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Role of long non-coding RNAs in lymphoma: A systematic review and clinical perspectives

Juan Yang[a,b], Xin Wang[a,b,c,d,*]

[a] Department of Hematology, Shandong Provincial Hospital Affiliated to Shandong University, Jinan, Shandong, 250021, China
[b] School of Medicine, Shandong University, Jinan, Shandong, 250012, China
[c] Shandong Provincial Engineering Research Center of Lymphoma, Jinan, Shandong, 250021, China
[d] Key Laboratory for Kidney Regeneration of Shandong Province, Jinan, Shandong, 250021, China

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ABSTRACT

Long non-coding RNAs (lncRNAs), are over 200 nucleotides in length, and they rarely act as templates for protein synthesis. Mounting studies have shown that lncRNAs play a crucial regulatory role in various processes that sustain life, such as epigenetic regulation, cell cycle control, splicing, and post-transcriptional regulation. LncRNAs were aberrantly expressed in most hematological malignancies including lymphoma, participating in tumor suppression or promoting oncogenesis and modulating key genes in different pathways. The specific expression patterns of lncRNAs in lymphoma make them good candidates to be used as diagnostic biomarkers or as therapeutic targets. LncRNAs can be targeted by multiple approaches including nucleic acid therapeutics, CRISPR/Cas genome editing techniques, small molecule inhibitors, and gene therapy. Efforts are made to develop therapeutic strategies aimed at targeting lncRNAs, but there are still some avenues to be covered before they can be applied to the clinical treatment of lymphoma.

1. Introduction

Recent advances in high-resolution microarray and whole genome sequencing technology have changed the customary idea that only 2% of the entire genome consists of protein-coding genes. While more than 90% of the human genome can be transcribed, a massive amount of this DNA is transcribed into non-coding RNA (ncRNA) (Mattick, 2001). ncRNA, once considered as “junk DNA” is probably one of the underlying reasons for the complexity of the genome. These can be classified into several types such as transfer RNAs(tRNAs), ribosomal RNAs (rRNAs), microRNAs(miRNAs), small interfering RNAs(siRNAs), small nucleolar RNAs(snoRNAs), circular RNAs (circRNAs), PIWI-interacting RNAs (piRNAs), and long non-coding RNAs (lncRNAs) (Zhang et al., 2016).

LncRNAs are defined as non-coding transcripts greater than 200 nucleotides in length. A commonly accepted classification method for lncRNAs, based on genomic location, divides them into 5 categories: sense, antisense, intronic, bidirectional, and intergenic (Ponting et al., 2009). They can also be classified as cis and/or trans acting molecules, according to their functionality (Mercer and Mattick, 2013; Quinn and Chang, 2016). Besides, some lncRNAs are classified in terms of their specific characteristics, such as pseudogenes, lncRNA-activating (lncRNA-a) genes, enhancer RNAs (eRNAs), telomere-associated ncRNAs (TERRAs), and so on.

Research conducted in lncRNAs, as with miRNAs, has yielded important results that represent them as molecules of large significance. Even though most lncRNAs have not yet been characterized, a majority of them have shown cell specific expression, preferential localization in the nucleus, and expression at lower levels when compared to mRNAs (Djebali et al., 2012; Quinn and Chang, 2016). Moreover, kinds of biological processes were associated with the expression and location of lncRNA *in vitro* and *in vivo*, including regulation of mRNA degradation, X-chromosome inactivation, chromatin remodeling, genomic imprinting, DNA looping, cell differentiation, as well as nuclear substructure constitution (Yoon et al., 2012; Wang and Chang, 2011). The modulation of gene expression at the epigenetic, transcriptional, and post-transcriptional levels are also attributed to their diverse and heterogeneous mechanisms of action (Yoon et al., 2012; Simon et al., 2011). Interestingly, recent studies have suggested that few of the lncRNAs may also have the capacity to encode proteins or short peptides. Schier et al had determined that a short peptide of 58 amino acid was encoded by a previously annotated ncRNA Toddler in zebrafish (Pauli et al., 2014). Nevertheless, it is still debatable whether lncRNAs play their roles by encoding small peptides (Guttman et al., 2013).

* Corresponding author.
E-mail address: xinw@sdu.edu.cn (X. Wang).

