Emerging role of long non-coding RNAs in normal and malignant hematopoiesis

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Abstract

Long noncoding RNAs (lncRNAs) have recently been discovered and are increasingly recognized as vital components of modern molecular biology. Accumulating evidence shows that lncRNAs have emerged as important mediators in diverse biological processes such as cell differentiation, pluripotency, and tumorigenesis, while the function of lncRNAs in the field of normal and malignant hematopoiesis remains to be further elucidated. Here, we widely reviewed recent advances and summarize the characteristics and basic mechanisms of lncRNAs and keep abreast of developments of lncRNAs within the field of normal and malignant hematopoiesis. Based on gene regulatory networks at different levels of lncRNAs participation, lncRNAs have been shown to regulate gene expression from epigenetics, transcription and post transcription. The expression of lncRNAs is highly cell-specific and critical for the development and activation of hematopoiesis. Moreover, we also summarized the role of lncRNAs involved in hematological malignancies in recent years. LncRNAs have been found to play an emerging role in normal and malignant hematopoiesis, which may provide novel ideas for the diagnosis and therapeutic targets of hematological diseases in the foreseeable future.

Keywords: Long non-coding RNA; Hematopoiesis; Hematological malignancies

Introduction

With the development of the genome-wide transcriptome studies, pervasive researches are currently focusing on non-protein-coding regulatory RNAs (ncRNAs), which were regarded as junk or noises of transcripts previously.[1] The concept that non-coding RNAs do play crucial roles in regulating gene expression at the levels of transcription, RNA processing, and translation has been recognized for several years.[2-4] According to the transcript size, ncRNAs are generally classified into two major groups: short ncRNAs (<200 nucleotides) or long ncRNAs (>200 nucleotides). MicroRNAs (miRNAs), a typical representative of short ncRNAs, have been best studied and known to induce mRNA degradation or block mRNA translation via the RNA interference pathway[1,4] and recognized as powerful regulators of numerous genes and pathways in the pathogenesis of hematological diseases.[5-8] In contrast, abundant long non-coding RNAs (lncRNAs) have recently been discovered and are increasingly recognized as vital components of modern molecular biology. Accumulating evidence shows that lncRNAs can modulate diverse biological processes such as cell proliferation, differentiation, pluripotency, apoptosis, and tumorigenesis.[9-13] The exploration of the characteristics and mechanisms of them is at a relatively initial stage yet, and especially the function of lncRNAs in the field of hematopoiesis remains to be further elucidated. In this review, we will succinctly summarize the characteristics and mechanisms of lncRNAs and focus on the latest progress of lncRNAs in normal and malignant hematopoiesis.

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Characteristics and Functions of Long Non-coding RNAs

Long non-coding RNAs are defined as a heterogeneous class of ncRNAs longer than 200 nucleotides which feature distinguishe them from small regulatory RNAs such as miRNAs, small nucleolar RNAs (snoRNAs), piwi-interacting RNAs (piRNAs), short interfering RNAs (siRNAs), and other short RNAs. LncRNAs could be localized to the nucleus or cytoplasm and are most abundant in the nucleus, which is different from mRNAs that are mostly transported to the cytoplasm.[14,15] According to the NONCODE database (current version v5.0, http://www.noncode.org), which is an integrated knowledge database dedicated to non-coding RNAs and currently recruits the lncRNA information of 17 species, there are 172,216 and 131,697 lncRNA transcripts of human and mouse at present, respectively.

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Due to the high heterogeneity of the sequence, structure and biological function of lncRNAs, there are various classification methods so far. Generally, in light of their proximity to protein-coding mRNAs, lncRNAs could be classified into the following categories[16]: (1) the long intergenic ncRNA (lincRNA), which comes from the region between two genes; (2) intronic lncRNA, which originates from the intron region of secondary transcript (sometimes mRNA precursor sequence); (3) sense lncRNA, which overlaps with one or more exons of another protein-coding gene of the synonymous chain; (4) antisense lncRNA, which overlaps with one or more exons of another protein-coding gene in the opposite strand; and (5) bidirectional lncRNAs, whose transcription start site is very close to the protein gene encoding on the antisense strand, but the direction of transcription is the opposite. Based on the features and special functions of lncRNAs, it also includes lncRNA-activating (lncRNA-a), transcribed pseudogene lncRNAs, telomere-associated ncRNAs (TERRAs), transcribed ultraconserved regions (T-UCRs), enhancer RNAs (eRNAs), circular RNAs, etc.[17-19]

According to recent advances, the characteristics of lncRNAs can be summarized as follows: Firstly, no different than mRNA, most lncRNAs whose promoter can also bind transcription factors are also polyadenylated, spliced, and modified with 5′-cap and poly-A tail, and also transcribed by RNA polymerase II (RNAPII). They have dynamic expression and different splicing modes during differentiation.[20,21] Secondly, lncRNAs are relatively conservative in function although they contain fewer longer exons and lower evolutionary sequence conservation compared with mRNAs.[22,23] Thirdly, most lncRNAs are expressed at relatively lower levels but have more obvious temporal and spatial expression specificity compared with mRNAs in the process of tissue differentiation and development.[24-26]

Up to now, the precise mechanism of lncRNA is not entirely clear. Nevertheless, based on gene regulatory networks at different levels of lncRNA participation, lncRNAs have been shown to regulate gene expression in three ways: epigenetics, transcription, and post-transcription[27-29] [Figure 1]. First, lncRNAs can catalyze the synthesis of chromatin remodeling complexes into specific genomic loci. For example, the recruitment of polycomb complex to the *HOXD* gene cluster by lncRNA *HOTAIR* and *Xist/RepA* results in three methylations (*me3K27*) of histone H3 27th lysine in the X chromosome and induces heterochromatin formation, which finally inhibits gene expression in this region.[30] Second, lncRNAs may participate in transcriptional regulation of target genes by regulating the transcription of neighboring protein-coding genes, interacting with transcription factors, or forming three-helix complexes with DNA. For instance, lncRNA *pncRNA-D* (promoter-associated ncRNA-D) can bind to the gene cyclinD1 and recruit RNA binding protein *TLS* (Translocated in LipoSarcoma) to regulate histone acetyltransferase activity of protein *CBP* and *P300*, and then inhibiting the transcription of *cyclin D1*.[31] Third, lncRNAs may affect any step in post-transcriptional gene expression including regulating alternative splicing of mRNA precursor, being spliced into non-coding small RNA, regulating mRNA stability and abundance, or the role of competitive endogenous RNA (ceRNA).[32-34]

Long Non-coding RNAs in Normal Hematopoiesis

Hematopoietic stem cells (HSCs) are characterized by the ability to execute a cascade of cell fates, including self-renewal, controlled expansion of progenitor cells, and timely differentiation into terminally mature blood cells.[35] The process of differentiation of hematopoietic lineages is critically driven by the interaction of external stimuli and intracellular regulatory programs. Lineage-specific lncRNA molecules are also emerging as important regulators of gene expression during hematopoiesis [Table 1 and Figure 2].

