Annals of Stem Cell Research & Therapy

Review Article
Published: 31 Mar, 2018

GFI1B in Stem Cell Biology and Cancer

Anguita E[1], Candel FJ[2], Chaparro A[1] and Roldán-Etcheverry JJ[1]*

[1]Department of Hematology, Hospital Clinico San Carlos, IdISSC, Complutense University of Madrid, Spain

[2]Department of Microbiology, Hospital Clinico San Carlos, IdISSC, Complutense University of Madrid, Spain

Abstract

GFI1B was identified by sequence homology with the oncogene GFI1 (Growth Factor Independence 1). Both GFI1 and GFI1B transcription factors have six C-terminal C2H2 zinc-fingers and an N-terminal SNAG (SNAIL/GFI1) transcriptional repression domain. While GFI1 is essential for neutrophil differentiation and is also necessary for B and T lymphopoiesis, GFI1B is required for development of erythroid and megakaryocytic lineages. However, mounting evidences indicate that GFI1B has also a prominent role in hematopoietic stem cell quiescence and, according to its function in cell differentiation and stem cell maintenance, in cancer. Here we will briefly review the last findings on these aspects.

Keywords: GFI1B; Stem cell; Hematopoiesis; Cancer; Leukemia; Lymphoma

GFI1 and GFI1B Role in Hematopoiesis

Hematopoiesis, the process of blood cells formation, has established the paradigm for cell differentiation from tissue specific stem cells, the Hematopoietic Stem Cells (HSC). This model is particularly relevant to understand the pathogenesis of blood malignancies. Hematopoiesis is regulated by transcription factors (TFs) that are essential to establish the normal cell balance and they also play a fundamental role in disease, particularly in cancer. Growth Factor Independence 1 (GFI1) and its homolog GFI1B are lineage-specific TFs required for hematopoiesis. GFI1B was identified by its sequence homology with GFI1 [1,2]. In fact, GFI1 and GFI1B have two domains with over 95% identity. The conserved N-terminal SNAG domain contains 20 amino acids, which recruit proteins that modify histones [2-4]. This domain has a nuclear localization motif and plays an important role in transcriptional repression through the binding of cofactors lysine-specific histone demethylase 1A (KDM1A, also known as LSD1) and RCOR1/2 (COREST) [3,5,6]. Also highly conserved, the C-terminal domain consists of six C2-H2 zinc fingers. Fingers 1, 2, and 6 are required for protein interaction, whereas fingers 3–5 are necessary to bind DNA at an AATC containing sequence [TAAATCAC (T/A)GC (A/T)] [7,8]. Between both domains, there is a region with unknown function that completely differs in both proteins. This area is responsible for the size difference in both proteins: GFI1 has 422 amino acids (55 KDa), while full size GFI1B comprises 330 amino acids (37 KDa, CCDS6957). There is also a short 284 amino-acid GFI1B isoform (CCDS48049) that lacks the first two zinc-finger domains as a result of an alternative splicing, skipping exon 5 (ENST00000372123.4). Although GFI1 and GFI1B are similar in structure and share functional mechanisms, they show distinct cell expression patterns and roles. Both GFI1 and GFI1B are important in the differentiation of the first adult type HSCs from common endothelial-blood progenitors in the aorta-gonad-mesonephros region, silencing the endothelial program. However, the expression pattern of both genes is different: Gfi1 is specifically expressed within the dorsal aorta in endothelial cells and cells within emerging intra-aortic hematopoietic clusters, whereas Gfi1b expression is more associated with the fully formed intra-aortic hematopoietic clusters [9]. Conditional knock-out mice indicated Gfi1b is required for HSC quiescence. In these experiments, Gfi1b deficient mice show expansion of functional HSCs in the bone marrow and blood with high production of reactive oxygen species (ROS) (Figure 1) [10]. Further inactivation of Gfi1 suggested that both TFs can partly compensate each other, but at least one of them is required by HSCs. In agreement with that, Gfi1b is highly expressed in HSCs and its expression decreases with differentiation to Multi Potential Progenitors (MPPs). In contrast, Gfi1 shows lowest levels in HSCs and is up regulated in the MPP fractions (Figure 1) [10]. Cell fate modification experiments have further supported the importance of Gfi1b for HSC biology. In fact, Gfi1b is among the essential TFs sufficient to generate HSCs. Mouse embryonic fibroblasts can be transformed into endothelial-like cells that subsequently generate hematopoietic progenitor cells (HPCs) *in vitro* by over-expressing Gfi1b, c-Fos, Gata2 and Etv6. Although Etv6 increases the efficiency of this process, the first three TFs are enough to

