



Review

Long non-coding RNAs in hematopoietic regulation

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ABSTRACT

Long non-coding RNAs (lncRNAs) have crucial roles via tethering with DNA, RNA or protein in diverse biological processes. These lncRNA-mediated interactions enhance gene regulatory networks and modulate a wide range of downstream genes. It has been demonstrated that several lncRNAs act as key regulators in hematopoiesis. This review highlights the roles of lncRNAs in normal hematopoietic development and discusses how lncRNA dysregulation correlates with disease prognoses and phenotypes.

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1. Introduction

The human genome is pervasively transcribed, with a percentage of almost 75% DNA sequence transcribed into RNAs. Nevertheless, only less than 2% of genome encodes proteins.¹ Previous research showed that, in general, the more complex the eukaryotes are, the larger amounts of non-coding RNAs (ncRNAs) they possess.² This suggests that ncRNAs play pivotal roles in the evolution of eukaryotic biological complexity and are indispensable components of transcriptomes.^{3,4} According to the length, ncRNAs are categorized into two main types: small ncRNAs and long non-coding RNAs (lncRNAs). Small ncRNAs include microRNAs (miRNAs), PIWI-interacting RNAs (pi-RNAs), small nuclear RNAs (snRNAs), small nucleolar RNAs (snoRNAs), and other classes of small regulatory RNAs.⁵ lncRNAs are currently defined as transcripts greater than 200 nucleotides with no apparent open reading frames (ORFs).⁶

As research continues, the number of lncRNAs increases constantly due to deeper and more sensitive RNA sequencing technologies.^{7,8} This exploding class of transcripts increasingly attracts attention of researchers. Although there are more and more documented lncRNAs,⁹ details about lncRNAs are still uncovered. Studies have revealed that several annotated lncRNAs turn to encode for small peptides. For instance, a micropeptide named myoregulin, which is essential for muscle performance, is encoded by a putative lncRNA.¹⁰ Also, lncRNA LINC00961 encodes for SPAR polypeptide, which is involved in mTORC1 pathway regulation and muscle regeneration.¹¹ Thus, with the help of these hidden peptides, lncRNAs could more finely regulate specific biological process.

Although lncRNAs are expressed at lower level than protein-coding genes, they tend to be more cell-type specific.^{1,3,8} Studies have shown that lncRNAs are restricted to be transcribed in precise developmental and cellular context,^{12–15} indicating they might act as ‘fine-tuners’ of cell fate. Moreover, it has been reported that lncRNAs participate in multiple important biological processes, including genomic imprinting, dosage compensation, pluripotency,^{15,16} cell differentiation and other pathological processes.^{17–20} For example, lncRNA *Xist* in X chromosome inactivation,^{21–23} *Kcnq1ot1* in genomic imprinting,^{24,25} *Evf2* in neural cell fate determination,²⁶ *linc-MD1* in muscle differentiation,^{27,28} *MALAT1* in diabetes and cancers.^{29,30}

While most well-characterized lncRNAs are shaped with 5' cap structure and 3' poly(A) tails, studies have revealed new formats: such non-polyadenylated lncRNAs are transcribed by RNA

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polymerase III, or processed by RNase P cleavage to generate a mature 3' end, or capped by snoRNP complexes at both ends, or by forming circular structures.^{31,32} Due to their structural diversity, ways of lncRNAs involved in diverse regulation are plentiful.³³ Evidence so far indicates that lncRNAs act mainly through interacting with RNA, DNA or protein.³⁴ In cytoplasm, lncRNAs can bind to protein or RNA: they can act as “miRNA sponge” to decoy specific miRNA and lead to miRNA inactivation; also, they could function as scaffold, tethering protein to form complex, due to their structural flexibility.^{34,35} In nucleus, lncRNAs cooperate with protein to regulate chromatin state *in cis* or *in trans*,^{36,37} they also guide protein to particular genomic loci via RNA-DNA interactions.⁷ Therefore, lncRNAs could modulate multiple cellular contexts, including chromatin remodeling, transcription, pre-mRNA splicing and RNA stability.^{35,38,39}

In this review, we discuss with a particular focus on how lncRNAs contribute to normal hematopoiesis, and how dysregulation of lncRNAs takes responsibility for malignant hematopoiesis.