LncRNAs in Erythropoiesis

Erythropoiesis is a developmental process that is critically controlled by multiple regulators to ensure the proper generation of mature red blood cells and the transportation of oxygen to tissues.[36] Inspired by the "chromatin-state maps" approach pioneered by Guttman *et al*[59] less than a decade ago, the Biomedical Research group of Cambridge identified the first erythroid-specific lncRNA *lincRNA erythroid prosurvival (lincRNA-EPS)*, which could facilitate erythropoiesis by repressing the expression of Pycard, a proapoptotic gene, without altering erythroid differentiation.[36,37] Subsequent studies also discovered multiple lncRNAs that are dynamically expressed during erythropoiesis and are targeted by key erythroid transcription factors such as *GATA1*, *TAL1*, or *KLF1*.[60] *AlncRNA-EC7* was one of the identified lncRNAs. Reduction of *alncRNA-EC7* expression in erythroblasts induced *BAND3* (a major anion exchange protein present on erythrocyte membranes[61]) gene expression via chromatin interactions between the *alncRNA-EC7* locus and the neighboring region of the *BAND3* promoter leading to impaired erythrocyte maturation.[36,38] Recently, a research group also released their findings that *lncRNA Fas-antisense 1 (Fas-AS1 or Saf)* was induced during differentiation through the activity of essential erythroid transcription factors *GATA-1* and *KLF1*. They further discovered that *Saf* was also negatively regulated by *NF-κB* and that over-expression of *Saf* in erythroblasts derived from $CD34^+$ hematopoietic stem/progenitor cells of healthy donors could reduce surface levels of *Fas* and consequently conferred protection against *Fas*-mediated cell death signals.[39,40] Although current studies of lncRNAs in erythropoiesis are largely done in the murine models, these advances expand the repertoire of lncRNA functions and provide a novel genetic pathway that can be exploited with effective targets for the treatment of various anemia-related diseases in the future.[36]

LncRNAs in Myeloid Hematopoiesis

Almost a decade ago, Zhang *et al*[62] unveiled the first myeloid lineage-specific lncRNA *HOTAIRM1* (HOX antisense intergenic RNA myeloid 1) which is transcribed between the human *HOXA1* and *HOXA2* genes. In-depth research revealed that *HOTAIRM1* contributed to three-dimensional conformational changes of chromosomes

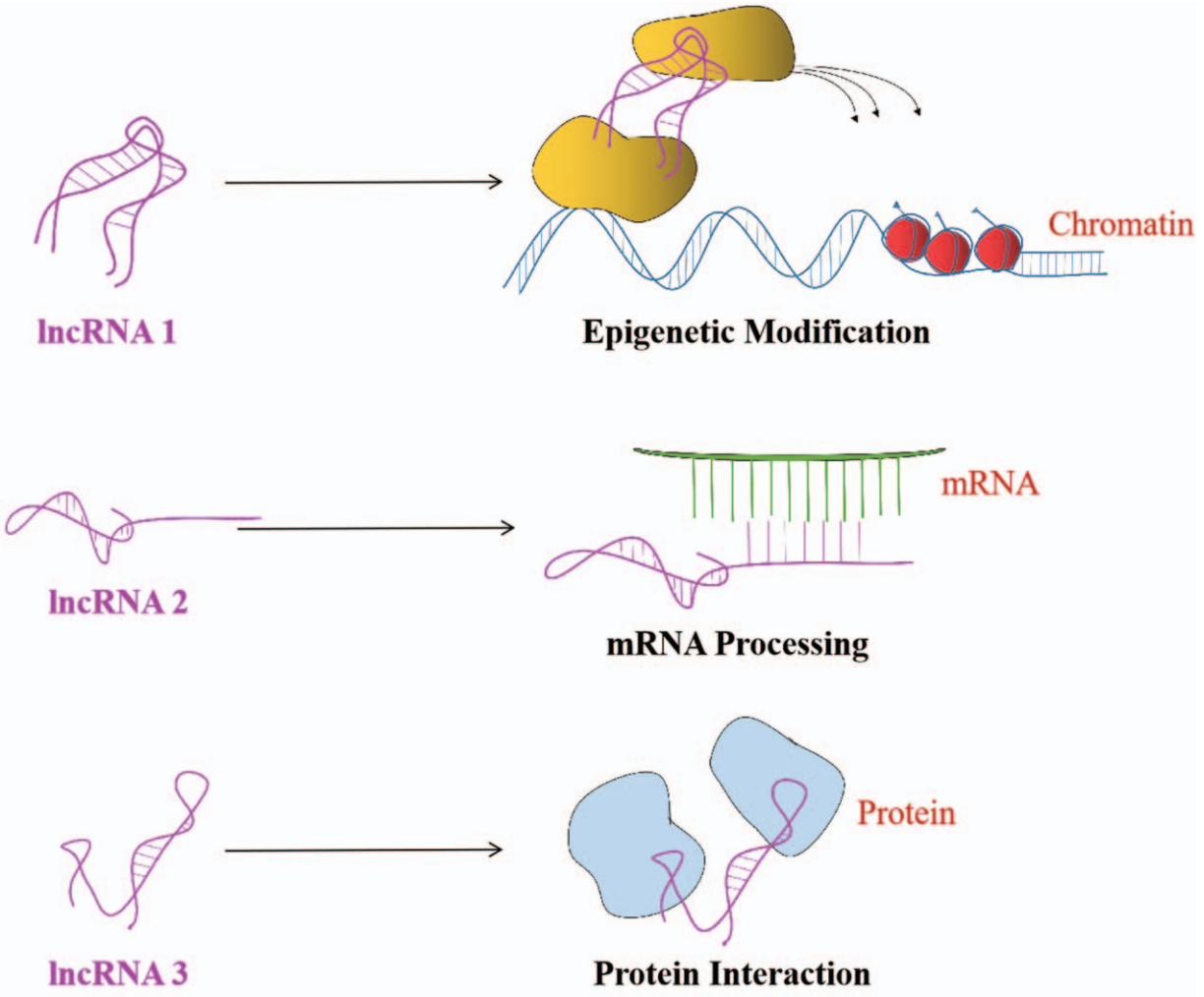

Figure 1: Schematic diagram of the basic regulatory mechanism of lncRNAs. The purple ones are lncRNAs. lncRNAs: Long non-coding RNAs.

which were required for the temporal collinear activation of *HOXA* genes.[41] Functional studies showed that knockdown of *HOTAIRM1* could quantitatively impaire all-*trans* retinoic acid (*ATRA*)-induced myeloid differentiation and selectively attenuated differentiation-related transcripts such as *CD11b*, *CD18*, *HOXA1*, and *HOXA4*.[62] Subsequent studies showed that the master transcription factor *PU.1* during myeloid differentiation could directly activate the expression of *HOTAIRM1* through binding to the regulatory region of *HOTAIRM1*.[41] A recent study revealed that the high expression of *HOTAIRM1* could enhance *ATRA*-induced *PML-RARA* degradation by affecting autophagic flux.[42] Conclusively, these advances indicate that *HOTAIRM1* may be a novel potential therapeutic target for acute promyelocytic leukemia (APL).