OPEN ACCESS

Correspondence:
Anguita E, Department of Hematology, San Carlos Clinical Hospital, San Carlos Sanitary Research Institute (IdISSC), 28040, Madrid, Spain, Tel: (0034) 91 330 3491/37 99; E-mail: eduardo.anguita@salud.madrid.org

Received Date: *01 Feb 2018*
Accepted Date: *29 Mar 2018*
Published Date: *31 Mar 2018*

Citation:
Anguita E, Candel FJ, Chaparro A, Roldán-Etcheverry JJ. GFI1B in Stem Cell Biology and Cancer. Ann Stem Cell Res Ther. 2018; 2(2): 1013.

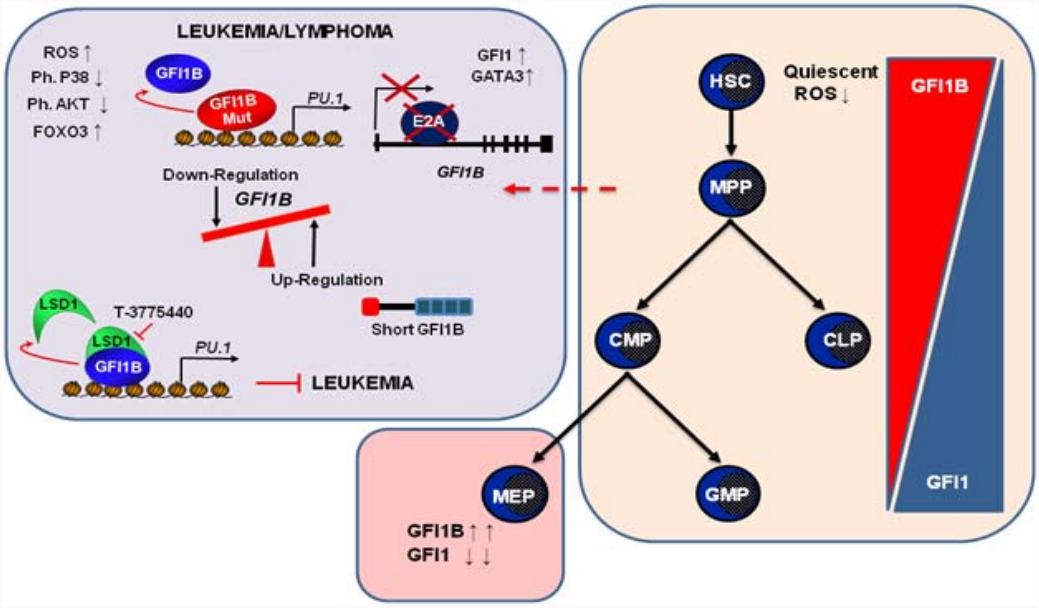

Figure 1: GFI1B role in hematopoietic stem cells (HSCs), lineage differentiation and blood malignancies.

