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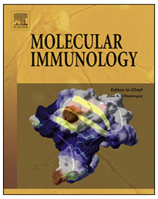

# Long non-coding RNA: Classification, biogenesis and functions in blood cells

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ABSTRACT

While there exist some long non-coding RNAs (lncRNAs) that are structurally similar to mRNAs (capped, spliced, poly a tail), not all of the lncRNAs exhibit these features. Structurally, lncRNAs are classified under the regulatory non-coding RNAs category these lncRNA molecules operate as signals, decoys, guides, and scaffolds. In eukaryotes, lncRNAs are transcribed by RNA Polymerase II and RNA Polymerase III at several loci of the genome. Unlike other protein-coding mRNAs, lncRNAs exhibit functional uniqueness by participating in and modulating the various cellular processes such as, histone modification, DNA methylation, and cellular transcription (Wei et al., 2017). LncRNA alters chromatin structure and DNA accessibility, thereby regulating patterns of gene expression (Wang et al., 2011b). Disordered lncRNA with quantitative or qualitative alterations lead to the progression of numerous diseases including blood associated diseases. LncRNAs not only regulate lineage commitment such as cardiovascular lineage but also contribute for the hematopoietic stem cell development with a significant role in myeloid and lymphoid lineage commitment. However, the key molecular functions of lncRNAs in hematopoiesis are still unclear, particularly, their functional role during megakaryocyte development from hematopoietic stem cells (HSCs) is largely unexplored. This review summarizes the current status of knowledge on lncRNAs classification, biogenesis and its role in blood cells.

## 1. Introduction

Many years of research on the transcriptome, accompanied by an advancement in sequencing technologies such as microarrays, deep RNA sequencing, and next-generation sequencing, have provided a mechanistic paradigm of eukaryotic gene expression (Wang et al., 2009;

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*Abbreviations:* rRNA, ribosomal RNA; tRNA, transfer RNA; ScRNA, small cytoplasmic/ conditional RNA; miRNA, MicroRNA; SnoRNA, small nucleolar RNA; lncRNA, long non-coding RNA; ncRNA, non-coding RNA; EndoSiRNA, endogenous small interfering RNA; PiwiRNA, Piwi-interacting RNA; ENCODE, encyclopedia of DNA elements; cisRNA, Cis-regulatory RNA; Tels RNA, telomere specific small RNA; prompts, promoter-upstream transcripts; tiRNA, transcription initiation RNA; SnRNA, small nuclear RNA; lincRNA, long intergenic non-coding RNA; CeRNA, competing endogenous RNA; HOTAIR, HOX transcript antisense RNA; PTV1, poly tropic virus 1; HOXa11-as, Homeo BoxA11-antisense RNA; MEG3, maternally expressed 3; MIAT, myocardial infraction associated transcript; PFL2, profilin 2; H19, imprinted maternally expressed transcript; ARSR, activated in RCC with sunitinib resistance; RNAi, RNA interfernce; NEAT1 RNA, nuclear enriched abundant transcript 1 RNA; DLEU2 RNA, deleted in lymphocytic leukemia 2; AlncRNA-EC7, bloodlinc; LincRNA EPS, LincRNAerythro id prosurvival; GATA1, globin transcription factor; TAL1, T-cell acute lymphocytic leukemia 1; KLF1, krupple like factor 1; PACER, P50 associated COX2 extragenic RNA; NRON, non-protein coding repressor of NFAT; Gas5, growth arrest specific 5; TINCR, terminal differentiation induced non-coding RNA; TP53COR1 (Linc-p21), tumor protein p53 pathway corepressor 1; XIST, X inactive specific transcript; PRC2, polycomb repressive complex 2; FENDRR, fetal-lethal (FOX1F1 adjacent) non-coding developmental regulatory RNA; TrxG/MLL, trithrox group/ myeloid lymphoid or mixed lineage leukemia group protein; LncHSC1, long non-coding RNA hematopoietic stem cell 1; ANRIL (CDKN2B-AS1), antisense non-coding RNA in the INK4 locus; CBX7, chromo box 7; Ink4, inhibitor of CDK4; LSD1/COREST/REST, RE1 silencing transcription factor; Dacor1, DNMT1 associated colon cancer repressed lncRNA 1; HOTAIRM1, HOX transcript antisense RNA myeloid specific 1; LUNAR1, leukemia associated non-coding IGF1R activated RNA; PARTICLE, promoter of MAT2A antisense radiation induced circulating lncRNA; DUM, developmental pluripotency associated 2 upstream binding muscle lncRNA; TARID, TCF21 antisense RNA inducing demethylation; HDAC1, histone deacetylase 1; EZH2, enhancer of ZEST polycomb repressive complex 2; DNMT3A, DNA methyl transferase 3 alpha; CRNDE, colorectal neoplasia differentially expressed; SPRINGHTLY, formerly sprouty 4 intron; HOST2, human ovarian cancer specific transcript 2; BGLT3, beta globin locus transcript 3; TUG1, taurine up-regulated 1; LINK A, long intergenic non-coding RNA; CHAST, cardiac hypertrophy associated transcript; TNBC, triple negative breast cancer; HBEGF, heparin binding EGF like growth factor; EGFR-GPNMB, epidermal growth factor receptor glycol protein non metastatic B; EGO, eosinophil granule ontogeny; LINC00173, long intergenic non-protein coding RNA 00173; AS-RBM15, antisense RNA binding protein; RUNX1, runt related transcription factor 1; LncMEGA1, transcription activation of an antisense long non-coding RNA