2. LncRNAs in normal hematopoiesis

Hematopoiesis is a dynamic process of formation of all kinds of blood cells. In vertebrate, there are multiple waves of hematopoiesis during development.⁴⁰ The first primitive wave produces unipotent blood cell types. It is transient and replaced by the definitive wave, which generates multipotent hematopoietic progenitors.^{40,41} The definitive wave produces long-term hematopoietic stem cells (LT-HSCs) which have robust multilineage repopulating hematopoietic activity. The blood cell development is intricate and well-regulated and the hematopoietic hierarchy serves as a good paradigm for research. Lots of factors and pathways are involved in this process, including lncRNAs.^{40,42–44} (See Fig. 1).

2.1. Hematopoietic stem cells (HSCs)

Mature blood cells derive from the hematopoietic stem cells (HSCs), which are able to self-renew and have the capacity to give rise to multipotent progenitors, then yielding red blood cells, megakaryocytes, monocytes and lymphocytes via unilineage differentiation. In general, HSCs have the potential to rebuild the entire blood system.⁴⁰ Observations suggest that several lncRNAs function as key regulators of HSC maintenance and differentiation.

To assess the functional lncRNAs in HSC, Goodell and her colleagues comprehensively identified lncRNAs specific to HSC.⁴⁵ They first identified and annotated two functional lncRNAs, named *lncHSC-1* and *lncHSC-2*. *lncHSC-1* is an HSC-specific lncRNA, whereas *lncHSC-2* occurs in both HSCs and other progenitors. Knockdown of *lncHSC-1* results in increased myeloid differentiation. However, knockdown of *lncHSC-2* promotes T cell differentiation and affects HSC self-renewal to some extent.⁴⁵ The *Dlk1-Gtl2* locus preserves LT-HSC function by inhibiting mitochondrial metabolism. Qian and colleagues described unique fingerprint lncRNAs in 17 Hematopoietic cell types and revealed that lncRNAs from the *Dlk1-Gtl2* Locus predominantly enriched in CD49b^{lo} LT-HSCs. These lncRNAs might also preserve LT-HSC function.⁴⁶ Furthermore, another study indicated that the imprinted lncRNA gene *H19* is highly expressed in long-term HSCs (LT-HSCs), regulating HSC self-renewal.⁴⁷ Conditional deletion of the maternal *H19* leads to LT-HSCs decrease and short-term HSCs (ST-HSCs) increase. *H19*-deficient HSCs lose their quiescence and begin to proliferate, and finally are exhausted. Interestingly, this phenomenon is due to the de-repression of Igf2 and Igf1r. In turn, *H19*-deficient phenotype can be partially rescued by inactivation of Igf1r.⁴⁷ Taken together, lncRNA *H19* modulates HSC quiescence

and self-renewal via the Igf2–Igf1r pathway. Similarly, lncRNA *Xist* deficiency in HSCs causes aberrant maturation and age-dependent-loss.⁴⁸ The metastasis-associated lung adenocarcinoma transcript 1, *MALAT1*, is a marker for lung cancer metastasis.⁴⁹ lncRNA *Malat1* is regulated by p53 and plays a significant role in maintaining the proliferation potential of early-stage hematopoietic cells.⁵⁰