achieve it [11]. More recently, Tsukada and colleagues have shown that teratomas derived from iPSCs obtained by reprogramming mice fibroblasts with Oct4, Sox2, and Klf4, generate *in vivo* functional long-term HSCs when hyper-express Gfi1b, c-Fos, and Gata2 [12]. GFI1 and GFI1B are also essential for lineage-specific differentiation. Knockout (KO) mice have revealed that Gfi1 is required for neutrophil differentiation; consistently, human GFI1 mutations are associated with severe congenital neutropenia [13,14]. Gfi1 is also necessary for B and T lymphopoiesis. Besides, Gfi1 is expressed in precursors of sensory neurons, the retina, specific lung cells, and in the central nervous system [15]. Instead, GFI1B is critical for expansion and differentiation of erythroid progenitors. Gfi1b KO embryos die by day E15 because of the lack of enucleated erythrocytes. Gfi1b KO mice also fail to develop megakaryocytes, but have arrested erythroid and megakaryocytic precursors in the fetal liver [16]. Loss of Gfi1b in adult mice stops erythroid development at an early progenitor stage, and blocks terminal megakaryocytic differentiation in the polyploid promegakaryocytes that fail to produce platelets [17]. In addition, moderate levels of GFI1B are expressed in immature B-cells, a subset of early T-cell precursors and peripheral blood granulocytes and monocytes [18,19]. GFI1B is very low or absent in Lymphoid-Primed Multipotent (LMPP), Common Lymphoid (CLP), Early Thymocyte (ETP), and Granulocyte-Monocyte Progenitors (GMPs) [20]. It seems that the short GFIB form is relevant for erythroid development as well as showing a stronger repressor activity than its long counterpart [21].The long GFI1B variant, for its part, has been found to be required for megakaryopoiesis, unlike the short variant which may, on the other hand, have an inhibitory effect on platelet production [22,23]. It has also been found that *in vitro* over-expression of Gfi1b inhibits myeloid differentiation of a myelomonocytic cell line, and that the lack of Gfi1 and Gfi1b expression produces a severe block in B cell development [2]. Although both proteins can greatly compensate for each other´s loss, they play unique differential roles *in vivo*. Consistent with this, Gfi1 hyper-expression can rescue erythroid and early megakaryocytic differentiation from adult mouse Gfi1b KO, but terminal megakaryocyte maturation defect cannot be compensated by Gfi1 or a Gfi1b hybrid containing the Gfi1 N-terminal portion [17]. These differences are patent in the inner ear where Gfi1b cannot replace Gfi1 function [24]. These findings show that GFI1B plays a major role in hematopoiesis. Its importance is also reflected by the strong control of its expression by several regulatory elements, particularly downstream the gene sequence, that bind both transcriptional activators and repressors [20,25-27]. This suggests that an appropriate GFI1B level may be relevant for its function.

GFI1B and Cancer

Consistent with Gfi1b function in megakaryopoiesis, different mutations in GFI1B are involved in platelet conditions [16,17,28]. However, in this review we shall focus on the recent insights on GFI1B role in cancer, particularly of hematopoietic lineages. When considering the development of acute leukemia, both mutations that block differentiation and those which promote proliferation or cell survival have been deemed necessary [29]. Besides its role in cell differentiation, GFI1B has pro-apoptotic activity when expressed in human CD34+ cells, disruption of these functions may contribute to leukemogenesis [30]. Initial expression studies found high levels of GFI1B in some primary CD34+ cells from human Acute Myeloid Leukemias (AMLs) and leukemic cell lines of erythroid and megakaryocytic lineages. Silencing GFI1B in these cell lines reduced proliferation and increased apoptosis [31]. High level of GFI1B expression was also observed in Chronic Myeloid Leukemia (CML), other Myelo Proliferative Neoplasms (MPN), AML, and B-lymphoblastic leukemias. Remarkably, the short GFI1B isoform was highly expressed in the leukemic cells. However, both isoforms were higher in CML after treating with tyrosine kinase inhibitors [32]. Silencing of both BCR-ABL1 and GFI1B in K562 CML cell line showed a cooperative anti-proliferative and pro-apoptotic effect [33]. In this context, the short form may be acting as a repressor over the long species. However, the low number of patients and controls analyzed implies that the conclusions of these works have to be taken with caution. In contrast, several pieces of evidence point to a GFI1B involvement in leukemia when its repressor function is reduced. In keeping with this, Gfi1b represses oncogene Meis1 [5]. Additionally, we have described a dominant negative GFI1B mutation, Asp262Asn