The lncRNA *EGO* (eosinophil granule ontogeny) is a novel, nested, non-coding RNA, expressed during eosinophil development from CD34$^+$ human HSCs and mature eosinophils. RNA silencing assays investigated that *EGO* regulated granule protein *MBP* (major basic protein) and *EDN* (eosinophil derived neurotoxin) transcript expression in developing CD34 hematopoietic progenitors.[43]

Lymphoid Differentiation-related lncRNAs

CD4$^+$ T cells play central roles in mediating adaptive immunity against various pathogens. With T-cell receptor activation by specific cytokines, naive CD4$^+$ T cells may differentiate into one of several lineages of T helper (Th) cells, including Th1, Th2, Th17, and inducible regulatory T cell (iTreg), as defined by their pattern of cytokine production and function.[63] The diversity of CD4$^+$ T-cell subsets enables the adaptive immune system to adapt to many challenges during the expression of genes encoding cytokines and transcription factors.[64]*NeST* (Nettoie Salmonella pas Theiler's; cleanup Salmonella not Theiler's), formally known as *Tmevpg1* or *IFNG-AS1*, is a long non-coding RNA specifically expressed in Th1 cells by a *T-bet* (a Th1-specific key transcription factor) dependent mechanism. *NeST* RNA was found to bind *WDR5*, a component of the histone H3 lysine 4 methyltransferase complex and to alter histone 3 methylation at the interferon-gamma locus, ultimately leading to the regulation of the expression of *IFN-γ*.[44,45] Another Th1-specific lncRNA is *linc-MAF-4* whose expression is negatively correlated with *MAF*, a Th2-associated transcription factor. Studies suggest that *linc-MAF-4* could

Table 1: Long non-coding RNAs involved in the normal hematopoiesis.

Hematopoiesis type	LncRNAs	Function	References
Erythropoiesis	*LincRNA-EPS*	Promotes erythropoiesis by inhibiting the expression of *PyCARD*	[36,37]
	AlncRNA-EC7	Down-regulation induces gene *BAND3* expression and leads to impaired erythrocyte maturation	[38]
	Fas-AS1 (or Saf)	Induced during differentiation through the activity of essential erythroid transcription factors *GATA-1* and *KLF1*	[39,40]
Leukemogenesis	*HOTAIRM1*	Knockdown results in quantitatively impaired ATRA-induced myeloid differentiation and selectively attenuated differentiation-related transcripts	[41,42]
	EGO	Regulates granule protein *MBP* and *EDN* transcript expression in developing CD34 hematopoietic progenitors	[43]
Th1 $CD4^+$ T	*NeST (Tmevpg1 or IFNG-AS1)*	Binds to *WDR5* and alters histone 3 methylation at the *IFN-γ* locus in Th1 cells by a T-bet dependent mechanism	[44,45]
	Linc-MAF-4	Regulates *MAF* transcription by recruitment of chromatin modifiers and down-regulation could skew T-cell differentiation toward Th2	[46]
Th2 $CD4^+$ T	*LincR-Ccr2-5'AS*	Regulates Th2-specific gene expression Th2 cell migration	[47,48]
	GATA3-AS1	Co-regulated by the same regulatory elements and might have shared functions with *GATA3* in Th2-cell response	[49]
	TH2-LCR	Transcribed from the *RAD50* locus and significantly required for expression of genes encoding Th2 cytokines	[50]
Th17 $CD4^+$ T	*Rmrp*	Regulates the function of *RORγt* transcriptional complexes at a subset of critical genes in the Th17 effector program	[51,52]
Treg	*Flicr*	Dampens the Treg signature and may lower Treg stability, allowing stronger antiviral responses by destabilizing *Foxp3*	[53]
	Lnc-EGFR	Positively correlates with expression of *EGFR/Foxp3* and augments immunosuppression by promoting Treg cell differentiation	[54]
$CD8^+$ T	*LncRNA-CD244*	Mediates *IFN-γ* and *TNF-α* expression and improves protective immunity of $CD8^+$ T cells by interacting with *EZH2*	[55,56]
B cell	*lncRNA-CSR*	Regulate the differentiation and antibody response of B cell	[57]
	CRNDE	Its expression in primarily pre-B1, pre-B2, and centroblasts is consistent with its role as a metabolic regulator	[58]

LincRNA-EPS: LincRNA erythroid prosurvival; *Fas-AS1 (or Saf)*: Fas-antisense 1; *HOTAIRM1:* HOX antisense intergenic RNA myeloid 1; *EGO*: Eosinophil granule ontogeny; *NeST* (Tmevpg1 or IFNG-AS1): Nettoie Salmonella pas Theiler's; cleanup Salmonella not Theiler's; *GATA3-AS1*: GATA3-Antisense1; *TH2-LCR:* TH2-locus control region; *Flicr*: Foxp3 long intergenic non-coding RNA; *Lnc-EGFR*: Lnc-epidermal growth factor receptor; *lncRNA-CSR*: LncRNA-class switch DNA recombination; *CRNDE*: Colorectal neoplasia differentially expressed; *PyCARD*: Human apoptosis-associated speck-like protein containing a CARD; *KLF1*: Kruppel-like factor 1; *ATRA*: All-trans retinoic acid; *MBP*: Major basic protein; *EDN*: Eosinophil derived neurotoxin; *RAD50*: Recombinant DNA repair protein; *RORγt*: Retinoid-related orphan receptor gamma-t; *EZH2*: Enhancer of zeste homolog 2.

regulate *MAF* transcription by recruiting chromatin modifiers and that down-regulation of *linc-MAF-4* could skew T-cell differentiation toward the Th2 phenotype.[46]