2.2. Erythroid, myeloid and lymphoid cells

With the help of next-generation sequencing of cells at key stages of erythropoiesis, erythroid specific lncRNA, lncRNA erythroid prosurvival (*lncRNA-EPS*), was annotated.⁵¹ Evidence suggests that, lncRNA-EPS promotes erythroid differentiation and inhibits apoptosis of mature erythrocytes. It is demonstrated that lncRNA-EPS represses many apoptotic gene, such as *Pycard*.⁵¹ In addition, *lncRNA-EPS*-deficient mice show enhanced inflammation, because lncRNA-EPS acts as a transcriptional brake to repress immune response genes expression by interacting with hnRNPL.⁵² Another lncRNA, lncRNA-EC7, derived from an enhancer region, could act *in cis* to activate its neighbor gene *BAND3*, which is a major anion transporter on erythrocyte membranes.⁴³ Also, enhancer derived (elncRNAs) *elncRNA-EC3* functions as *cis*-regulator to promote *KIF2A* expression during erythropoiesis.⁴³ *Shlnc-EC6* is highly expressed in late stage of erythroid cells and regulates murine erythroid enucleation via Rac1/PIP5K signal pathway.⁵³ Long noncoding monocytic RNA (lnc-MC) promotes monocyte/macrophage differentiation by soaking up miR-199a-5p and releasing ACVR1B expression.⁵⁴ Moreover, Eosinophil Granule Ontogeny (*EGO*) is an lncRNA involved in eosinophil development.⁵⁵ *EGO* is highly expressed in mature eosinophils and diminished *EGO* leads to decreased basic protein expression and eosinophil derived neurotoxins, which are essential components of eosinophil development.⁵⁵ *HOXA* transcript antisense RNA myeloid-specific 1 (*HOTAIRM1*) is an lncRNA expressed from the human *HOXA* cluster.⁵⁶ This lncRNA specifically occurs in myeloid lineage and implicates in the regulation of granulocytic differentiation.⁵⁷ Knockdown of *HOTAIRM1* in NB4 promyelocytic leukemia cells inhibits *HOXA1* and *HOXA4* expression, as well as CD11b and CD18, the hallmarks of mature granulocytes.⁵⁸ Nonetheless, the exact mechanisms still await for clarification.

Lymphocyte development involves a complex series of tightly choreographed events. Cao and his colleagues identify *lnc-DC* and make elaborate explanation on its role in human dendritic cell differentiation.⁵⁹ lnc-DC is exclusively expressed in classical antigen-presenting DCs (cDCs). Knockdown of lnc-DC during human monocyte-derived DCs (Mo-DC) differentiation results in impaired DC differentiation along with down-regulated expression of numerous DC-function-related genes. Mechanistically, lnc-DC binds to STAT3 and enhances its phosphorylation, which is a novel mechanism of lncRNAs, involving in the posttranslational modification.⁵⁹ BIC is a primary microRNA (pri-miR-155) and can be processed to miR-155. B cell lymphomas patients show accumulation of miR-155 and ncRNA BIC.⁶⁰ High levels of B-cell receptor triggers BIC expression, indicating BIC might involve in the selection of B cells.⁶¹

Moreover, lncRNAs also implicate in the modulation of innate immune and inflammatory responses.^{34,62,63} *Lethe*, a mammalian pseudogene lncRNA, is usually induced by inflammatory cytokines via NF- κ B.⁶⁴ Conversely, *Lethe* could bind to RelA, a subunit of NF- κ B, and functions as a NF- κ B decoy molecule, forming a negative feedback loop.⁶⁴ Similarly, the p50-associated COX-2 extragenic RNA (*PACER*) also acts as a decoy lncRNA for the NF- κ B signaling pathway and interacts with NF- κ B subunit p50 to sequester it away from *PTGS2* promoter.⁶⁵

