ) association site phosphorylated at Y730 of c-Kit [89]. PLC-γ exists in two isoforms, PLC-γ 1 and PLC-γ 2, wherein both are composed of two SH2 domains, one SH3 domain, one PH domain, and a catalytic domain. Although PLC-γ 1 is ubiquitously expressed, PLC-γ 2 is mainly indicated in the hematopoietic system [90]. PLC hydrolyzes the phosphoinositide PIP2, thereby generating the second messengers DAG and inositol-1,4,5-trisphosphate (IP3).

The SCF triggers the multiple SFK members including Src, Tec, Lyn, and Fyn for their association with pY568 and pY570 in the JM domain of c-Kit [91-95]. After SCF stimulation in BMMC, Src kinase, and PI3K signaling pathways converge to turn on Rac1 and JNK, promoting cell proliferation [88]. However, inhibition of SCF-induced proliferation reduces the expression of the Lyn [92]. Gene transcription, induced by SCF, is also facilitated by activation of members of the SFK, leading to activation of the Ras/MAPK pathway [81,96].

In the JAK/STAT pathway, the Janus Kinases (JAKs) are cytoplasmic tyrosine kinases activated through ligand stimulation of cytokine receptors. Downstream of JAKs are the Signal Transducers and Activators of Transcription (STATs), which are phosphorylated by JAKs. STAT protein is a class of transcription factors with DNA binding domains, an SH2 domain, and a carboxy-terminal trans-activating domain. SCF induces activation of the JAK/STAT pathways. JAK2 associates with c-Kit and later undergoes phosphorylation after SCF stimulation [97]. The activation of JAK2 leads to phosphorylation of STAT1α, 3, 5A and 5B [98]. SCF-induced JAK/STAT activation is involved in fetal liver hematopoietic progenitor cell proliferation and differentiation [99]. However, SCF (100 ng/ml) activates JAK/STAT pathway in MO7e and HCD57 cells [100].

Pathways regulating hematopoiesis

LT-HSCs are identifying in human bone marrow CD34+ CD38- CD90+ isolated cells which can repopulate a lethally irradiated animal and establish a life-long supply of all hematopoietic lineages. Also, CD34+ or CD34lo cells have higher repopulating potential characterized by side population analysis by flow cytometry [101]. CD34+ cells promote adhesion with decreased proliferation due to their cell cycle expression kept in the niche [102]. Further, ST-HSCs result in all hematopoietic lineages, but only 8-10 weeks. Assume that ST-HSCs is an intermediate cell stage between LT-HSCs and the more lineage-restricted progenitors as they are the Common Myeloid Progenitor (CMP) and the Common Lymphoid Progenitor (CLP) population. In

a further set of decisions, CLPs translated into the different cells of the lymphatic lineage like B-lymphocytes, T-lymphocytes and NK cells. In contrast, CMP differentiates into cells of the myeloid lineage like granulocytes, macrophages, erythrocytes, and thrombocytes. Besides, numerous pathways with their role in regulating hematopoiesis are enumerated in Table 6 (searched from PUBMED).

Majorly, hematopoiesis pathway involves lymphoid (T-cells, B-cells, natural killer cells, and Dendritic Cells (DC)); myeloid (Red Blood Cells (RBCs)), granulocytes (neutrophils, eosinophils, basophils)); mast cells; monocyte-macrophages; and megakaryocytes-platelets; and an additional mechanism for generating DC. The HSC differentiation of mature hematopoietic cells, cell surface markers, transcription factors, and the growth factors that impact the differentiation is represented in Figure 2.

The CD34+ CD38+ CD45RA+ CD10+ from in vitro culture of bone marrow CLPs characterized the B-cell, NK, and DC progenitors [103]. Also, injected CD34+ CD10+ cells into fetal thymic organs successfully promoted into T-cells [103]. The PU.1 promotes IL-7Ra (a diagnostic marker for murine and human marrow CLPs) and EBF1 expression, while Ikaros promotes Flt3 receptor expression, important for B-cell and T-cell development [104]. Deleting or inhibiting the Notch receptor signaling promotes B-cells progress and inhibits T-cell formation [105]. B-cells was characterized by a CD19+ marker but derived from CD34+ CD19- CD10+ cells. The c-Kit and FLT3 activate the B-cell proliferation and survival, whereas, cytokine IL-7 promotes CD19 expression [106]. The transcription factors, FoxP1, E2A/E47, and EBF, regulates the B-cell development. However, interacting chemokine receptor and ligand (CCR9 and CCL25, respectively) endorse immature T-cell progenitors to migrate towards the thymus [107]. These developing cells characterized by CD34+ CD1a- as Early Thymic Progenitors (ETP), however, CD1a+ CD4- CD8- recognized as pro-T-cells. The SCF, Flt3, and BMP promoted T-cell development and required for maintenance of the undifferentiated lymphoid precursors [108,109]. A bipotent T/NK Progenitor (TKNP) found in the human fetal thymus was characterized using CD34+ CD7+ CD1a, which found as the immediate precursor of NK Progenitors (NKP) and T-cells in the thymus [109].