Hu *et al*[47,48] identified 1524 lincRNA clusters from early T-cell progenitors to terminally differentiated T-helper subsets, among which *lincR-Ccr2-5′AS*, regulated by *GATA*-3 (a zinc-finger transcription factor, highly expressed in Th2 cells and critical to Th2 differentiation by regulating Th2 gene expression), was considered to be an essential part of the regulation in Th2-specific gene expression and important for Th2 cell migration. In the same year, another research group also reported a *GATA-3*-associated lncRNA *GATA3-AS1* which was specifically expressed in primary Th2 cells. Their results indicate that the expression of *GATA3-AS1* and *GATA3* might be co-regulated by the same regulatory elements and might have shared functions in Th2 cell responses.[49] By whole-genome sequencing (RNA-seq), Spurlock *et al*[50] identified a cluster of antisense lncRNAs *TH2-LCR*, which was transcribed from the *RAD50* locus that is co-expressed with *IL4*, *IL5*, and *IL13* genes under Th2 polarizing conditions. Their analyses demonstrated that *TH2-LCR* is significantly required for the expression of genes encoding Th2 cytokines.

The differentiation of Th17 cells requires the nuclear hormone receptor *RORγt* which focuses on the activity of a cytokine-regulated transcriptional network including genes encoding the signature Th17 cytokines (IL-17A, IL-17F, IL-22).[65] Huang and colleagues identified the lncRNA *Rmrp*, RNA component of mitochondria RNA-processing endoribonuclease (RNase *MRP*), as a key *DDX5* (*DEAD*-box protein 5, an RNA helicase possessing an important role in gene expression)-associated RNA, which could regulate the function of *RORγt* transcriptional complexes at a subset of critical genes implicated specifically in the Th17 effector program.[51,52]

Regulatory T cells (Tregs) characterized by the transcription factor *FoxP3* are a fundamental component in maintaining immune homeostasis by negatively regulating several immunocyte lineages, especially during autoimmune, tumor, and lymphoproliferative pathologies.[66] A

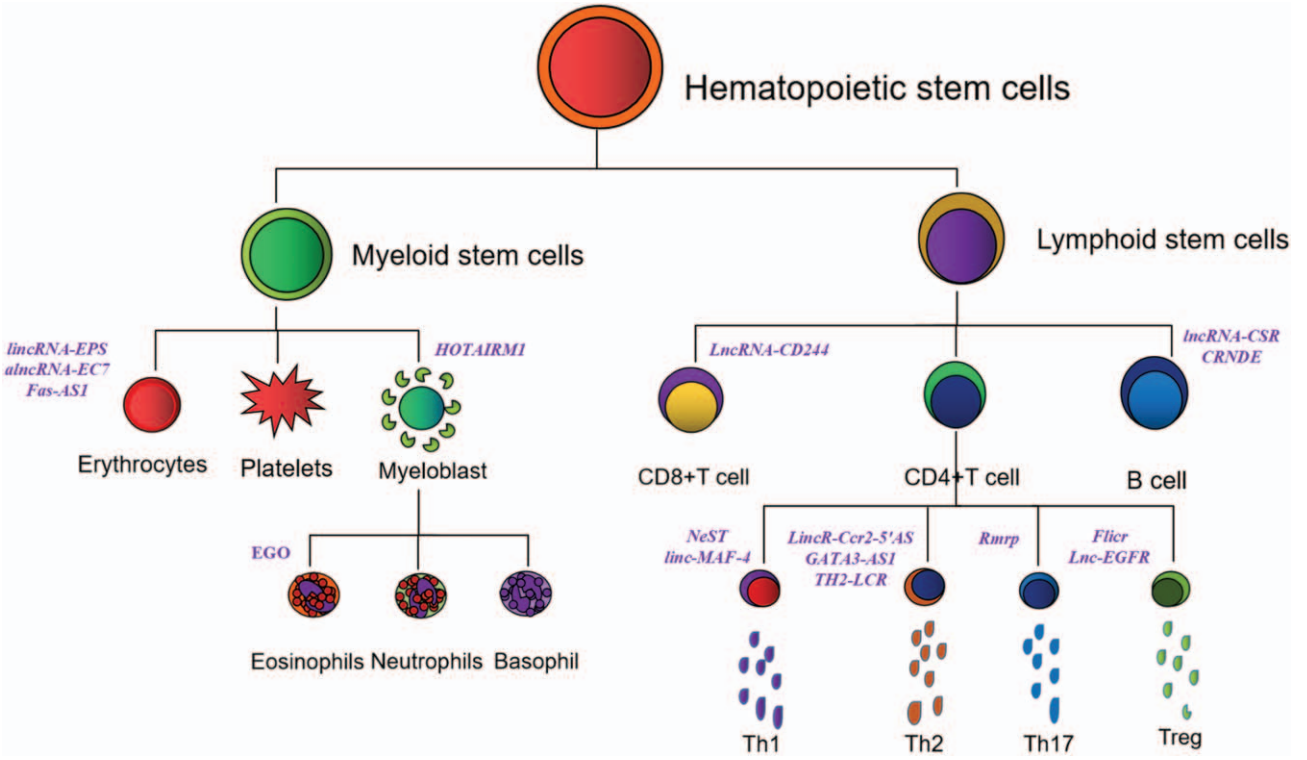

Figure 2: Schematic diagram of lncRNA regulating normal hematopoietic differentiation. The purple ones are the name of lncRNAs. lncRNAs: Long non-coding RNAs; Th1: Type 1 helper T cells; Th2: Type 2 helper T cells; Th17: Type 17 helper T cells; Treg: Regulatory T cells; *lincRNA-EPS*: lincRNA erythroid prosurvival; *Fas-AS1 (or Saf)*: Fas-antisense 1; *HOTAIRM1*: HOX antisense intergenic RNA myeloid 1; EGO: Eosinophil granule ontogeny; *NeST* (Tmevpg1 or IFNG-AS1): Nettoie Salmonella pas Theiler's; cleanup Salmonella not Theiler's; *GATA3-AS1*: GATA3-antisense 1; *TH2-LCR*: TH2-locus control region; *Flicr*: Foxp3 long intergenic non-coding RNA; *lnc-EGFR*: Lnc-epidermal growth factor receptor; *lncRNA-CSR*: LncRNA-class switch DNA recombination; *CRNDE*: Colorectal neoplasia differentially expressed.