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Lowe et al., 2017; McGettigan, 2013; Martin and Wang, 2011; Qian et al., 2014). This led to tremendous progress in understanding the intricate structure of the genome and transcriptome. The genome of humans and other multicellular eukaryotes is mostly comprised of non-protein coding DNA (Kaikkonen et al., 2011; Palazzo and Lee, 2015a). This is transcribed into different categories of non-coding RNAs that include structural RNAs (rRNAs and tRNAs) and regulatory RNAs (scRNA, miRNA, snoRNA, lncRNA) (Hemberg et al., 2012). Only a fraction (~2%) of the genome is translated into coding transcripts that include the coding RNAs (Palazzo and Lee, 2015). Non-coding RNAs (ncRNAs) are found to deliver housekeeping functions in several biological processes by taking part in the regulatory mechanism of gene expression at the transcriptional and post-transcriptional level (Palazzo and Lee, 2015; Mattick and Makunin, 2006; Esteller, 2011). The lncRNA sequence may be present as introns and intergenic region in the same set of genes that encode proteins (Brown et al., 2008; Deveson et al., 2017). Two decades back the discovery of small ncRNA opened the avenues for the existence of other functional ncRNAs. This led to some uncertainty about the uncharacterized world of functional ncRNAs and junk RNA (Palazzo and Lee, 2015; Wang et al., 2011a). In past several years, our knowledge of ncRNA has been expanding and that makes feasible to classify ncRNAs in different categories of regulatory non-coding RNAs, such as endogenous small interfering RNAs (endo-siRNAs) (Castel and R a, 2013; Okamura and Lai, 2008), PIWI-associated RNAs (piRNAs) (Okamura and Lai, 2008; Costa, 2008), and long non-coding RNAs (lncRNAs) (Long et al., 2017). But, the functional significance of these ncRNA is yet to be deciphered for further characterization. Recent scientific literature provides barely sufficient data to postulate the consequential role of lncRNAs in blood cell development and blood-related diseases (Alvarez-Dominguez and Lodish, 2017). Over the past two decades, many research groups have uncovered the key role of lncRNAs in hematopoiesis. LncRNAs are a class of large size non-coding RNAs which play the key regulatory role in cellular processes such as proliferation, differentiation, and development. They are also known to be involved in the development of several diseases with their changed expression levels such as *GAS5LincRNA-p21, HOTAIR, MALAT1, NEAT1,* and *H19* in colorectal cancer, *HOTAIR, MALAT1, NEAT1, BANCR,* and SOX2-OT in lung cancer and *HULC, HOTAIR, HOTTIP* and *ZFAS1* in liver cancer and so many lncRNAs in breast, pancreatic, ovarian cancers and leukemia (Bhan et al., 2017; Ohtsuka et al., 2018). This review is a compendium of literature on lncRNAs, their expression and function in blood cells with a specific focus on megakaryocytes. Also, the review highlights the mechanism through which lncRNAs participate in different regulatory functions.

## 2. Classification of non-coding RNAs

Human genome analysis contributed to the first discovery of long sequences of ncRNA such as tRNA and rRNA (Wright and Ea, 2011). In addition to this, other lncRNA sequences were also identified whose function is not found in proteins translation machinery. When these long sequences of non-coding RNA were compared to ENCODE consortium data, it was found that several classes of ncRNA molecules are generated through pathways similar to that of protein-coding genes (Derrien et al., 2012; Harrow et al., 2012; Consortium et al., 2012). These findings in relation to previous studies sparked on the diversity of non-coding RNA, ncRNAs are classified into two major categories: structural non-coding RNAs and regulatory non-coding RNAs (Fig. 1). Structural non-coding RNAs comprise of rRNAs and tRNAs. Regulatory non-coding RNAs are further divided into three classes, small, medium and long non-coding RNAs (Ponting et al., 2009; Alvarez-Dominguez and Lodish, 2017). further, miRNA, siRNA, piRNA, cisRNA, telsRNA were considered as short non-coding RNA with a size between 20–50 nucleotides, and snoRNA, prompts, tiRNA, snRNA and many more (Fig. 1) are classified as medium non-coding RNA with a size between 50–200 nucleotides (Nagano and Fraser, 2011; O'Day and Lal, 2010). And a large class of RNA with maximum regulatory potency containing greater than 200 nucleotides are classified as long non-coding RNA (Derrien et al., 2012; Wang et al., 2014). With increasing studies on highly abundant and functionally important categories of lncRNAs (such as intronic, antisense, lincRNA, cisRNA, ceRNA etc), we provide, with sufficient clarity, the classification of ncRNAs and list out all the existing lncRNAs (Fig. 1) (Ma et al., 2013; Gullerova, 2015).

## 3. LncRNAs (long non-coding RNAs)

Generally lncRNAs are defined as long RNA transcripts of more than 200 nucleotides that cannot be translated into proteins (Guo et al., 2016). These are also referred as competing endogenous RNAs (ceRNAs) (Wang et al., 2018a) e.g. *HOTAIR* (Liu et al., 2014; Cai et al., 2017)*, PTV1* (Huang et al., 2017)*, HOXa11-AS* (Cui et al., 2017)*, MEG3* (Peng et al., 2015; Yan et al., 2017)*, MIAT* (Qu et al., 2017; Yan et al., 2015)*, PFL* (Liang et al., 2018)*, MALAT1* (Wang et al., 2016; Qu et al., 2017; Liang et al., 2018)*, H19* (Liang et al., 2016) *and* ARSR (Qu et al., 2016). They play an important role in the fine-tuning of the translation machinery and in its regulation by modulating the crucial functions of other ncRNAs such as miRNAs, snoRNAs etc. (Long et al., 2017; Paraskevopoulou, 2016; Nitzan et al., 2014). lncRNAs are not only originate from their own promoters but also originate from the promoters shared with divergently transcribed coding or non-coding genes, or from enhancer sequences (Al-Tobasei et al., 2016; Hu et al., 2012). Presence of lncRNAs is reported in many organisms like zebrafish (Pauli et al., 2012), tetrapod (Jenkins et al., 2015), roundworm (Nam and Bartel, 2012), mammal (Chen et al., 2016) and other organisms (Table 1). Previous studies revealed large-scale catalog of lncRNAs as putative transcripts within the human genome that do not encode proteins but many of them show poly-A + tail and 5′cap (Derrien et al., 2012). However, recent studies using Ribosome profiling, or Ribo-Seq, and mass spectrometry showed the presence of lncRNA with an open reading frame, that unveils translational ability to encode proteins (Wang et al., 2017a; Bazin et al., 2017). Few studies also shed light on the existence of lncRNAs with a high probability of coding peptides based on their location to nearby protein-coding genes with shorter and fewer exons (Fadista et al., 2014; Jia et al., 2010; Liu et al., 2018; Vance and Ponting, 2014). lncRNAs possess distinctive evolutionarily conserved patterns, with a higher degree of tissue specificity (Vance and Ponting, 2014). Many years of research identified a multitude of regulatory paradigms controlled by several identified lncRNAs that affect the wide range of cellular activities and functionally associated with normal development and pathophysiology of quite a few diseases (Cipolla et al., 2018; Melissari and Grote, 2016; Giroud and Scheideler, 2017). These include several types of cancer, neurological and cardiovascular conditions, immunological and metabolic disorders (Cipolla et al., 2018). Due to RNA sequencing and other new techniques, a greater number of lncRNA classes have been observed (Kung et al., 2013). Several classes of lncRNAs have been discovered on the basis of diverse parameters such as transcript length, association with annotated protein-coding genes, and mRNA resemblance among others (Zhang et al., 2014a; Costa, 2005; Kumari and Sampath, 2015). However, several challenges have been encountered during the annotation and interpretation of non-coding transcriptome data due to the absence of an unambiguous classification framework. These classes of RNA molecules are distinguished from other RNAs based on certain unique features (Hu et al., 2015). These include alternative forms of biogenesis (Spurlock et al., 2016), unique regulatory mechanisms (Marchese et al., 2017; Wang and Chang, 2012), cis-regulatory activities (Kornienko et al., 2013; Pelechano and Steinmetz, 2013), and functionally structured RNA-binding domains (Zampetaki and Albrecht, 2018). In spite of various research groups focusing on lncRNAs, there still exists unidentified and unaccounted information regarding the function and structure of lncRNA.