CMPs also knew as CFU-GEMM results in all types of the myeloid lineage. CMPs differentiates into intermediate MPP, such as Granulocyte-Monocyte Progenitors (GMP), which produces neutrophils, eosinophils, basophils, and monocyte or macrophages, and Megakaryocyte-Erythroid Progenitors (MEP) that produces erythroid and megakaryocytes. The CMP, GMP, and MEP are deficient in lymphoid markers, CD10, CD7, and IL-7Ra, but characterized by CD34+ CD38+ markers from human marrow and cord blood which have CD45RA and IL-3Ra expression. Although, CD45RA- IL-3Ralo characterized the CMPs whereas, CD45RA+ IL-3Ralo and CD45RA- IL-3Ra- markers characterized the GMPs, and MEPs, respectively. The myeloid marker, CD33 is highly expressed on CMPs but lost beyond the myelocyte stage. Therefore, it is a known target for treating certain types of Acute Myeloid Leukemia (AML) [110]. In contrast, Flt3 expression found positive in around 40-80% of human CD34+ bone marrow and cord blood cells and contributed for long-term repopulation. Colony forming assay revealed that higher GM colonies identified in Flt3+ population and Flt3- shows more erythroid colonies [111]. PU.1 and GATA-1 control lineage bifurcation between the MEP and GMP populations, respectively. PU.1 promotes GMP formation whereas, GATA-1 influences MEP development.

In colony forming assay, MEP differentiates into Burst Forming Unit-Megakaryocytic (BFU-Mk) or Burst Forming Unit-Erythroid (BFU-E), and later into Colony Forming Units-Megakaryocytic (Mk-CFU) or Colony Forming Units-Erythroid (E-CFU), respectively. These colonies are further mature terminally into megakaryocyte or platelet or erythroid cells. MEP cells controlled by transcription factors (SCL, GATA-1, GATA-2, and NF-E2), cell surface molecules (TER119, CD235a/glycophorin A), and cytokines (IL-3, SCF, EPO, and TPO). Similarly, EPO and TPO play an indispensable role in MEP downstream signaling by binding to their respective cell surface receptors to stimulate the growth of MEP progenitors. The restricted transcription factors, Fli-1 and EKLF, decide the fate of MEPs towards BFU-Mk and BFU-E formation, respectively. Interestingly, GATA-1 and CP1 promote to express EKLF. Alternatively, megakaryocytic lineage express CD41, CD61, CD42, glycoprotein V, von Willebrand factor, platelet factor 4 and platelet proteins. In contrast, lost expression of CD41 after MEP progress

S. No.	Pathways	Role	PMID
1	Cell death pathway	RIPK1 is a critical modulator of both tonic and TLR-responsive inflammatory and cell death pathways in human macrophage differentiation.	30250197
2	HSCs Survival pathways	cpsf1 inactivation implicates this gene in the maintenance and survival of key cell lineages, including normal HSCs and a subset of the diverse neural crest-derived lineages in zebrafish.	21330472
3	Innate immune pathway	The prominent role of the innate immune pathway in regulating hematopoiesis. Increased activation of the innate immune pathway may contribute to dysregulated hematopoiesis, dysplasia, and clonal expansion in myelodysplastic syndromes.	20359630
4	Jak/STAT, PI3K/AKT, and MAPK pathways	Binding of IL-31 to its receptor activates Jak/STAT, PI3K/AKT, and MAPK pathways. IL-31 acts on a broad range of immune- and non-immune cells and therefore possesses potential pleiotropic physiological functions, including regulating hematopoiesis and immune response, causing inflammatory bowel disease, airway hypersensitivity, and dermatitis.	18926762
5	Leptin-signaling pathways	Role of leptin in immunity and leptin-signaling pathways involved in modulating immune homeostasis and autoimmune pathogenesis. leptin in regulating hematopoiesis and lymphopoiesis	17349207
6	Megakaryopoiesis	ATP-binding cassette (ABC) transporters regulate megakaryopoiesis and platelet activity, the underlining mechanisms and their association with atherosclerosis and atherothrombosis.	28641133
7	Nuclear inositide pathways	phosphoinositide-phospholipase PI-PLCγ1 is essential for regulating hematopoiesis, particularly along myeloid and erythroid lineage.	25307310
8	Shh and Wnt Signaling Pathways	Regulating the proliferation of hematopoietic progenitor cells (HPCs).	26378473
9	Wnt and Notch signaling pathways	Wnt and Notch signalings are integrated and are selectively regulating hematopoiesis. Upregulates proliferation potential of hematopoietic progenitors	20217087
10	Wnt/β-catenin network	Wnt/β-catenin signaling pathway has been shown to play an important role in controlling the proliferation, survival, and differentiation of hematopoietic cells. Thus any aberrant signaling through this pathway may have a negative influence on hematopoiesis.	18726147