recent study identified a lncRNA *Flicr* whose expression profile and genomic localization displayed Treg specificity, partially overlapping *Foxp3*. Further assays revealed that *Flicr* dampens the Treg signature and may lower Treg stability, allowing stronger antiviral responses by destabilizing *Foxp3*.[53] Another novel Treg-related lncRNA is *lnc-EGFR* (lnc-epidermal growth factor receptor), whose up-regulation positively correlates with the expression of *EGFR/Foxp3*. Mechanism research shows that *lnc-EGFR* is a potential enhancer of *EGFR* and its downstream *AP-1/NF-AT1* axis, and could augment immunosuppression by promoting Treg cell differentiation which may offer a potential therapeutic target for certain carcinomas.[54]

Wang *et al*[55,56] revealed that the expression of CD244, a T-cell-inhibitory molecule in $CD8^+$ T-cell immune responses during tuberculosis (TB) infection, correlated with high levels of a lncRNA *lncRNA-CD244*. Functional assays demonstrated that *lncRNA-CD244* could mediate *IFN-γ* and *TNF-α* expression and improve the protective immunity of $CD8^+$ T cells by interacting with *EZH2* (enhancer of zeste homolog 2, a chromatin-modification enzyme).[56]

B cells develop from the common lymphoid progenitor cells in the bone marrow and the initial antigen-independent phase is characterized by immunoglobulin gene rearrangements.[67] As the central drivers of immune humoral response, B cells development and function are influenced by a series of gene regulation.[68] Using RNA-seq and *de novo* transcript assembly, researchers have identified several lncRNAs involved in the development, activation, proliferation, and differentiation of B cells, such as *lncRNA-CSR* and *CRNDE*.[57,58,69]

Long Non-coding RNAs in Malignant Hematopoiesis

In addition to the normal hematopoietic process regulated by a variety of lncRNAs, abnormal interference of lncRNA regulation also inevitably leads to hematopoietic dysfunction, mainly in the occurrence of leukemia, lymphoma, and myeloma. At present, several lncRNAs related to hematological malignancies have been identified and summarized in the following sections [Table 2 and Figure 3].

AML-related lncRNAs

The expression of nuclear paraspeckle assembly transcript 1 (*NEAT1*), a novel lncRNA localized specifically to nuclear paraspeckles, has a vital regulatory role in many human malignancies[70,99] and was indicated to be repressed by *PML-RARα* in *de novo* APL samples. Furthermore, significant *NEAT1* up-regulation was observed during (*ATRA*)-induced NB4-cell differentiation.[71]

Another group performed transcriptome-wide lncRNA expression profiling of acute myeloid leukemia (AML) and identified that lncRNAs up-regulated in AML are associated with a lower degree of DNA methylation and

Table 2: Long non-coding RNAs involved in the malignant hematopoiesis.

Hematologic disease	LncRNAs	Function	References
APL	*NEAT1*	Repressed by *PML-RARα* in *de novo* APL	[70,71]
AML	*RUNXOR*	Interactions with the *RUNX1* promoter and enhancer and up-regulated in AML	[72]
	IRAIN	Interactions with the *IGF1*R promoter and enhancer DNA sequences and down-regulated in AML	[73]
	LOC285758	Regulates proliferation of AML cell lines by enhancing the expression of *HDAC2*	[74,75]
	CCDC26	Controls growth of myeloid leukemia cells through regulating the expression of KIT in patients with relapsed AML	[76]
CML	*PLIN2*	Positive correlates with *CEBPA* in CML via *GSK3* and Wnt/β-catenin signaling	[77]
	LncRNA-BGL3	Functions as a ceRNA for binding a subset of microRNAs to cross-regulate *PTEN* expression	[78,79]
	HOTAIR	Plays a crucial role in the development of *MDR* to imatinib by a *PI3K/Akt*-dependent way	[80]
	HULC	Positively correlates with imatinib-induced apoptosis of CML cells and inhibits c-Myc expression and *PI3K/Akt* pathway activity	[81]
	UCA1	Important modulator of multidrug resistance protein-1 for *IM* resistance in CML	[82]
ALL	*LUNAR1*	Correlates with its coding neighbor gene *IGF1R* and up-regulated in primary T-ALL samples with a Notch mutation	[83,84]
	BALR-2	Knockdown leads to apoptosis of B-ALL cell lines and up-regulation correlates with poor patient response to prednisone	[85]
CLL	*CRNDE*	Hypermethylation correlates with a poor outcome in patients with CLL	[86]
	AC012065.7	Hypomethylation correlates with a poor outcome in patients with CLL	[86]
	MIAT	Positively correlates with aggressive CLL carrying either 17p-, 11q-, or 13p-	[87]
B-cell lymphoma	*FAS-AS1*	Regulates Fas-mediated apoptosis by inhibiting *EZH2* in NHL	[88,89]
Burkitt lymphoma	*MINCR*	Knockdown associated with a reduction in *MYC* binding to the promoters of certain cell cycle genes in *MYC*-positive Burkitt lymphomas	[90]
DLBCL	*PANDA*	Down-regulated in patients with DLBCL and functions as a tumor suppressor gene through silencing *MAPK/ERK* signaling pathway	[91,92]
HL	*LINC00116 and LINC00461*	Over-expressed in HL	[93]
	FLJ42351	A remarkable RS cell-specific expression in HL	[93]
MM	*MEG3*	Plays an essential role in osteogenic differentiation in bone marrow MSCs partly by activating transcription of *BMP4* in MM	[94]
	MALAT1	Initiates the activation of Sp1 on *LTBP3* promoter in MSCs from MM	[95]
MDS	*Linc-RPIA*	Binds miR-429 and may be involved in the regulation of tumor-related genes, including *FOXO1* and *TP53*	[96]
	HOXB-AS3	Promote myeloid cell proliferation and was an adverse prognostic marker in MDS patients with a low IPSS index	[97]
AA	*TDRG1*	Regulated by *FGF1* and enhance the proliferation of BMSCs	[98]