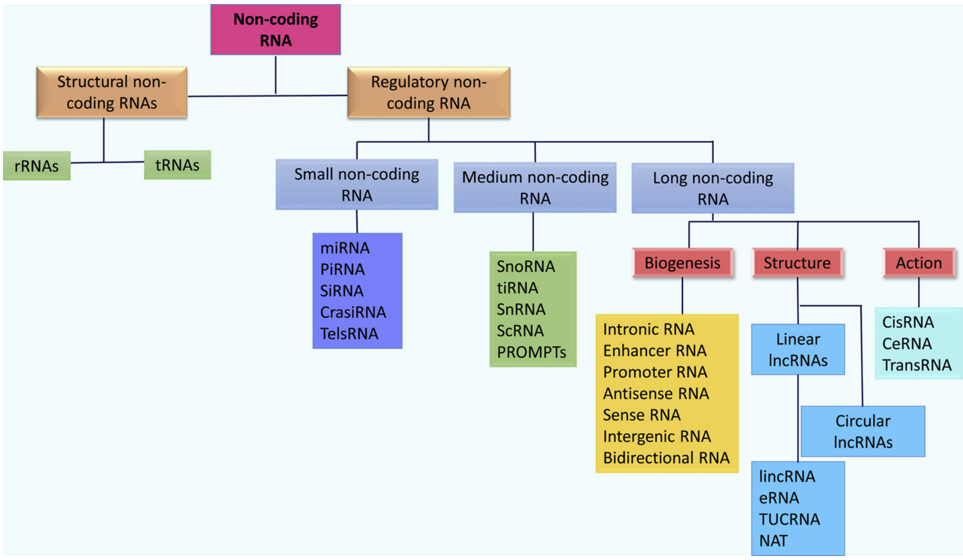


**Fig. 1.** Classification of long non-coding RNAs. Schematic depicts the placement and classification of long non-coding RNAs into classes and sub-classes according to their action, biogenesis and structure.

***Abbreviations:*** ncRNA: non-coding RNA, tRNA: transfer RNA, miRNA: micro RNA, piRNA: piwi RNA, siRNA: small interfering RNA, tiRNA : transcription initiation RNA, crasiRNA : Centromere repeat associated small interacting RNA, telsRNAs : telomere-specific small RNA, snoRNA : small nucleolar RNA, snRNA : small nuclear RNA, scRNA: small cytoplasmic RNA, cis-lncRNA: cis-acting long non coding RNA, trans-lncRNA : trans-acting long non coding RNA, ceRNA : competing endogenous RNA, eRNAs: enhancer-derived RNAs, NATs: natural antisense transcript, TUCRNAs: transcribed ultraconserved RNAs, lincRNAs : Long intergenic noncoding RNAs.

### *3.1. Biogenesis*

Long non-coding RNAs play an important role in different aspects of human development and disease (Schmitz et al., 2016; Delás and Hannon, 2017). Understanding the biogenesis of lncRNAs is beneficial in not only differentiating it from other types of RNAs but also to decipher its functional significance. The biogenesis of lncRNAs is cell type- and stage-specific which is under the control of cell type- and stage-specific stimuli (Akerman et al., 2017; Morán et al., 2012). Different classes of lncRNAs transcribed from several DNA elements such as enhancers, promoters, and intergenic regions in eukaryotic genomes (Wu et al., 2017) (Fig. 2). Different mechanisms involved in lncRNA biogenesis such as cleavage by ribonuclease P (RNaseP) to generate mature ends, formation of small nucleolar RNA (snoRNA) and protein (snoRNP) complex caps at their ends, and the formation of circular structures (Vicens and Westhof, 2014; Chen, 2016). Recently unique sub-nuclear structures known as “paraspeckles” have been identified around specific lncRNAs during their biogenesis (Naganuma and Hirose, 2013). RNAi analyses of 40 paraspeckle proteins (PSPs) brought out the discovery of four PSPs that are required for paraspeckle formation (Yamazaki and Hirose, 2015; Krol, 2017). Overall, mechanisms of synthesis and regulation of different lncRNAs are not completely uncovered, however the next few years will deepen our insight into the biogenesis and functions of lncRNAs with the help of various techniques, such as ChIRP-Seq (Chromatin Isolation by RNA purification), crosslinking immunoprecipitation (CLIP), ribosome profiling, RNA structure mapping, and phylogenetic lineage tracing, targeted genome engineering by CRISPR and advanced genetic screens (Yoon and Gorospe, 2016; Salehi et al., 2017; Li et al., 2014a).

### *3.2. Functional role and mechanism of action*

In the previous studies many members of the lncRNA group have been functionally characterized in different types of cells and disease conditions (Li et al., 2014a; Neguembor et al., 2014) There is a considerable number of lncRNAs with the potential to participate in both normal and aggressive disease state by regulating the biological processes such as cell differentiation, cell lineage determination, organogenesis, and tissue homeostasis along with cell pluripotency induction, X-inactivation and gene imprinting (Kazemzadeh et al., 2015). Notably, a large number of lncRNAs have been associated with numerous diseases, such as diabetes, rheumatoid arthritis, neurodegenerative disorders, atherosclerotic coronary artery disease, and various types of cancer (Wu et al., 2014; Li et al., 2013). Knowledge of lncRNAs’ functions is adding another layer of complexity to our understanding of the mechanism of lncRNA. However, according to the current research, lncRNAs are involved in both the activation and inhibition of the gene expression. This is attained through a range of diverse molecular

**Table 1**
LncRNAs examples in vertebrates and invertebrates. lncRNAs and their length in different organisms (vertebrates and invertebrates).

| Animal kingdom | Length of lncRNAs | Organisms | Examples of lncRNAs | References |
|---|---|---|---|---|
| **Vertebrate** | 2.3-17.2 *1000 basepairs. | Mammal eg. Mus musculus, | *Xist, Tsix, H19, Air, HOTAIR, Nron, AK043754, AK082072, AK082467, TCONS_00062870*<br>*TCONS_00244288* | (Kutter et al., 2012; Raghuwanshi et al., 2018; Tran et al., 2016) |
| | | Sus | *TCONS_00791385*<br>*TCONS_00323177*<br>*TCONS_791379*<br>*TCONS_00815876*<br>*TCONS_00512109*<br>*TCONS_853343* | |
| | 556 basepairs | Actinopterygii e.g. Danio rerio | *HoxAa, myo18a* | (Ma et al., 2007; Nitzan et al., 2014) |
| | 500 basepairs | Aves e.g. Gallus gallus domesticus, Didelphimorphia | *AK043754, AK082072, AK082467 and Rmst* | (Raghuwanshi et al., 2018) |
| **Invertebrates** | 415-378 basepairs | Chromadorea e.g. C. elegans | *linc-41, NATs* | (Garzon et al., 2014; Hu et al., 2012) |
| | | Insecta eg. Drosophila melanogaster | *roX1 and roX2* | (Hu et al., 2016) |