(c.784G>A, g. 135865264G>A in GRCh37/hg19), associated with Myelodysplastic Syndrome (MDS) transformation to AML. This mutation promotes the survival of normal and MDS human bone marrow CD34+ cells and skews lineage output of these normal adult primary cells and human cord blood common myeloid progenitors towards myeloid lineage. This mutant operates mainly through master hematopoietic regulator PU.1 (SPI1) (Figure 1) [34]. Consistently, PU.1 is up-regulated in JAK2 V617F-positive MPNs [35]. Corroborating the previous publication, Thivakaran et al. have very recently reported that GFI1B expression in AML samples is lower than in MDS and normal controls. Also, these authors found that low GFI1B expression in blast cells is associated with an inferior prognosis of MDS and AML patients. Although expression experiments in malignancy are difficult to compare with a normal counterpart and these were based on retrospective analysis, animal models in this publication strongly support the connection between low levels of GFI1B and myeloid malignancy, showing that loss/reduced expression of Gfi1b dose accelerated AML and MPN. These authors point to the ROS/p38/Akt/FoXO3 signalling cascade as one of the major players in this effect (Figure 1) [36]. As a consequence of this, GFI1B has turned out to be an anti-leukemia target. A recent report shows that a LSD1 inhibitor disrupts the LSD1–GFI1B interaction, inducing de-repression of GFI1B target genes (particularly PU.1), causing granulomonocytic transdifferentiation [37]. This recapitulates to great extent the dominant negative GFI1B mutant effect (Figure 1). However, in GFI1B expressing acute erythroleukemia and acute megakaryoblastic leukemia cell lines the drug has anti-leukemic effect both in xenograft and *in vitro* models that could be attributed to the cell identity modification. If this action is only cell context dependent and if it is related to the inhibition of the short form when it predominates, is something to be elucidated. Interestingly, the short form has been described to interact more efficiently with LSD1 than the full-length one [21]. Changes in GFI1B regulatory elements may also take part in blood neoplasms. A C>G transversion in GFI1B downstream region (rs621940, g.135870130C>G in GRCh37/hg19), has been associated with MPN patients and normal carriers of JAK2 V617F mutation, but not with normal unmutated individuals [38]. We also found GFI1B promoter mutations in human leukemias. Nevertheless, no clear connection between these mutations and the disease was demonstrated [39]. Like GFI1, GFIB has been associated to the pathogenesis of lymphoid malignancies. Consistent with the importance of GFI1B block in myeloid leukemias, TCF3 (E2A) prevention of T-lymphocyte progenitor transformation relies on GFI1B repression [40,41]. TCF3 is involved in human lymphoid leukemias and Tcf3 KO develops T-cell lymphoma. Ectopic expression of Tcf3 in Tcf3 -/- cells induces growth arrest and apoptosis, together with direct up-regulation of Gfi1b, but no Gfi1 (Figure 1). Gfi1b increased expression in these cells has the same consequences [42]. Another finding supporting the implication of GFI1B reduction in lymphoma comes from those expressing BCL6 (B-Cell Lymphoma 6). This is relevant because this gene is frequently expressed in T and B cell lymphomas. Also, BCL6 chromosomal rearrangements and/or mutations are associated with human lymphomas [43]. Gfi1b is a retrovirus integration site in diffuse large B cell lymphomas of mice containing the human BCL6 transgene, but it is not in the control ones. Again, Gfi1b expression was decreased in the first lymphomas compared with the latest. Besides, GFI1B was decreased in human BCL6 positive T and B cell lymphomas [44]. Outside the blood setting, GFI1B or GFI1 mutually exclusive activation has been associated with medulloblastoma. In most cases this is due to structural changes that juxtapose the coding sequences to active enhancer elements [45]. Paradoxically, these observations suggest that GFI1B contributes to cancer development when its expression is increased or reduced. More data is required to understand the context effect or the splicing variant contribution. However, other genes have been related to malignancy both when up regulated and functionally inactivated, including key regulators of hematopoiesis like PU.1 which is, as we said, a GFI1B target [35]. This may be the case of other critical factors for stem cell biology regulation, commitment and differentiation [36,46,47].

Acknowledgement

AC is supported by “Hay esperanza” foundation.