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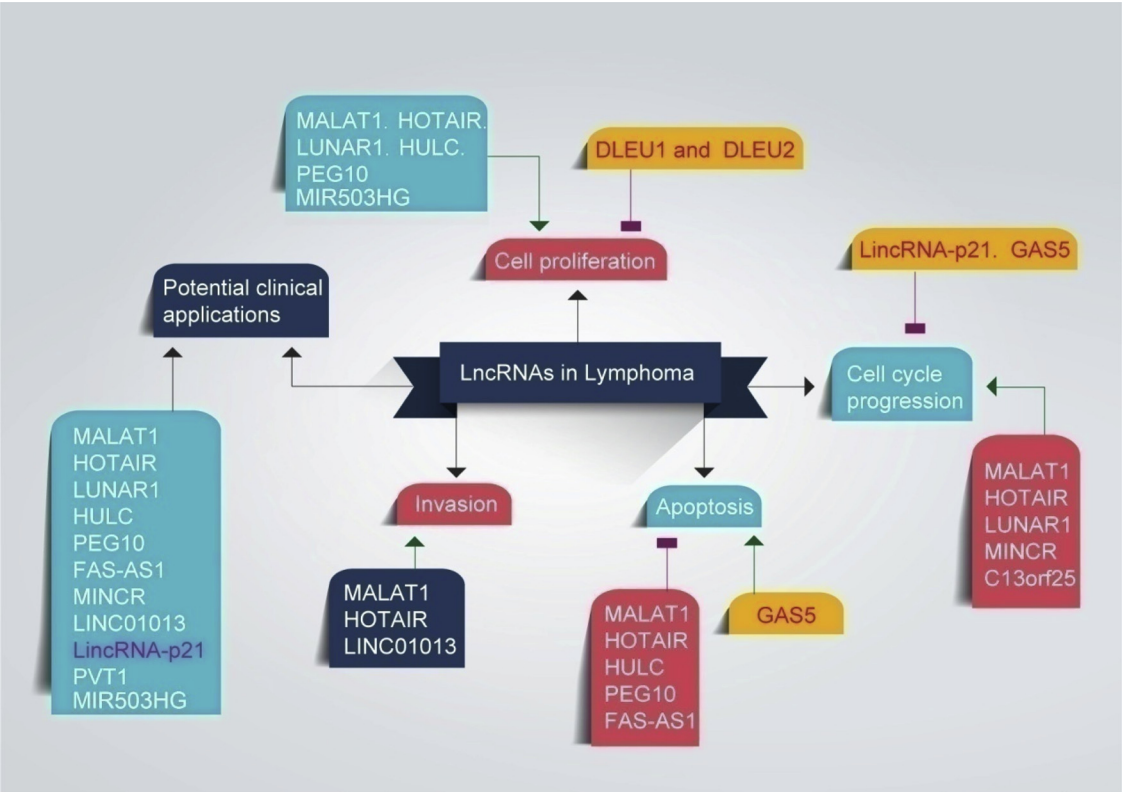

Fig. 1. The functions of lncRNAs in lymphoma. LncRNAs usually act as oncogenes or tumor suppressor genes, play multiple roles such as regulating cell proliferation, cell cycle progression, apoptosis, and invasion in the context of lymphoma. Some of them could serve as prognostic markers, diagnostic markers, metastasis markers or therapeutic targets, and have the potential of the clinical application. Green arrows indicate these lncRNAs play a promoting role and purple arrows indicate inhibiting roles. LncRNAs in white font indicate oncogenes and those in purple font indicate tumor suppressor genes. Several lncRNAs have multiple functions. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

Considering all of this, the best way to define lncRNAs might be as functional long RNAs (Mercer and Mattick, 2013).

Accumulating evidences suggest that the development, progression, metastasis and prognosis of cancers were involved in the dysregulation of lncRNAs (Winkle et al., 2017), such as breast cancer (Deng et al., 2016), cutaneous melanoma, colorectal cancer (Alidoust et al., 2018), renal cell carcinoma, and lung cancer (Inamura, 2017). Additionally, the oncogenic or tumor-suppressive processes was also associated with the dysregulation of lncRNAs. These findings suggested that lncRNAs may play a vital role in tumor, as well as in lymphoma (Fig. 1).