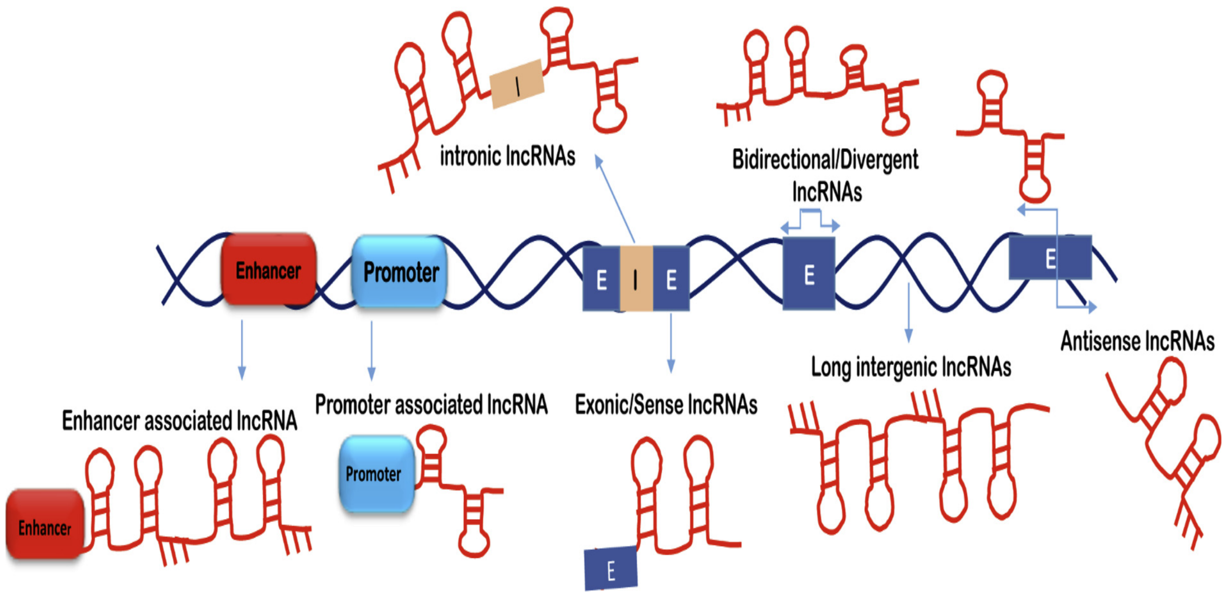
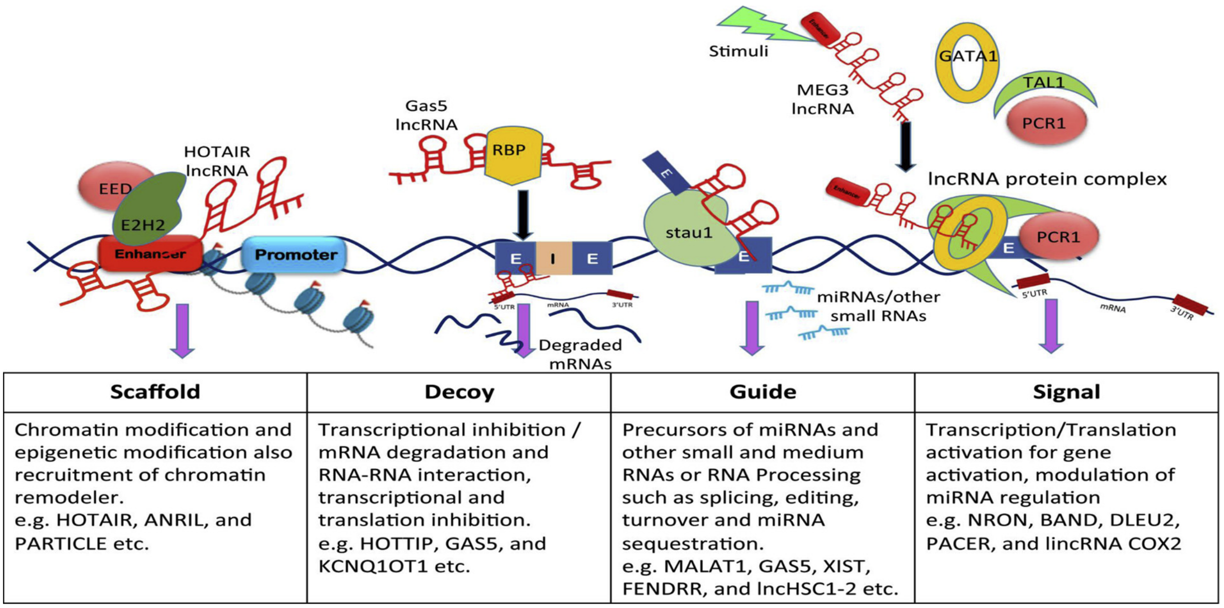


**Fig. 2.** Overview of biogenesis of lncRNA. lncRNAs are pervasively interspersed in the genome with various possible locations. The figure summarizes the diverse range of lncRNAs based on their transcriptional origin: a) whole or partial natural antisense transcripts (NAT), b) coding genes, c) between genes, d) within introns, e) Promoter[blue], and f) Enhancer [red](I = Intron; E = Exon) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).



| Scaffold | Decoy | Guide | Signal |
|---|---|---|---|
| Chromatin modification and epigenetic modification also recruitment of chromatin remodeler.<br>e.g. HOTAIR, ANRIL, and PARTICLE etc. | Transcriptional inhibition / mRNA degradation and RNA-RNA interaction, transcriptional and translation inhibition.<br>e.g. HOTTIP, GAS5, and KCNQ1OT1 etc. | Precursors of miRNAs and other small and medium RNAs or RNA Processing such as splicing, editing, turnover and miRNA sequestration.<br>e.g. MALAT1, GAS5, XIST, FENDRR, and lncHSC1-2 etc. | Transcription/Translation activation for gene activation, modulation of miRNA regulation<br>e.g. NRON, BAND, DLEU2, PACER, and lincRNA COX2 |

**Fig. 3.** Mechanisms of lncRNA action. LncRNAs exert or execute their functions by the above depicted molecular mechanisms.

mechanisms that are summarized as the four manners, (signal, decoy, guide, and scaffold) (Rinn and Chang 2012; Wang and Chang, 2012; Quinn and Chang, 2015) (Fig. 3).