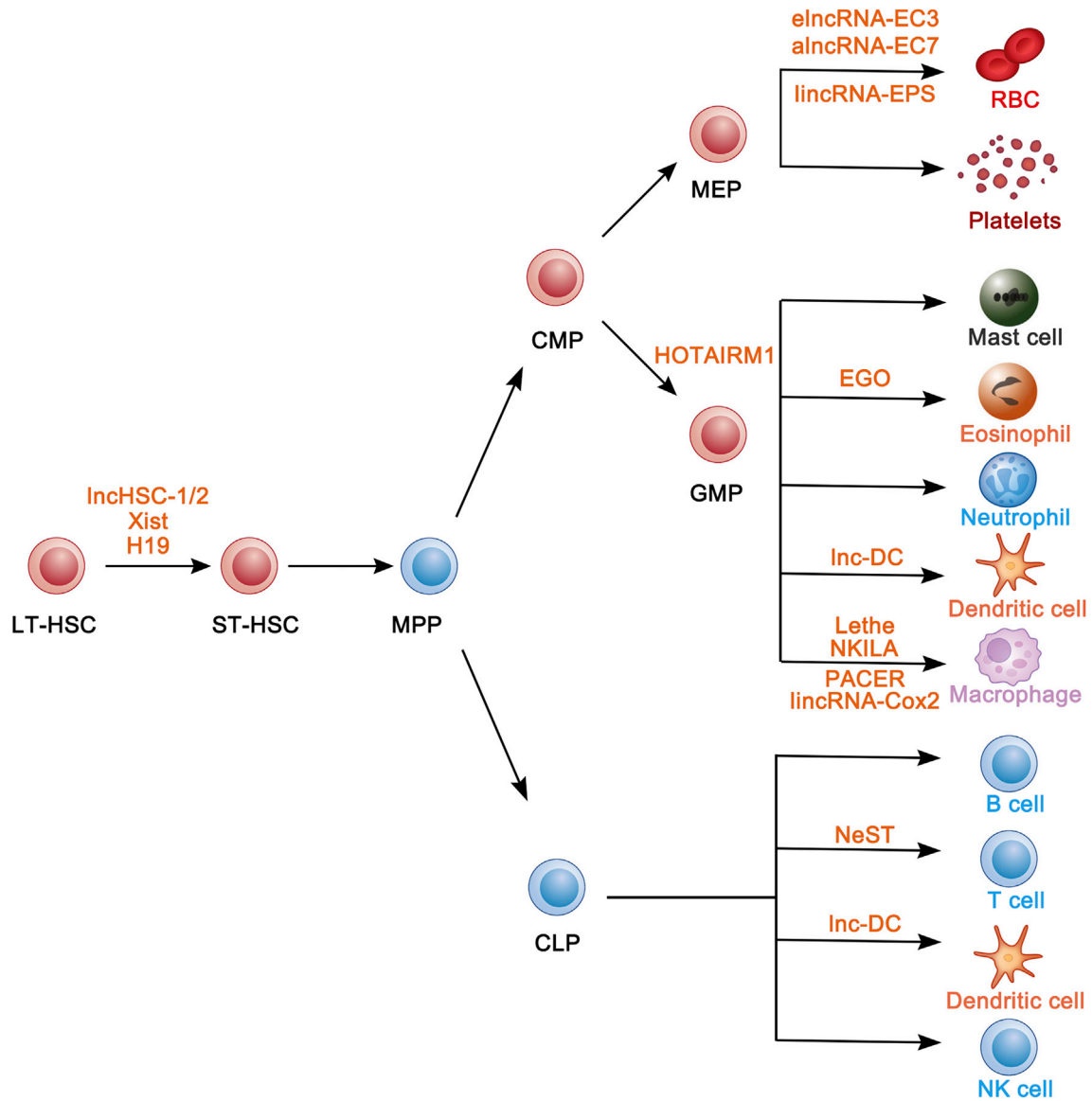


Fig. 1. lncRNAs in normal hematopoiesis. Several lncRNAs are involved in the blood cell development. *lncHSC-1/2*, *Xist* and *H19* regulate HSC quiescence and self-renewal. *lincRNA-EPS*, *alncRNA-EC7* and *elncRNA-EC3* modulate red blood cell formation. *HOTAIRM1* functions in granulocytic differentiation. *EGO* promotes eosinophil differentiation. *lincRNA-Cox2*, *NKILA*, *PACER*, and *Lethe* participate in the innate immune response. *NeST* correlates to T cell formation. *linc-DC* is essential for dendritic cell differentiation.

Another NF- κ B interacting lncRNA, *NKILA*, could suppress breast cancer metastasis via negative regulating NF- κ B signaling.⁶⁶ Additionally, *lincRNA-Cox2* modulates the expression of inflammatory molecules by interacting with hnRNP-A/B and hnRNP-A2/B1 in innate immune response.⁶⁷ lncRNA *NeST*, also known as *Tmevpg1*, occurs in CD8⁺ T and CD4⁺ T helper 1 (Th1) cells, could control microbial susceptibility through its control of *IFN- γ* gene.^{68–71}

3. lncRNAs in malignant hematopoiesis

As we described above, normally expressed lncRNAs ensure healthy hematopoietic development. Conversely, dysregulated lncRNAs trigger blood diseases.^{72–77} (See Fig. 2).