APL: Acute promyelocytic leukemia; AML: Acute myeloid leukemia; CML: Chronic myeloid leukemia; T-ALL: T-cell acute lymphocytic leukemia; B-ALL: B-cell acute lymphocytic leukemia; CLL: Chronic leukemia; DLBCL: Diffuse large B-cell lymphoma; NHL: Non-Hodgkin lymphoma; HL: Hodgkin lymphoma; MM: Multiple myeloma; MDS: Myelodysplastic syndromes; AA: Aplastic anemia; ceRNA: Competitive endogenous RNA; *NEAT1*: Nuclear paraspeckle assembly transcript 1; *RUNXOR*: RUNX1 overlapping RNA; *PLIN2*: Perilipin 2; *lncRNA-BGL3*: LncRNA-BetaGlobinLocus3; *HOTAIR*: Hox transcript antisense RNA; *HULC*: Highly up-regulated in liver cancer; *UCA1*: Urothelial carcinoma-associated 1; *LUNAR1*: LeUkemia-induced non-coding activator RNA; *BALR-2*: B-ALL-associated long RNA-2; *CRNDE*: Colorectal neoplasia differentially expressed; *MIAT*: Myocardial infarction-associated transcript; *MINCR*: MYC-induced lncRNA; *PANDA*: P21-associated ncRNA DNA damage activated; *MEG3*: maternally expressed gene 3; *MALAT1*: Metastasis-associated lung adenocarcinoma transcript 1; *RUNX1*: Runt-related transcription factor 1; *IGF1R*: Insulin-like growth factor-1 receptor; *HDAC*: Histone deacetylase; *CEBPA*: CCAAT/enhancer-binding protein-α; *GSK-3*: glycogen synthase kinase-3; *PTEN*: Gene of phosphate and tension homology deleted on chromosome 10; *MDR*: Multidrug resistance; *IM*: Imatinib; *EZH2*: Enhancer of zeste homolog 2; *MAPK/ERK*: Mitogen-activated protein kinase/extracellular regulated protein kinases; RS: Reed-Sternberg; MSC: Mesenchyma stem cell; *BMP4*: Bone morphogenetic protein 4; *LTBP3:* Latent-transforming growth factor beta-binding protein 3; IPSS: International prognostic integration system; *FGF1*: Fibroblast growth factor 1.

a higher ratio of being bound by transcription factors such as *SP1*, *STAT4*, *ATF-2*, and *ELK-1* compared with those down-regulated in AML. Moreover, they found that a novel lncRNA *LOC285758* is associated with the poor prognosis in patients with AML and regulates the proliferation of AML cell lines by enhancing the expression of *HDAC2* (histone deacetylase 2), a potential therapeutic target in AML blasts.[74,75]

Accumulating evidence has shown that the insulin-like growth factor type I receptor (*IGF1R*) is one of the most important regulators in the progression and therapeutic resistance of AML.[100] A novel intragenic lncRNA *IRAIN* was discovered to directly interact with the IGF1R promoter and enhancer chromatin DNA sequences. Moreover, *IRAIN* was down-regulated both in leukemia cell lines and high-risk patients with AML.[73]