In previous studies it was observed that lncRNAs crosstalk with many epigenetic factors or interface with them to regulate gene expression and modulate nuclear architecture (Hanly et al., 2018; Heo et al., 2013; Mercer and Mattick, 2013). LncRNAs also helps in developmental processes by co-regulating their own and neighboring protein-coding gene expression (Quinn and Chang, 2015; Luo et al., 2015). Some lncRNAs have been found to participate in signal transduction via playing role as a regulator to initiate, elongate or to terminate combinatorial actions of transcription factors (Long et al., 2017). There exist few lncRNAs that are involved in significant biological events such as multi-dimensional spectra of post-transcriptional RNA modification. These modifications include splicing, editing, localization of mRNA *alncRNA-EC7, BAND3, DLEU2,* and *lincRNA-EPS* lncRNAs are transcribed from the enhancer region that has a crucial role in the activation of the neighboring gene (Zhang et al., 2009). These lncRNAs also have a function in the development of red blood cells via stimulating erythroid gene expression and prompting erythroid progenitors proliferate (Marchese et al., 2017; Wang and Chang, 2012; Schmitz et al., 2016; Koerner et al., 2009; Delaval and Feil, 2004; Alvarez-Dominguez et al., 2014, 2017). In addition, studies have also demonstrated that these lncRNAs interface epigenetic regulation of erythropoiesis by targeting the key transcription factor (GATA1, TAL1, and KLF1) and catalytic proteins or subunits of large chromatin remodeling machinery as well as miRNAs (Tian et al., 2016). Recently it was observed that lncRNA maternally expressed gene 3 (MEG3) which functions as a tumor suppressor is significantly downregulated in AML. MEG3 is transcriptionally activated by Wilms' tumor 1 (WT1) and its cofactor

**Table 2**
Long non-coding RNAs in hematopoiesis. list of all the LncRNAs (with functions) involved in human hematopoiesis and associated diseases.

| lncRNA | Aliases for lncRNA gene | Abbreviation | Hematologic disease | Function | Molecular mechanism | References |
|---|---|---|---|---|---|---|
| alncRNA-EC7 | Bloodlinc, and Gm11616 | Erythroid developmen- al long intergenic non-protein coding transcript | Hereditary hemolytic anemias | Potentiates erythroblast proliferation and enucleation during red blood cell development | Promote red cell maturation by regulating neighboring gene encoding BAND 3 | (Luo et al., 2015) |
| BGLT3 | BGL3, CTD-2643I7.1 LncRNA-BGL3, and LINC01083 | Beta globin locus transcript 3 | CML (chronic myeloid leukemia) | Regulator of BCR and ABL mediated cellular transformation | Competitive endogenous RNA cross-regulating the expression of the tumor suppressor PTEN | (Kuvardina et al., 2015) |
| CDKN2B-AS1 | ANRIL, P15AS, NCRNA00089, CDKN2B-AS, and PCAT12 | CDKN2B antisense RNA 1 | leukemia | Induced cell cycle disorder, differentiati-on block, and apoptosis arrest in blood cells | Silenced p14, p15, and p16, which are repressors of leukemia | (Zhao et al., 2014; Zhan et al., 2018) |
| DLEU2, DLEU1 | MIR15AH-G, TRIM13O-S, BCMSUN, RFP2OS, ALT1, LEU2, RFP2, and DLB2 | Deleted in lymphocytic leukemia 2 | CLL (chronic lymphocytic leukemia) | Regulate pivotal oncogenes, tumor suppressors or relevant pathways in malignant hematopoiesis | Epigenetic tumor suppressor mechanism via regulate NF-kB activity. | [180] |
| EGOT | EGO, and NCRNA00190 | Eosinophil granule ontogeny transcript | Erythro leukemia, myeloid leukemia and Myeloproliferative disorder | Myeloid and erythroid development | Compromises the expression of several proteins major basic protein and eosinophil derived neurotoxin (EDN) that are important for eosinophil development | (Lin et al., 2016) |
| GAS5 | NCRNA00030, and SNHG2 | Growth arrest specific 5 | B-cell lymphoma, T-cell leukemia, Acute myeloid leukemia | Normal cell growth arrest in T-cell lines and non-transformed lymphocytes | Glucocorticoid receptors antagonist. Regulated by mTOR pathway | [181, 182] |
| H19 | D11S813E, ASM, ASM1, NCRNA00008, and LINC00008 | H19, imprinted maternally expressed transcript | CML, AML, adult T-cell leukemia /lymphoma and leukemia subtypes | During growth and development of HSC reduced quiescence and compromise it's function Oncogene/ tumor suppressor | Genomic imprinting of its neighboring gene IGF2 and Dlk1, also bind PRC2 and Igf2 to promote chromatin remodeling and post-transcriptional processes. | [183] |
| IGF1R-AS | IRAIN | IGF1R antisense imprinted non-protein coding RNA | Leukemia, Acute Myeloid and Pancreatic Cancer | Promoting cell growth through the PI3K/Akt signaling pathway | Interacts with chromatin DNA at promoter and enhancer regions of the IGF1R gene to form an intrachromosomal enhancer/promoter loop. | [184] |
| LincRNA-EPS |  | LincRNA erythroid prosurvival |  | Essential for dynamic terminal differentiation of erythroid cells. | Mediated anti-apoptotic activity by repressing many proapoptotic genes e.g. pycard | [185] |
| LncHSC1 |  |  |  | Essential in myeloid differentiation and HSC self-renewal and lineage commitment | Regulated by hematopoietic TFs including Erg, Fli1, Lmo2, Meis1, Gata2, Runx1, PU.1, Scl, Lyl1, and Gata2 | (Quinn and Chang, 2015) |
| LncHSC2 |  |  |  | involved in HSC self-renewal and T cell differentiation | Close to genes *Pml,* and *Itpkb* | (Quinn and Chang, 2015) |
| LUNAR1 | Leukemia-Induced Noncoding-Activator RNA, and AC036108.4 | Leukemia-associated non-coding IGF1R activator RNA 1 | Acute T Cell Leukemia and Diffuse Large B-Cell Lymphoma. | Controlling leukemogenesis | NOTCH1-regulated. Activation of IGF1R expression in cis by recruitment of the Mediator complex and RNA polymerase II to the IGF1R enhancer | [186] |
| MAFTRR | Linc-MAF-4 | MAF transcriptional regulator RNA | Different allergies and auto immunity | Key role in T lymphocyte | Increases the expression of MAF and skews T-cell differentiation toward the Th2 phenotype | [187] |
| MALAT1 | NCRNA00047, LINC00047 PRO2853, NEAT2, and HCN | Metastasis associated lung adenocarcinoma transcript 1 | Tongue Cancer and Leukemia, Acute Monocytic | Form molecular scaffolds for ribonucleopro-tein complexes | Promote cell cycle progression and proliferation and maintaining undifferentiated status of early-stage hematopoietic cells by regulating the expression of oncogenic transcription factor B-MYB | [188] |
| MEG3 | GTL2, NCRNA00023, LINC00023, and onco-lncRNA-83 | Maternally expressed 3 | Kagami-Ogata Syndrome and Phaeochromocytoma, acute myeloid leukemia | Involve in myeloid differentiation and inhibits tumor cell proliferation by recruiting the PRC2 complex. | Regulation of the Rb-p16INK4a pathway, regulate tumor suppressor p53 pathway. | [189] |
| TUG1 | FLJ20618, NCRNA00080, LINC00080, and TI-227H | Taurine up-regulated 1 | Chronic lymphocytic leukemia and multiple myeloma | Promotes cell proliferation of tumor cells. | PRC2 binding to repress cell-cycle regulation genes. Induced by p53 | [190] |
| XIST | NCRNA00001, DXS1089, swd66, SXI1, LINC00001, LINC00001, DXS1089, and DXS399E | X inactive specific transcript | Fibrosis, leukemia, and histiocytic sarcoma | Required for hematopoietic stem cell survival and function | Not described | [191] |