References

1. Rödel B, Wagner T, Zörnig M, Niessing J, Möröy T. The human homologue (GFI1B) of the chicken GFI gene maps to chromosome 9q34.13-A locus frequently altered in hematopoietic diseases. Genomics. 1998;54(3):580-2.
2. Tong B, Grimes HL, Yang TY, Bear SE, Qin Z, Du K, et al. The Gfi-1B proto-on co-protein represses p21WAF1 and inhibits myeloid cell differentiation. Mol Cell Biol. 1998;18(5):2462-73.
3. Grimes HL, Chan TO, Zweidler-McKay PA, Tong B, Tsichlis PN. The Gfi-1 proto-on co-protein contains a novel transcriptional repressor domain, SNAG, and inhibits G1 arrest induced by interleukin-2 withdrawal. Mol Cell Biol. 1996;16:6263-72.
4. Saleque S, Kim J, Rooke HM, Orkin SH. Epigenetic regulation of hematopoietic differentiation by Gfi-1 and Gfi-1b is mediated by the cofactors Co REST and LSD1. Mol Cel. 2007;27(4):562-72.
5. Chowdhury AH, Ramroop JR, Upadhyay G, Sengupta A, Andrzejczyk A, Saleque S. Differential transcriptional regulation of meis1 by Gfi1b and its co-factors LSD1 and Co REST. PloS One. 2013;8:e53666.
6. Upadhyay G, Chowdhury AH, Vaidyanathan B, Kim D, Saleque S. Antagonistic actions of R cor proteins regulate LSD1 activity and cellular differentiation. Proc Natl Acad Sci USA. 2014;111:8071-6.
7. Lee S, Doddapaneni K, Hogue A, McGhee L, Meyers S, Wu Z. Solution structure of Gfi-1 zinc domain bound to consensus DNA. J Mol Biol. 2010;397(4):1055-66.
8. Zweidler-McKay PA, Grimes HL, Flubacher MM, Tsichlis PN. Gfi-1 encodes a nuclear zinc finger protein that binds DNA and functions as a transcriptional repressor. Mol Cell Biol. 1996;16:4024-34.
9. Thambyrajah R, Patel R, Mazan M, Lie-a-Ling M, Lilly A, Eliades A, et al. New insights into the regulation by RUNX1 and GFI1(s) proteins of the endothelial to hematopoietic transition generating primordial hematopoietic cells. Cell Cycle. 2016;15:2108-14.
10. Khandanpour C, Sharif-Askari E, Vassen L, Gaudreau MC, Zhu J, Paul WE, et al. Evidence that growth factor independence 1b regulates dormancy and peripheral blood mobilization of hematopoietic stem cells. Blood. 2010;116(24):5149-61.
11. Pereira CF, Chang B, Qiu J, Niu X, Papatsenko D, Hendry CE, et al. Induction of a hemogenic program in mouse fibroblasts. Cell Stem Cell. 2013;13(2):205-18.
12. Tsukada M, Ota Y, Wilkinson AC, Becker HJ, Osato M, Nakauchi H, et al. In vivo generation of engraftable murine hematopoietic stem cells by Gfi1b, c-Fos, and Gata2 over expression within teratoma. Stem Cell Reports. 2017;9(4):1024-33.
13. Karsunky H, Zeng H, Schmidt T, Zevnik B, Kluge R, Schmid KW, et al. Inflammatory reactions and severe neutropenia in mice lacking the transcriptional repressor Gfi1. Nat Genet. 2002;30(3):295-300.
14. Person RE, Li FQ, Duan Z, Benson KF, Wechsler J, Papadaki HA, et al.

Mutations in proto-oncogene GFI1 cause human neutropenia and target ELA2. Nat Genet. 2003;34(3):308-12.

15. Wallis D, Hamblen M, Zhou Y, Venken KJ, Schumacher A, Grimes HL, et al. The zinc finger transcription factor Gfi1, implicated in lymphomagenesis, is required for inner ear hair cell differentiation and survival. Development. 2003;130(1):221-32.