Table 6: Pathways regulating hematopoiesis.

but a continued expression of CD71 at the BFU-E stage reported. These premature erythrocytes later promote erythroid membrane proteins, erythroid enzymes, and hemoglobin. Megakaryocytes pathway involves the generation of promegakaryoblasts that leads to megakaryoblasts and in turn forms megakaryocytes. Megakaryocyte or platelet produces from the CFU-Mk stage wherein, cell division fails to replicate DNA but leads to produce larger cells containing 4N to 128N in nuclei. Pro-platelets produced by cytoplasmic fragmentation of megakaryocytes, afterward, 2,000-3,000 platelets made from single megakaryocyte cells [112]. Among multiple cytokines (SCF, GM-CSF, IL-3, IL-6, IL-7, IL-11, and TPO), the TPO and IL-3 are required for platelets generation [113]. GATA-1 and GATA-2 expression promote erythroid and megakaryocytic lineage differentiation, respectively but GATA-2 instead contributes to the proliferation of progenitor cells [114]. The SCF, GM-CSF, IL-3, and TPO arose before the CFU-E stage afterward, EPO helps to prevent apoptosis, induce hemoglobin synthesis and generate pro-erythroblasts. Consequently, EPO is not required at this stage which proceeds through nucleated normoblast to enucleated RBCs [115]. Cells with low expression of proliferative genes (GATA-2, c-Myb, c-Myc, and c-Kit) and high expression of differentiation-promoting genes (glycophorin A, and B globins) improve lineage commitment to erythroid cells [116-118].

GMP differentiated into neutrophils, eosinophils, and basophils passing through intermediate stages of myeloblast, promyelocyte, myelocyte, metamyelocyte, and mature granulocyte. Neutrophils and monocytes identified using CD11B, CD13, CD14, CD15, and CD16 markers. Nevertheless, G-CSF, GM-CSF, and IL-3 are critically stimulating the generation of granulocytes. The C/EBPα is interacting with c-Jun which increases the activity of PU.1, whereas inhibiting Pax-5 (paired box gene 5), and other lymphoid transcriptional elements, leads to GMP lineage commitment. This association of c-Jun raised PU.1 expression, which controls granulocytic with low, and monocytic with high lineage commitment. The lineage commitment pathway by PU.1 contains the antagonistic role of Egr1/2-Nat2, which drives macrophage gene expression and inhibits neutrophil gene expression. On the contrary, Gfi-1 is the downstream target of C/EBPα, which represses the interaction of Egr-1/2 and Nab-2 [119,120]. Furthermore, GMP differentiates into eosinophil-basophil progenitors that generate eosinophils under the influence of cytokines IL-3, IL-5, and GM-CSF and transcriptional regulators like GATA-1, PU.1, and C/EBP [121]. Interestingly, IL-5 is specific for eosinophils, and their overproduction leads to death, eosinophilia [122]. Nonetheless, GATA-1 has an essential role in eosinophil generation, while this finding ineffective in megakaryocytes, erythroid and mast cell lineage development [122]. However, basophils drew from a bipotent precursor with both eosinophil and basophil differentiation capacity [123]. The expression of CD34, c-Kit, and CD13 characterized the mast cell and basophil progenitors [124,125]. Cord blood progenitors cultured with IL-3 differentiates basophil [126,127]. The IL-3, TGF-β, and IL-18, synergistically inhibits eosinophil differentiation and increase IL-4/histamine production in basophils. Similarly, GM-CSF and IL-5 promote basophil production [123]. In contrast, SCF and IL-3 besides TPO, leukotriene D4, T helper type II (Th2), IL-4, IL-5, IL-6, and IL-9 are vital for mast cell development [128-131]. Additionally, SCF alone activates proliferation and degranulation in human mast cells [132]. GATA-2, associated with proliferation does not antagonize PU.1, results in increased PU.1 expression which promotes mast cell differentiation [43]. Besides, GMP differentiates into another lineage called as Macrophage Dendritic Progenitor (MDP) which gives both monocytes, macrophages, and lymphoid or non-lymphoid and plasmacytic dendritic cells. CD115, M-CSFR receptor expression recognizes the monocyte development from MDP [133]. Human monocytes expressing CD64+ CD14+ CD16-, hold higher CCR2 (chemokine) receptor and low CX3CR1 expression. They have high phagocytic/myeloperoxidase activity, superoxide release, and monocyte also secretes IL-10 on stimulating with Lipopolysaccharide (LPS). In contrast, lower CD16+ monocytes expression shows the opposite effect. PU.1 antagonizes GATA-1, GATA-2 and C/EBPα, which in turn inhibits MEP, mast cell, and granulocytic formation respectively to commit cells into the monocytic lineage [43,134].