(*continued on next page*)

**Table 2** (*continued*)

| lncRNA | Aliases for lncRNA gene | Abbreviation | Hematologic disease | Function | Molecular mechanism | References |
|---|---|---|---|---|---|---|
| Neat1 | Non-Protein Coding RNA 84, MENepsilon/Beta<br>NCRNA00084,<br>LINC00084, TncRNA, and VINC | Nuclear Paraspeckle Assembly Transcript 1 | Relapsing-remitting multiple sclerosis and Dengue | Act as a transcriptional regulator for numerous genes involved in cancer progression and viral infection | Forms the core structural component of the paraspeckle sub-organelles | [192] |

Ten-eleven translocation-2 (TET2). TET2 mutations dysregulate the WT1-MEG3 exis and promote leukemogenesis (Lyu et al., 2017; Williams et al., 2011). Taken together, it is observed that several lncRNAs' expression prolongs as a molecular signal in cellular function.

LncRNAs exhibit decoy type of molecular activity by binding to transcription factors or proteins and thereby titrate away protein factors from their action on target DNA. Some lncRNAs execute themselves as a sponge or molecular sink for several RBPs (RNA binding Proteins) (He et al., 2016). These RBPs function as chromatin modifiers, transcription factors and also regulators of their neighboring protein-coding genes (He et al., 2016). LncRNAs like *snoRNAs, MALAT1* and *NEAT1*. functioning as a sponge or molecular sink to miRNAs (Wang et al., 2016; Liu et al., 2017a; Xiao et al., 2015), also can mediate changes in the transcriptome of cells by negatively acting on effector molecules such as transcription factors, cell receptors, growth factors and splicing regulators. (Fu, 2014; Tripathi et al., 2010; Cooper et al., 2014). In B-cell and T-cell leukemia, lncRNA Gas5 (Growth arrest-specific 5) functions as a tumor suppressor by targeting cancer-promoting miRNAs like miR21 (Wen et al., 2017). Gas5 was also shown to act as a growth arrest- and starvation- associated repressor of the glucocorticoid receptor (GR) (Kino et al., 2010). LncRNA Gas5 was also recognized for growth arrest in both leukaemic and untransformed human T-lymphocytes.(Williams et al., 2011). *LncRNAs such as HOTAIR and linc-p21,* previously described as crucial regulators of the epigenime, they function as the RNAs which recruit chromatin modifiers to regulate gene expression via affecting the process of transcription (Hung and Chang, 2011; De Lucia and Dean, 2011). Another example of guide lncRNA is *FENDRR* (Fetal-lethal noncoding developmental regulatory RNA). Its function is clearly delineated in mouse mesoderm lineage development (Grote et al., 2013). It is associated with PRC2 and TrxG/MLL complexes via dsDNA/RNA triplex formation. It thereby brings PRC2 and TrxG/MLL along with itself close to an associated target gene (*Foxf1* and *Pitx2*) involved in differentiation of lateral mesodermal lineage derivatives including blood cells (Grote et al., 2013; Grote and Herrmann, 2013). Recently reported lncRNAs, *lncHSC1* and *lncHSC2*, in an in vitro study using human hematopoietic stem cells, are involved in self-renewal and in early lineage decisions specifically for myeloid differentiation, while *lncHSC6* has a crucial role in HSC differentiation (Luo et al., 2015). *lncHSC4* is also important for blood cell differentiation and the development of erythroid lineage by regulating Kif1, GATA1, and Tal1, but the molecular mechanism is not clear (Luo et al., 2015). LncRNAs have an impact primarily on transcriptional regulation, while *HOTAIR, ANRIL* represents a prototype of a lncRNA which directly modulates the activity of transcription factors and multiple effector molecules by serving as a scaffold for their assembly (Rinn and Chang 2012; Quinn and Chang, 2015; Spitale et al., 2011). It would be interesting to investigate further how lncRNAs achieve transcriptional regulation through the assembly of scaffolding complexes, which may have the action on transcriptional activation or repression for both the development of an organism and on-set of disease (Chen et al., 2015; Wierzbicki, 2012). Some interesting studies on lncRNAs such as *ANRIL* or *CDKNB2-AS1* which tightly interact with multiple components in polycomb repressive complex-1 (PCR1) and polycomb repressive complex-2 (PCR2) and form heterochromatin surrounding the INK4 locus and that results in INK4 gene silencing through chromatin methylation (Aguilo et al., 2011). *HOTAIR* lncRNA is also closely associated with chromatin remodeling complexes by binding to PRC2 and LSD1/CoREST/REST complex at both the 5′ domain and 3′ domain, respectively (Arrial et al., 2009; Bhan and Mandal, 2015). Through histone methylation lncRNAs, such as *XIST* (Corbel et al., 2013)*, Dacor1, HOTAIRM1, Fendrr, LUNAR1 (Leukemia-Associated Non-Coding IGF1R Activator RNA 1)* and *PARTICLE* mediate chromatin remodeling gene expression (Schmitz et al., 2016). LncRNAs, *PARTICLE* (O'Leary et al., 2015)*, DUM* and *lincP21* (Bao et al., 2015) and many more are involved in epigenetic mechanism in coordination with multiple DNA methyltransferases (DNMTs) and histone methyltransferases (SETDB1) (Zhao

**Table 3**
**Role lncRNAs in erythro-megakaryopoiesis lineages and in hematopoietic tumors.** Role of few lncRNAs involved in fundamental processes of gene regulation, differentiation, apoptosis of stem cells and progenitors of Erythro-megakaryopoiesis and their applications in hematopoietic tumors.