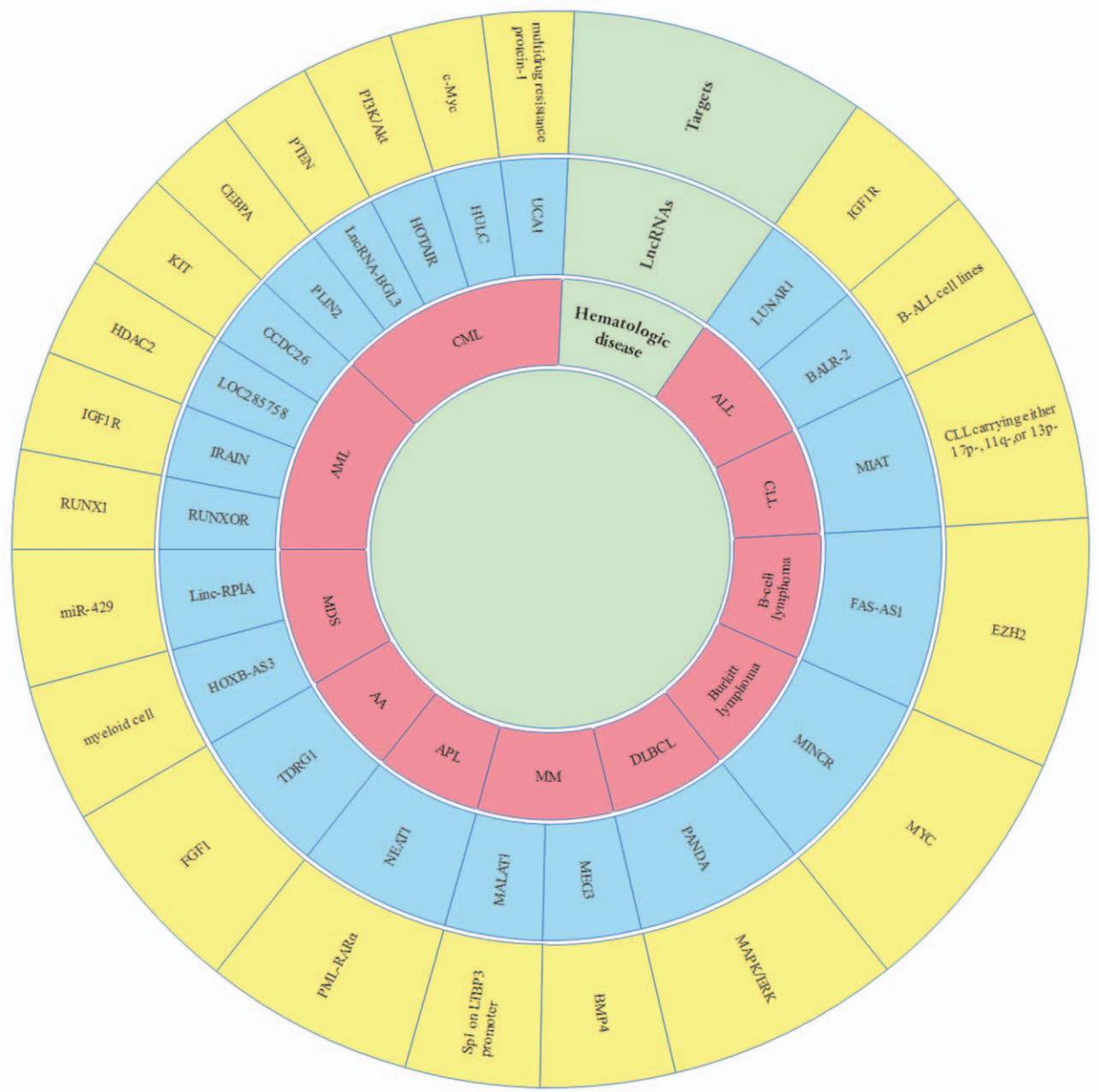

Figure 3: The relationship between lncRNA and its targets on the hematological diseases. The inner red part of the circle is the name of hematologic disease. The middle blue part of the circle is the name of lncRNAs. The outer yellow part of the circle is the target of hematologic disease regulated by lncRNAs. lncRNAs: Long non-coding RNAs; APL: Acute promyelocytic leukemia; AML: Acute myeloid leukemia; CML: Chronic myeloid leukemia; B-ALL: B-cell acute lymphocytic leukemia; CLL: Chronic leukemia; DLBCL: Diffuse large B-cell lymphoma; NHL: Non-Hodgkin lymphoma; HL: Hodgkin lymphoma; MM: Multiple myeloma; MDS: Myelodysplastic syndromes; AA: Aplastic anemia; *NEAT1*: Nuclear paraspeckle assembly transcript 1; *RUNXOR*: RUNX1 overlapping RNA; *PLIN2*: Perilipin 2; *lncRNA-BGL3*: LncRNA-BetaGlobinLocus 3; *HOTAIR*: Hox transcript antisense RNA; *HULC*: Highly up-regulated in liver cancer; *UCA1*: Urothelial carcinoma-associated 1; *LUNAR1*: LeUkemia-induced non-coding activator RNA; *BALR-2*: B-ALL-associated long RNA-2; *CRNDE*: Colorectal neoplasia differentially expressed; *MIAT*: Myocardial infarction-associated transcript; *MINCR*: MYC-induced lncRNA; *PANDA*: P21-associated ncRNA DNA damage activated; *MEG3*: Maternally expressed gene 3; *MALAT1*: Metastasis-associated lung adenocarcinoma transcript 1; *RUNX1*: Runt-related transcription factor 1; *IGF1R*: Insulin-like growth factor-1 receptor; *HDAC:* Histone deacetylase; *CEBPA*: CCAAT/enhancer-binding protein-α; *GSK-3*: Glycogen synthase kinase-3; *PTEN:* Gene of phosphate and tension homology deleted on chromosome 10; *EZH2*: Enhancer of zeste homolog 2; *MAPK/ERK*: Mitogen-activated protein kinase/extracellular regulated protein kinases; *BMP4:* Bone morphogenetic protein 4; *LTBP3:* Latent-transforming growth factor beta-binding protein 3; *FGF1*: Fibroblast growth factor 1.

Distinctive lncRNA profiles were found associated with common recurrent mutations in AML, such as *FLT3-ITD* (internal tandem duplications in the FLT3 gene) or *NPM1*, *CEBPA*, *IDH2*, and *RUNX1* genes.[101] Utilizing a novel R3C (RNA-guided chromatin conformation capture) method,[102] Wang *et al*[72] described a *RUNX1*-intragenic lncRNA *RUNXOR* (RUNX1 overlapping RNA), which is transcribed by an upstream promoter and overlaps with *RUNX1* (one of the most frequently mutated genes in AML[103]). *RUNXOR* was up-regulated in both AML samples and Ara-C-treated cell lines. The in-depth study showed that *RUNXOR* directly interacted with the *RUNX1* promoter and enhancer chromatin DNA sequences through its 3′-terminal fragment.

Another lncRNA *CCDC26*, which is thought to transcriptionally regulate a set of genes and associated with pediatric AML,[104,105] was also proved to controls growth of myeloid leukemia cells through regulation the expression of *KIT*,[76] a receptor tyrosine kinase that have been considered to up-regulated in leukemia stem cells from patients with AML who relapsed after chemotherapy.[106]

CML-related lncRNAs

A comprehensive analysis of lncRNAs in human chronic myeloid leukemia (CML) cells was performed and a novel lncRNA *lncRNA-BGL3* was observed to serve as a key regulator of *Bcr-Abl*-mediated cellular transformation. Functional assays suggested that *lncRNA-BGL3* was highly induced in response to the disruption of *Bcr-Abl* expression or by inhibiting *Bcr-Abl* kinase activity in cell lines and patients with CML. Notably, *lncRNA-BGL3* may function as a ceRNA that binds a subset of microRNAs to cross-regulate *PTEN* (phosphatase and tensin homolog, a critical tumor suppressor gene) expression.[78,79]

Hughes *et al*[77] identified more than 900 lncRNAs which are regulated by *CEBPA* (CCAAT/enhancer-binding protein-α), a critical regulator of myeloid differentiation, and many of them are induced during myeloid differentiation of AML cell lines including lncRNA *PLIN2*. Another group recently further investigated the potential roles of *CEBPA*-related lncRNA *PLIN2* during CML. Results indicated that both *CEBPA* and *PLIN2* were up-regulated in the process of CML and there was a positive correlation between *CEBPA* and *PLIN2* in patients with CML. Moreover, they found that *CEBPA*-mediated up-regulation of *PLIN2* expression promotes the development of CML via GSK3 and Wnt/β-catenin signaling.[107]

Recent studies have also reported some newly discovered lncRNAs that are associated with CML. For instance, lncRNA *HOTAIR* may play a crucial role in the development of multidrug resistance (MDR) to imatinib in CML via a *PI3K/Akt*-dependent mechanism.[80] Another lncRNA *HULC* was also revealed to be positively correlated with imatinib (IM)-induced apoptosis of CML cells and lead to the reduction of c-Myc expression and inhibition of *PI3K/Akt* pathway activity.[81]*lncRNA UCA1* was identified as another important modulator of multidrug resistance protein-1 (*MDR1*) which is considered as the main reason for IM resistance in CML cells.[82]

T-lymphocytic leukemia-related lncRNAs

LUNAR1 (LeUkemia-induced non-coding activator RNA) is a pivotal lncRNA involved in T-cell leukemia (T-ALL), an aggressive hematological neoplasm derived from malignant T-lymphocyte progenitors with aberrant *NOTCH1* signaling.[108] Evidence indicated that *LUNAR1* is highly correlated with its coding neighbor gene *IGF1R*, which has been previously suggested to play a role in T-ALL.[83,84] Trimarchi *et al*[84] have revealed that the expression of *LUNAR1* was up-regulated in primary T-ALL samples especially in ones with a Notch mutation, while down-regulated upon Notch inhibition.

B-lymphocytic leukemia-related lncRNAs

Unbiased microarray profiling was performed on human B-ALL samples and indicated that the expression of a subset of lncRNAs, termed *BALRs* (B-ALL associated long RNAs), corresponds with specific cytogenetic abnormalities in B-ALL. A functional assay suggested that knockdown of *BALR-2* (a lncRNA among BALRs) led to apoptosis of B-ALL cell lines alone and up-regulated *BALR-2* was correlated with poor patient response to prednisone and worse overall survival.[85]

By employing methyl-CpG-binding domain protein-enriched genome-wide sequencing (MBD-Seq), Subhash *et al*[86] identified 5800 hypermethylated and 12,570 hypomethylated chronic lymphocytic leukemia (CLL)-specific differentially methylated genes (*cllDMGs*), among which hypermethylated *CRNDE* and hypomethylated *AC012065.7* were two novel lncRNAs validated in CLL samples. Notably, survival analysis revealed that hypermethylation of *CRNDE* and hypomethylation of *AC012065.7* were correlated with poor outcome in patients with CLL. In addition, lncRNA *MIAT* is another lncRNA whose expression level was considered to be positively correlated with the aggressive CLL forms carrying either 17p-deletion, 11q-deletion, or trisomy 12 over indolent form carrying 13p-deletion.[87]