3.1. Chronic myelogenous leukemia (CML)

Chronic myelogenous leukemia (CML), also known as chronic myeloid leukemia, is characterized by unregulated growth of

myeloid cells, especially immature granulocytes in bone marrow. The main cause of CML is Bcr–Abl translocation. It has been suggested that *lncRNA-BGL3* acts as a tumor-suppressor in Bcr–Abl-mediated CML.⁷⁸ BGL3 inhibits tumorigenesis by sensitizing Bcr–Abl-positive K562 leukemic cells to undergo imatinib-induced apoptosis. Mechanistically, BGL3 functions as a competitive endogenous RNA (ceRNA) for tumor suppressor gene Phosphatase and Tensin homolog (*PTEN*).⁷⁸ Another lncRNA involved in the Bcr–Abl-induced hematopoietic malignancies is *H19*.⁷⁹ In contrast to BGL3, *H19* facilitates Bcr–Abl-mediated leukemogenesis.⁷⁹ Loss of imprinting leads to *H19* activation, which is found to be a frequent event in adult T-cell leukemia/lymphoma (ATL).⁸⁰

3.2. Chronic lymphocytic leukemia (CLL)

B cell chronic lymphocytic leukemia (CLL), is a malignancy diagnosed by demonstration of an abnormal population of B lymphocytes in blood. Remarkably, deletion of 13q14.3 occurs in more

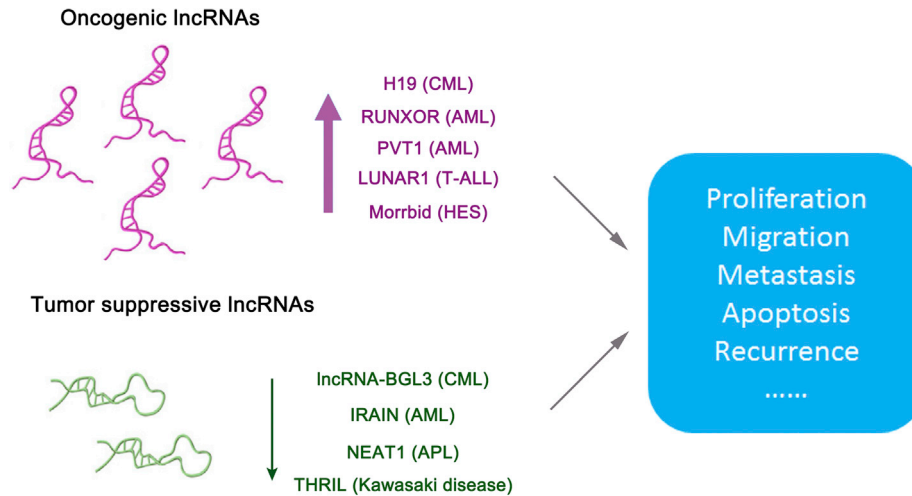


Fig. 2. LncRNAs in malignant hematopoiesis. Some lncRNAs share close relationship with hematopoietic diseases. They act as oncogenic or tumor suppressive lncRNAs. *H19* and *lncRNA-BGL3* are associated with chronic myeloid leukemia (CML). *RUNXOR*, *PVT1* and *IRAIN* are involved in acute myeloid leukemia (AML). *LUNAR1* acts as an oncogene in T cell acute lymphoblastic leukemia (T-ALL). *Morrbid* is highly expressed in patients with hypereosinophilic syndrome (HES). *NEAT1* expression is repressed in *de novo* acute promyelocytic leukemia (APL) patients. Similarly, Kawasaki disease patients with severe symptoms show decreased *THRIL* expression.

than 50% patients.^{81–86} Two lncRNAs, *DLEU1* and *DLEU2*, are found to be transcribed from this genomic region and display hypermethylation in CLL patients. It has been demonstrated that these two lncRNAs could regulate NF- κ B signaling pathway, affecting leukemia cell survival.⁸³ Besides, deleting *DLEU2* in mice results in CLL, and this phenotype is discovered to have a correlation with abnormal cell-cycle progression.^{87,88}