| Sl.No. | LncRNAs | Function/Role | References |
|---|---|---|---|
| 1 | AS-RBM15 | Proliferation and terminal differentiation of erythrocytes | (de Freitas and da Costa Maranduba, 2015; Staerk and Constantinescu, 2012) |
| 2 | LincRNA-EPS | Cell survival, proliferation and differentiation of erythrocytes, anti-apoptotic activity during erythropoiesis | (Cipolla et al., 2018; Katsushima et al., 2016) |
| 3 | Shlnc-EC6 | Erythropoiesis | (Anon., 2019) |
| 4 | HOTAIRM1, EGO | Myeloid differentiation | [192] |
| 5 | LINC00173 | Regulate blood homeostasis | (Trimarchi et al., 2014) |
| 6 | LRRC75A-AS1, CRNDE, LINC01268, HOTAIRM1, H19, LINC00926, FAM30A | Prognostic indicator in Acute Myeloid Leukemia (AML) | [193] |
| 7 | AL356475.1, AC011498.1, AC092811.1, LINC00158, LINC00504 and UCA1 | Biomarker for cytogenetically normal acute myeloid leukemia | [194,195,196] |
| 8 | Fas-AS1 or Saf | Modulates a critical cell death program in erythropoiesis | [197] |
| 9 | XIST | Absence cause hematologic cancers | [191] |
| 10 | H19 | Regulates hematopoietic stem cell quiescence | [183] |
| 11 | Lnc-DC | Positively regulates differentiation of myeloid DC progenitors | [198] |

et al., 2016a; Merry et al., 2015). Even with all the prevailing literature on lncRNAs, we suggest future work to provide new insights to our understanding of the possible role of lncRNAs in the development of blood lineages.

## 4. LncRNA and diseases

LncRNAs is a crucial class of ncRNAs, involved in modulating gene expression in diverse diseases conditions (Tables 2 and 3). LncRNAs play a role in affecting the fundamental features of the epigenome that is reflected during the expression of protein-coding as well as non-coding transcripts. A series of independent studies demonstrated that lncRNAs serve as the source of various short regulatory RNAs (Röther and Meister, 2011). However, mounting evidence show the requirement of various lncRNAs in discrete cellular functions such as cell differentiation and development through different regulatory pathways (Fatica and Bozzoni, 2014). In human cells there are some examples of lncRNAs, such as *SNHG7* (Shan et al., 2018), *CRNDE* (Wang et al., 2017b), *PVT1* (Zeng et al., 2015), *AFII3014* (Zeng et al., 2017), *SHG1 and NCKI-AS1* (Li et al., 2018), *SPRIGHTLY* (Zhao et al., 2016b), *HOST2* (Liu et al., 2017b; Wang et al., 2018b), and *BX35664* (Liu et al., 2016), whose expression has remarkable effects on numerous vital cellular processes. LncRNAs impact cellular processes by affecting the regulatory mechanism of mRNA transcription, alternative splicing and translation that tear down the physiological processes which are associated with cell proliferation, pluripotency, differentiation (Boland et al., 2014; Guttman et al., 2011), and apoptosis (Rossi and Antonangeli, 2014) (Fig. 4). Many of lncRNAs and their products have been linked to clinical disease phenotypes via the regulation of alternative splicing, silencing and post-transcriptional modification of mRNA (Li et al., 2014b). In past couples of years, siRNA mediated exploitation of lncRNAs has been shown with significant potential for effective diseases treatment (Prabhakar et al., 2017). This opens a new avenue for future research to dwell into using lncRNA as a potential therapeutic target. Because of its inhibitory functions with tissue specificity in the regulation of specific target gene, lncRNAs serve as potential therapeutic value (Gomes et al., 2017). Various types of lncRNAs *HOTAIR, ceRNAs, BGLT3,* and *CDKN2B-AS1* have altered their own expression in various disease conditions such as cancers, leukemia, diabetes, and autoimmune diseases (Yuan et al., 2017). Currently, some studies revealed that inhibition of upregulated lncRNAs like *TUG1 (taurine up-regulated 1)* (Viereck et al., 2016), *LINK-A* (long intergenic non-coding RNA for kinase activation), and *CHAST* (cardiac hypertrophy-associated transcript) (Viereck et al., 2016) by several methods like RNA interference (RNAi), degradation by RNase H, activating antisense oligonucleotides (ASOs), or gross deletion/alteration at the DNA level using CRISPR/Cas9 genome editing methods may be effective for the treatment of various diseases (Anon., 2019). For example, significantly reduced expression of *TUG1* an intergenic lncRNA, found in placental abnormalities triggers the poor transformation of the spiral arteries in the trophoblast. The silencing/knocked down *TUG1* expression levels through the transfection of *TUG1* siRNAs, lead to a suppressive effect on trophoblasts by inhibiting cell proliferation, invasion, migration and promoting cell apoptosis (Xu et al., 2017). Furthermore, *TUG1* is highly expressed in GSCs (glioma stem cells) and maintained the stemness features of glioma cells, triggered through the Notch signaling pathway (Katsushima et al., 2016). Targeting *TUG1* by antisense oligonucleotides (ASO) with a potent drug delivery system (DDS), provided an effective and selective antitumor effects to control the population of glioma cells (Katsushima et al., 2016). A cytoplasmic lncRNA, *LINK-A* is necessary for the progression of tumor formation and metastasis of many cancer types including Triple-Negative Breast Cancer (TNBC). *LINK-A* is required for the proper activation and stabilization of Hypoxia-Inducible Factors (HIF1αs) targeted transcriptional program. This program is involved in TNBC progression, recurrence, and metabolic reprogramming (Lin et al., 2016). Furthermore, in cardiomyocytes, upregulated *CHAST* as a budding lncRNA candidate influences cardiomyocyte hypertrophy, GapmeR-mediated silencing of *CHAST* was sufficient to prevent and attenuate TAC (Transverse aortic constriction) induced pathological cardiac remodeling with no early signs on toxicological side effects, which highlight a therapeutic role of lncRNAs in heart diseases (Viereck et al., 2016). Although several groups have investigated possible roles for lncRNAs as key regulators of the pathogenic and oncogenic states of acute leukemia. *LUNAR1* lncRNA over-expression is associated with T cell acute lymphoblastic leukemia and diffuse large B-cell lymphoma disease conditions. Knockdown of *LUNAR1* significantly supports a mechanism that control cell division of cancerous cells (Trimarchi et al., 2014).