DC-derived from both myeloid and lymphoid progenitors, classified into proliferative Early DC Progenitors (EDCP), Late DC Progenitors (LDCP) with limited proliferative capacity, and non-proliferative Gr1hi monocytic and DC precursors potential. EDCP are lineage-negative cells characterized by c-Kit, while LDCP is negative c-Kit, but express CD11. Further, mature DCs classed into "migratory" DCs (mDCs) (non-lymphoid) and lymphoid tissue-resident, “plasmacytic” DCs (pDCs,) produces interferons, and “conventional” DCs (cDCs) (opposes mDCs with pDCs). During inflammation, the GM-CSF, and TNF-α differentiate monocyte to cDC, whereas M-CSF and TGF-β1 facilitate Langerhans Cell (LC) development although TPO show synergism with Flt3L and G-CSF while, alone increases pDC development and mobilization [135]. Flt3L activates STAT3 which decreases DC numbers whereas, Gfi-1 activates them which reduces lymphoid-derived DCs while increasing LC production [136,137]. M-CSF activates STAT5 that promotes cDC development which suppresses IRF-8 (ICSBP) and supports the inhibition of pDC development. Overwhelmingly, GM-CSF generates pDCs without STAT5, which increases STAT3 activation and IRF-4 expression [138]. Interestingly, STAT3 signaling increased PU.1 expression and formed both cDC and pDC [139].

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 [69]. 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 [140]. 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. The myelopoiesis is accomplished by precise regulation of interaction of GATA-1 (42.7 kDa) and c-Jun (41.9 kDa) with PU.1, a transcription factor that controls erythroid and myeloid development, respectively [5]. Nevertheless, sequence comparison of c-Jun and GATA-1 motifs reveals the extensive similarity between the two proteins. This analogy agrees with the observation that GATA-1 and c-Jun compete for the same binding site on PU.1. Therefore, the elucidation of the molecular mechanism underlying this interaction is required which is not yet known. Furthermore, it has been noted that a large number of stem cells (2×10^6 CD34+ cells/kg recipient body weight) is needed for a successful BMT [71]. Thus, the study of proliferation is inevitable

to identify a capable molecule that transiently expands stem cells. Moreover, SCF regulates the downstream kinase signaling by interacting with c-Kit, which is prominently present on HSCs to derive proliferation [80]. The SCF binding to c-Kit monomer extracellular region triggers dimerization and induces autophosphorylation of c-Kit in the intracellular region. These phosphorylated residues are docking sites for SFK, Cbl, SHP-2, Lnk, and APS binds at Y568; SHP-1 at Y570; Grb2 at Y703; p85 and p110 (subunit of PI3K or CrkL) at Y721; phospholipase C at Y730; p85 associated with Crk at Y900; and Grb2, Grb7 and APS at Y936 [80]. These interactions suggest that these targets can modulate well established signaling routes like PI3K, Src family kinases, MAPK pathways and phospholipases that further regulate proliferation and mitogenic index of hematopoietic cells. This phenomenon revealed that proliferation would likely be improved by the synergistic effect of drugs and cytokines. Additionally, it can also be enhanced by abrogating the negative regulator of c-Kit which would lead to their autophosphorylation of tyrosine residues and inhibition of dephosphorylation. This binding would likely play an essential role in regulating tyrosine phosphorylation and cell proliferation.

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Author Contributions

P.K.R. and G.U.G. conceived the idea and designed the outline of the review. P.K.R wrote the review with input and critical guidance from G.U.G.

Conflict of Interest

All authors declare that they do not have conflicts of interest.

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