16. Saleque S, Cameron S, Orkin SH. The zinc-finger proto-oncogene Gfi-1b is essential for development of the erythroid and megakaryocytic lineages. Genes Dev. 2002;16:301-6.

17. Foudi A, Kramer DJ, Qin J, Ye D, Behlich AS, Mordecai S, et al. Distinct, strict requirements for Gfi-1b in adult bone marrow red cell and platelet generation. J Exp Med. 2014;211(5):909-27.

18. Tabrizifard S, Olaru A, Plotkin J, Fallahi-Sichani M, Livak F, Petrie HT. Analysis of transcription factor expression during discrete stages of postnatal thymocyte differentiation. J Immunol. 2004;173(2):1094-102.

19. Vassen L, Okayama T, Möröy T. Gfi1b: Green fluorescent protein knock-in mice reveal a dynamic expression pattern of Gfi1b during hematopoiesis that is largely complementary to Gfi1. Blood. 2007;109(6):2356-64.

20. Moignard V, Macaulay IC, Swiers G, Buettner F, Schütte J, Calero-Nieto, et al. Characterization of transcriptional networks in blood stem and progenitor cells using high-throughput single-cell gene expression analysis. Nat Cell Biol. 2013;15:363-72.

21. Laurent B, Randrianarison-Huetz V, Frisan E, Andrieu-Soler C, Soler E, Fontenay M, et al. A short Gfi-1B isoform controls erythroid differentiation by recruiting the LSD1–CoREST complex through the dimethylation of its SNAG domain. J Cell Sci. 2012;125:993-1002.

22. Chen L, Kostadima M, Martens JHA, Canu G, Garcia SP, Turro E, et al. Transcriptional diversity during lineage commitment of human blood progenitors. Science. 2014;345(6204):1251033.

23. Polfus LM, Khajuria RK, Schick UM, Pankratz N, Pazoki R, Brody JA, et al. Whole-Exome Sequencing Identifies Loci Associated with Blood Cell Traits and Reveals a Role for Alternative GFI1B Splice Variants in Human Hematopoiesis. Am J Hum Genet. 2016;99(2):481-8.

24. Fiolka K, Hertzano R, Vassen L, Zeng H, Hermesh O, Avraham KB, et al. Gfi1 and Gfi1b act equivalently in haematopoiesis, but have distinct, non-overlapping functions in inner ear development. EMBO Rep. 2006;7(3):326-33.

25. Anguita E, Villegas A, Iborra F, Hernández A. GFI1B controls its own expression binding to multiple sites. Haematologica. 2010;95(1):36-46.

26. Xu W, Kee BL. Growth factor independent 1B (Gfi1b) is an E2A target gene that modulates Gata3 in T-cell lymphomas. Blood. 2007;109(10):4406-14.

27. May G, Soneji S, Tipping AJ, Teles J, McGowan SJ, Wu M, et al. Dynamic analysis of gene expression and genome-wide transcription factor binding during lineage specification of multipotent progenitors. Cell Stem Cell. 2013;13(6):754-68.

28. Songdej N, Rao AK. Inherited platelet dysfunction and hematopoietic transcription factor mutations. Platelets. 2017;28:20-6.

29. Gilliland DG. Molecular genetics of human leukemias: new insights into therapy. Semin Hematol. 2002;39(4):6-11.

30. Osawa M, Yamaguchi T, Nakamura Y, Kaneko S, Onodera M, Sawada KI, et al. Erythroid expansion mediated by the Gfi-1B zinc finger protein: role in normal hematopoiesis. Blood. 2002;100:2769-77.

31. Elmaagacli AH, Koldehoff M, Zakrzewski JL, Steckel NK, Ottinger H, Beelen DW. Growth factor-independent 1B gene (GFI1B) is over expressed in erythropoietic and megakaryocytic malignancies and increases their proliferation rate. Br J Haematol. 2007;136(2):212-9.

32. Vassen L, Khandanpour C, Ebeling P, van der Reijden BA, Jansen JH, Mahlmann S, et al. Growth factor independent 1b (Gfi1b) and a new splice variant of Gfi1b are highly expressed in patients with acute and chronic leukemia. Int J Hemato. 2009;89(4):422-30.