## 5. LncRNAs in hematopoiesis and perspective role in megakaryocytopoiesis

LncRNAs play an essential role in maintaining the hematopoietic stem cell pool in humans. They are known to be paramount for lineage-specific differentiation. For example: *shlnc-EC6* is a lncRNA associated with erythroid differentiation (Wang et al., 2015), *HOTAIRM1* is cell-cycle regulator during myeloid maturation in addition to granulocytic differentiation (Wei et al., 2016; Zhang et al., 2014b). EGO positively regulates several genes important for eosinopoiesis (Wagner et al., 2007). *LINC00173* is subjected to in vitro granulocytic differentiation, myeloid colony-formation and function (Schwarzer et al., 2017) (Table 2). Mouse and human hematopoiesis share similar development

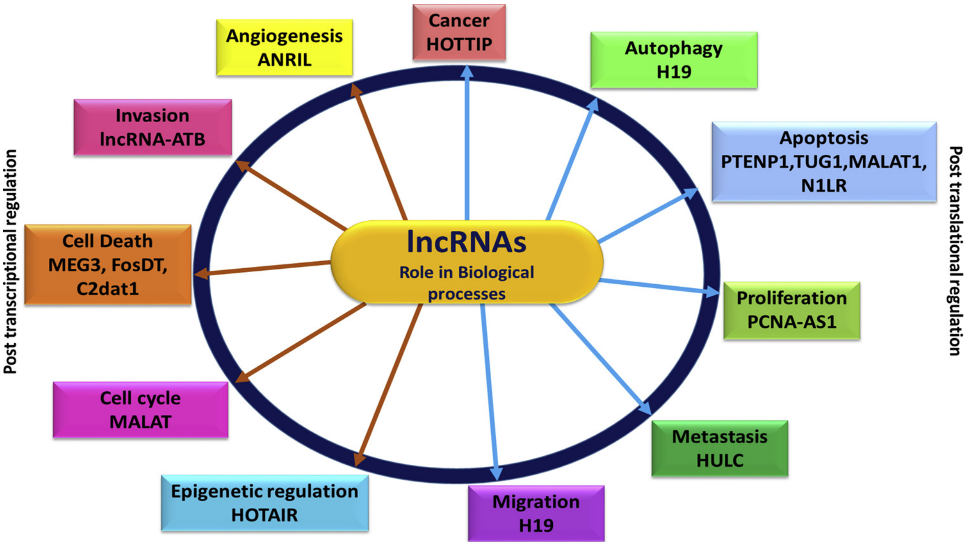


**Fig. 4.** Functions of lncRNA. LncRNAs regulate various cellular processes by post-transcriptional and post-translational modifications as depicted above.

process (Staerk and Constantinescu, 2012; de Freitas and da Costa Maranduba, 2015). However, the lncRNAs involved in mouse and human hematopoiesis are poorly conserved, indicating that lncRNAs evolved differently (Kutter et al., 2012). Finally, lncRNAs represent a vastly unexplored area in the development of megakaryocytes. Megakaryocytes (MKs), among the largest cells in the bone marrow, are generated from hematopoietic stem cells (HSCs) in a sequential process called megakaryocytopoiesis in which HSCs undergo MK-progenitor (MP) commitment and maturation to terminally differentiated MK. Megakaryocytopoiesis is controlled by a complex network of bone marrow niche factors (Raghuwanshi et al., 2018). Among the multiple classes of regulatory factors, lncRNAs are an important regulatory factor in MK development and platelet production. Very little is noted about the role of lncRNAs in megakaryocytopoiesis. Past studies showed that some of the lncRNAs are aberrantly expressed in myeloid progenitors and MK (Table 3). The first lncRNA reported in MK is *AS-RBM15* located on chromosome 1 and has total nucleotide length of 52,797 bp. The transcript of *AS-RBM15* is transcribed in an antisense manner and overlapped with 5′ UTR of a protein-coding gene RBM15 *(RNA Binding Protein 15)* (Tran et al., 2016). RBM15 plays a major role in the growth and apoptosis of cells especially blood cells, by regulating several signaling pathways such as Notch and Wnt signaling (Kazemzadeh et al., 2015). The expression of RBM15 is highly marked during hematopoiesis specially in myeloid differentiation and other hematopoietic cell lineages via a mechanism that is mediated by stimulation of Notch signaling via RBPJkappa (Ma et al., 2007) and occurs at more moderate levels during megakaryopoiesis. The differential expression of RBM15 plays a key role in the development of myeloid, megakaryocytic, and progenitor compartments and disorders related to their abnormal functioning (Ma et al., 2007). Recent emerging evidence indicates that lncRNA, *AS-RBM15* is an anti-sense RNA transcript involved in the regulation of the transcription and translation of the RBM15 protein in megakaryocytes (Garzon et al., 2014). RBM15 is a very important controlling component of MK terminal differentiation (Hu et al., 2016). Furthermore, RUNX1 is a transcription factor that represses the erythroid gene expression program during megakaryocytic differentiation (Kuvardina et al., 2015). It counter balances the activity of RBM15 and *AS-RBM15* as a result of the expression pattern of erythroid genes. These genes are restricted by epigenetic repression of the erythroid master regulator krueppel-like factor 1 (KLF1) during megakaryocytic differentiation (Lyu et al., 2017). Not only the activation of lncRNA *AS-RBM15* but also *lnc-MEGA1* has a direct regulatory role in the induction of RBM15 protein synthesis by putative RNA interaction with polysome containing mRNA (Zhao et al., 2014). Moreover, current studies demonstrated that high level of *AS-RBM15* expression indicates that the function of RUNX1 influences the balance between erythroid and megakaryocytic differentiation (Tran et al., 2016). Taken together, we could reveal that *AS-RBM15* is a key player in the network of transcription factor RUNX1 that promotes proliferation and differentiation of megakaryocytes and inhibits the erythroid gene expression program (Tran et al., 2016; Zhao et al., 2014).

Scientific evidences showing that lncRNAs biological functions should not be ignored. These lncRNAs are crucial and required as a combination of complementary approaches. These approaches vary depending on their mode of action in megakaryocyte development and disease processes. Furthermore, these lncRNAs may be involved in multiple pathways related to MK developmental processes.

## 6. Conclusions and perspective

Although thousands of lncRNAs are expressed during hematopoiesis, the studies of specific lncRNAs with experimentally verified functions are limited. This increasing requirement for deciphering the exact functions of lncRNAs in megakaryocyte development rises further investigative questions. Fewer studies to date have outlined their significance in erythro-megakaryopoiesis with regards to lineage-specific development.

In the presence of varied physiological conditions, it is crucial to have primarily an in-depth understanding of the changes in the lncRNA transcriptome in MKs with specific focus on how these alterations indicate their importance in megakaryocyte development and progression. Such studies might help in the identification of novel cellular pathways involved in the production of mature MKs from hematopoietic stem-progenitor cells (HSPCs). It is important to comprehend lncRNA profile since it can provide information on the direct inference of MK lineage relationship and functional similarity with the hematopoietic hierarchy, including erythroid progenitor and stem cell populations. Further, lncRNA profiling in MK populations may prove to be not only novel but also, powerful approach for identifying and predicting their new developmental roles in terminal megakaryopoiesis followed by platelet formation. In conclusion, at present limited studies exist which explore the significance of lncRNAs in modulating transcriptional and post-transcriptional regulations during megakaryopoiesis. Thus, future studies are necessitated to fully explore the importance of these unique classes of RNA molecules in different aspects of platelet biogenesis.

## Conflict of interest

Authors have no conflict of interest.

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