3.3. Acute myeloid leukemia (AML)

Acute myeloid leukemia (AML) progresses rapidly and patients often die within weeks if untreated. Surprisingly, more than 55% adult AML patients are found to be associated with recurrent genetic abnormalities.^{89–91} lncRNAs have been described to involve in AML and used as biomarkers for outcome.⁹² For instance, lncRNA *IRAIN*, an intragenic lncRNA transcribed from the antisense direction of Insulin-like Growth Factor type I Receptor gene (*IGF1R*), is implicated in AML cell growth.⁹³ Moreover, the hypermethylation of lncRNA *MEG3* promoter is often observed in AML patients, and might serve as a biomarker for poor prognosis.^{94,95} lncRNA *HOTAIRM1*, an lncRNA located between *HOXA1* and *HOXA2*, might provide novel insights into AML treatment, due to the well-known feature of dysregulated *HOX* genes in AML.^{96–98} The *RUNX1* overlapping RNA (*RUNXOR*), an lncRNA transcribed from *RUNX1* promoter and overlapping with *RUNX1*, could initiate leukemogenesis through interacting with *RUNX1*.⁹⁹ Other lncRNAs correlate with AML include *PVT1* and *NEAT1*.^{100–103}

3.4. Acute lymphoblastic leukemia (ALL)

Acute lymphoblastic leukemia (ALL) patients carry large number of immature lymphocytes. Several functional lncRNAs have been reported to contribute to ALL progression. For example, lncRNA *LUNAR1* acts as an oncogenic gene in T cell acute lymphoblastic leukemia (T-ALL).¹⁰⁴ *LUNAR1* works by enhancing *IGF1R* mRNA expression and modulating Notch signaling pathway.¹⁰⁴ Also, the lncRNA B-ALL-associated long RNAs-2 (*BARL-2*) is annotated to have correlation with corticosteroid treatment response in B-ALL.¹⁰⁵

Intriguingly, it has been proposed that the famous lncRNA *Xist* is associated with hematological cancer.⁴⁸ Actually, X chromosome

aneuploidies have been documented to be with different human cancers, such as breast and ovarian cancers.^{106,107} Given the significant role of *Xist* in this process,^{108,109} it is reasonable that *Xist* might be linked to blood tumor. Another strong evidence is that *Xist* deletion in female mice results in myeloproliferative neoplasm and myelodysplastic syndrome (mixed MPN/MDS).⁴⁸

3.5. Immunological diseases

Myeloid RNA regulator of Bim-induced death (*Morrbid*) is a conserved lncRNA, which implicates in the regulation of lifespan of short-lived myeloid cells, such as neutrophils and eosinophils.¹¹⁰ Interestingly, *Morrbid* is highly expressed in patients with hypereosinophilic syndrome (HES), a disease characterized by a persistently elevated eosinophil count in the blood. *In vivo* loss-of-function study shows that *Morrbid* deficiency results in short-lived myeloid cell reduction, and *Morrbid*-deficient mice are more vulnerable when facing bacterial infection. Mechanism behind this regulation is that *Morrbid* works *in cis* to repress its neighbor gene *Bcl2l11*, a pro-apoptotic molecular, by recruiting PRC2 to its promoter. Given the function of *Morrbid* during the myeloid cell regulation, it might serve as a potential therapeutic target in inflammatory diseases.¹¹⁰ Furthermore, TNF α and hnRNPL related immunoregulatory lncRNA (*THRIL*) also plays an important role in inflammatory immune responses.¹¹¹ By way of interacting with hnRNPL and binding to TNF α promoter, *THRIL* promotes TNF α transcription and thus implicates in the innate immune response. In turn, high levels of TNF α decrease *THRIL* expression. Consistent with this discovery, Kawasaki disease patients with severe symptoms show decreased *THRIL* level, and this might be a potential biomarker for inflammatory diseases.¹¹¹ Consistently, given the significant role of lncRNAs in inflammatory response, it is tantalizing to uncover new drug targets and effective therapeutic by intervene these crucial lncRNAs.^{64,67}

4. Conclusions

lncRNAs have gained increasing attention, as their physiological and pathological functions are being gradually understood. Among them, several lncRNAs are key regulators of normal hematopoiesis, and their dysregulation could lead to hematopoietic disorders.

Therefore, the comprehensive characterization of lncRNAs in blood development might not only help us better understand hematopoiesis but provide a new set of opportunities for future clinical translation.

Conflicts of interest

The authors declare no conflict of interest.

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