Lymphoma and multiple myeloma-related lncRNAs

Viré *et al*[88] firstly reported a lncRNA corresponding to an antisense transcript of Fas (*FAS-AS1*) which could effectively regulate Fas-mediated apoptosis in non-Hodgkin lymphoma (NHL). Results suggested that the *FAS-AS1* expression was repressed because of its promotor being hyper-methylated by *EZH2* (enhancer of zeste homologue 2), a histone-lysine N-methyltransferase enzyme that participates in histone methylation and leads to transcriptional repression, which is often mutated or over-expressed in lymphomas.[88] Functional assays indicated that treatment with Bruton's tyrosine kinase (*BTK*) inhibitor or *EZH2* knockdown significantly could decrease the levels of *EZH2* and then enhancing Fas-mediated apoptosis, which may provide a novel therapeutic target in lymphomas.[89]

Burkitt lymphoma is an aggressive hematological neoplasm with a poor prognosis and the deregulation of the oncogenic transcription factor MYC is considered to be the major driving force in lymphoma development.[109] Doose *et al*[90] identified 13 lncRNAs differentially expressed in IG-*MYC*-positive Burkitt lymphoma, among which a lncRNA named *MYC*-induced lncRNA (*MINCR*) showing a strong correlation with *MYC* expression in *MYC*-positive lymphomas. *MINCR* knockdown was associated with a reduction in *MYC* binding to the promoters of selected cell cycle genes. These findings suggested novel therapeutic opportunities for the fight against not only malignant lymphoma but possibly, all cancers that rely on *MYC* expression.

The long non-coding RNA *PANDA* (P21-associated ncRNA DNA damage activated), which is induced in a

p53-dependent manner and interacts with the transcription factor *NF-YA* to limit expression of pro-apoptotic genes,[91] was recently reported to be down-regulated in patients with diffuse large B-cell lymphoma (DLBCL) and functioned as a tumor suppressor gene through silencing *MAPK/ERK* signaling pathway.[92]

A differential expression profiling between Hodgkin lymphoma (HL) and normal germinal center (GC)-B cells was performed and selected two lncRNAs (*LINC00116 and LINC00461*) which was over-expression in HL, DLBCL and lymphoblastoid cell lines, and another lncRNA (FLJ42351) which has a remarkable Reed-Sernberg (RS) cell-specific expression in HL and part of Burkitt lymphoma cell lines.[93]

Multiple myeloma (MM) is another large class of hematological malignancy characterized by the impaired osteogenic differentiation of mesenchymal stromal cells (MSCs). Zhuang *et al*[110] revealed that lncRNA maternally expressed gene 3 (*MEG3*, a tumor suppressor) played an essential role in osteogenic differentiation in bone marrow MSCs, partly by activating transcription of *BMP4*, a member of the transforming growth factor (*TGF*) family and participate in embryonic development, hematopoietic development, and mesenchymal development.[94,110] Functional assays indicated that *MEG3* knockdown significantly reduced the expression of key osteogenic markers, including Runt-related transcription factor 2, osterix, and osteocalcin.[110]

Furthermore, another research group also reported an MM-related lncRNA *MALAT1* (metastasis-associated lung adenocarcinoma transcript 1), which have been widely considered to play a role in the development of numerous cancers,[111,112] could initiate the activation of the key transcription factor *Sp1* on Latent TGF-binding proteins (*LTBP3*, an important regulator for efficient secretion, folding, and activation of TGF-s and regulates the bioavailability of TGF- especially in the bone[113]) promoter in MSCs from MM.[95]

Myelodysplastic syndromes and aplastic anemia-related lncRNAs

Myelodysplastic syndromes (MDSs) are a group of myeloid clonal diseases with a high risk of transformation to AML.[114] Up to now, the molecular pathogenesis of MDS remains to be explored. Liu *et al*[96] have developed a network-based lncRNA co-module function annotation method, which integrated correlations between lncRNA, protein-coding genes and non-coding miRNAs, and generated lncRNA expression profiles from the HSCs from patients with MDS and healthy donors. *Linc-RPIA* was identified to potentially bind miR-429, which act as tumor-suppressor, and may be involved in the regulation of tumor-related genes, including *FOXO1* and *TP53*.[96] A recent study revealed *HOXB-AS3*, a lncRNA located at the human *HOXB* cluster, maybe a potential risk factor in myeloid neoplasm especially MDS.[97] They demonstrated that high expression of *HOXB-AS3* could promote myeloid cell proliferation which was consistent with previous researches.[101,115] Furthermore, clinical correlation analysis also showed that *HOXB-AS3* was an adverse prognostic marker in patients with low IPSS index, compared with higher risk ones.[97]

Aplastic anemia (AA) is a group of hematopoietic failure syndrome caused by multiple factors.[116] At present, the underlying molecular mechanisms of AA are largely unknown. In a research of bone marrow mesenchymal stem cells (BMSCs) differentiation from AA patients, Jiang *et al*[98] found fibroblast growth factor 1 (*FGF1*) could regulate the expression of lncRNA *TDRG1* through promoting acetylation in the TDRG1 promoter, thus enhancing the proliferation of BMSCs. This finding is a novel insight into the treatment of aplastic anemia patients. However, more research is needed to deepen the explanation of the relationship between lncRNA and AA.

Conclusion and Future Perspectives

To date, there is a large body of evidence to suggest that long non-coding RNAs are becoming fundamental regulators in diverse biological processes including cell proliferation, differentiation, pluripotency, apoptosis, and tumorigenesis and are increasingly recognized as vital components of modern molecular biology. With the publication of various studies in succession, the role of lncRNAs in hematopoiesis shows up prominently. Here we widely reviewed recent advances and summarize the characteristics and basic mechanisms of lncRNAs and keep abreast of developments of lncRNAs within the field of normal and malignant hematopoiesis. Based on gene regulatory networks at different levels of lncRNAs participation, lncRNAs have been shown to regulate gene expression from epigenetics, transcription, and post-transcription. The expression of lncRNAs is highly cell-specific and critical for the development and activation of hematopoiesis. Moreover, we also summarized the role of lncRNAs involved in hematological malignancies in recent years. With the advent of the post-genome era, there must be many additional hematopoiesis-related lncRNAs to be discovered and the underlying precise mechanisms also need to be further excavated. We believe that lncRNAs may provide novel ideas for the diagnosis and therapeutic targets of hematological diseases in the foreseeable future.

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Conflicts of interest

None.

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