33. Koldehoff M, Zakrzewski JL, Beelen DW, Elmaagacli AH. Additive anti leukemia effects by GFI1B-and BCR–ABL-specific siRNA in advanced phase chronic myeloid leukemic cells. Cancer Gene Ther. 2013;20:421-7.

34. Anguita E, Gupta R, Olariu V, Valk PJ, Peterson C, Delwel R, et al. A somatic mutation of GFI1B identified in leukemia alters cell fate via a SPI1 (PU. 1) centered genetic regulatory network. Dev Biol. 2016;411(2):277-86.

35. Irino T, Uemura M, Yamane H, Umemura S, Utsumi T, Kakazu N, et al. JAK2 V617F-dependent up regulation of PU. 1 expression in the peripheral blood of myeloproliferative neoplasm patients. PloS One. 2011;6:e22148.

36. Thivakaran A, Botezatu L, Hönes JM, Schütte J, Vassen L, Al-Matary YS, et al. Growth factor independence 1b. A key player in the genesis and maintenance of acute myeloid leukaemia and myelodysplastic syndrome. Haematologica. 2018;103(4):614-25.

37. Ishikawa Y, Gamo K, Yabuki M, Takagi S, Toyoshima K, Nakayama K, et al. A Novel LSD1 Inhibitor T-3775440 Disrupts GFI1B-containing complex leading to trans differentiation and impaired growth of AML cells. Mol Cancer Ther. 2017;16(2):273-84.

38. Hinds DA, Barnholt KE, Mesa RA, Kiefer AK, Do CB, Eriksson N, et al. Germ line variants predispose to both JAK2 V617F clonal hematopoiesis and myeloproliferative neoplasms. Blood. 2016;128(8):1121-8.

39. Hernández A, Villegas A, Anguita E. Human promoter mutations unveil Oct-1 and GATA-1 opposite action on Gfi1b regulation. Ann Hematol. 2010;89(8):759-65.

40. Zörnig M, Schmidt T, Karsunky H, Grzeschiczek A, Möröy T. Zinc finger protein GFI-1 cooperates with myc and pim-1 in T-cell lymphomagenesis by reducing the requirements for IL-2. Oncogene. 1996;12(8):1789-801.

41. Scheijen B, Jonkers J, Acton D, Berns A. Characterization of pal-1, a common pro viral insertion site in murine leukemia virus-induced lymphomas of c-myc and Pim-1 transgenic mice. J Virol. 1997;71(1):9-16.

42. Xu W, Kee BL. Growth factor independent 1B (Gfi1b) is an E2A target gene that modulates Gata3 in T-cell lymphomas. Blood. 2007;109(10):4406-14.

43. Migliazza A, Martinotti S, Chen W, Fusco C, Ye BH, Knowles DM, et al. Frequent somatic hyper mutation of the 5'noncoding region of the BCL6 gene in B-cell lymphoma. Proc Natl Acad Sci USA. 1995;92:12520-4.

44. Baron BW, Anastasi J, Bies J, Reddy PL, Joseph L, Thirman MJ, et al. GFI1B, EVI5, MYB-Additional genes that cooperate with the human BCL6 gene to promote the development of lymphomas. Blood Cells Mol Dis. 2014;52:68-75.

45. Northcott PA, Lee C, Zichner T, Stütz AM, Erkek S, Kawauchi D, et al. Enhancer hijacking activates GFI1 family oncogenes in medulloblastoma. Nature. 2014;511(7510):428-34.

46. Moreau-Gachelin F, Wendling F, Molina T, Denis N, Titeux M, Grimber G, et al. Spi-1/PU.1 transgenic mice develop multistep erythroleukemias. Mol Cell Biol. 1996;16(5):2453-63.

47. Rosenbauer F, Wagner K, Kutok JL, Iwasaki H, Le Beau MM, Okuno Y, et al. Acute myeloid leukemia induced by graded reduction of a lineage-specific transcription factor, PU.1. Nat Genet. 2004;36(6):624-30.