2. Studies detailing the expression profiling of lncRNAs in lymphoma

In recent years, increasing studies determining the expression profiles of several lncRNAs have been conducted in lymphoma. The most common methods used to do so are microarray assays and RNA-sequencing(RNA-Seq). We have summarized several representative studies, to demonstrate that certain lncRNAs or lncRNA groups found dysregulated in large scale samples might be useful for the diagnostic, prognosis prediction or subtype classification of lymphoma (Table 1).

A study demonstrated for the first time, the various expression profiles of lncRNA in Hodgkin Lymphoma(HL), suggesting that HL cell lines have a specific expression pattern. Subsequently, they conducted detailed studies of 3 lncRNAs (FLJ42351, LINC00116, and LINC00461), by qRT-PCR and observed that all of them were upregulated in HL cells. In addition, RNA-FISH of the 3 lncRNAs revealed a tumor cell specific staining in 4 of the HL cases. They also revealed 475 differently expressed lncRNAs between germinal center(GC) B-cell and HL cell lines. 59 out of 475 differentially expressed lncRNAs were in close vicinity to differentially expressed mRNA, implying a potential cis-regulatory function (Anfossi and Calin, 2016; Tayari et al., 2016). The study may represent a novel approach for the specific identification of transformed B-cells in lymphoma tissue.

Another microarray analysis was preformed to explore the expression of lncRNA profile in follicular lymphoma (FL) in 3 human primary FL3a samples and 3 reactive lymphaticnodes (RLN) tissues. Among the 10 altered lncRNAs they studied, ENST0000043340 showed a statistically significant upregulation. This data revealed that ENST00000545410 plays a potential role in the pathogenesis of FL3a and may present itself as a novel molecular marker in FL (Pan et al., 2016).

Researchers carried out a next generation RNA-sequencing in Mantle cell lymphoma(MCL). Compared to non-lymphoma control samples, 10 different lncRNAs were identified to be highly upregulated in MCL samples, while ROR1-AS1(also known as RP11-24 J) topped the list. Further studies focusing on ROR1-AS1, indicated that it was mainly localized in the nucleus, physically in association with subunits of PRC2 complex such as EZH2 and SUZ12 and influenced the transcription of SOX11 in MCL cells. In addition, ROR1-AS1 overexpression might also impact chemo-resistance of MCL cells. Taken together, their results were likely to represent ROR1-AS1 as a novel biomarker or therapeutic target for MCL (Hu et al., 2017).

Previously, several scholars have recognized novel and cancer-associated abnormally expressed lncRNAs by whole transcriptome analysis in natural killer/T cell lymphoma(NKTCL). Interestingly, several cancer-associated lncRNAs such as ZFAS1, SNHG5, MIR155HG, and some antisense transcripts of growth regulating genes were dysregulated in NKTCL cases. These lncRNAs may play an important role in NKTCL pathobiology and NK cell activation, and they may be used as biomarkers or therapeutic targets in the near future (Baytak et al., 2017).

Table 1
Studies detailing expression profiling of lncRNAs in Lymphoma.

Lymphoma subtype	Sample grouping	Results	Type of profiling	References
HL	6 HL cells vs. 11 normal B-cell subsets	3 lncRNAs (FLJ42351, LINC00116, and LINC00461) were upregulated in HL and revealed a tumor cell specific staining	Microarray analysis	Anfossi and Calin (2016) and Tayari et al. (2016)
HL	HL cell lines vs. GCB cells	59 out of 475 defferentially expressed lncRNAs impling a potential cis-regulatory fucntion	Microarray analysis	Anfossi and Calin (2016) and Tayari et al. (2016)
FL	3 FL3a samples vs. 3 RLN tissues	ENST00000545410 (RP11-625 L16.3) was upregulated in FL3a.	Microarray analysis	Pan et al. (2016)
MCL	MCL tumor samples/4 MCL cell lines vs. normal controls	Identified a functional lncRNA ROR-AS1(RP11-24 J) involved with regulation of gene transcription via associating with PRC2 complex.	Next generation RNA-sequencing	Hu et al. (2017)
NKTCL	NKTCL cell vs. normal NK cell	ZFAS1, SNHG5, MIR155HG, and some antisense transcripts of growth regulating genes were dysregulated in NKTCL cases.	Whole transcriptome analysis	Baytak et al. (2017)
DLBCL	1043 DLBCL patients none group	A six-lncRNA signature may serve as a composite biomarker for risk stratification of DLBCL patients at diagnosis.	GEO database	Sun et al. (2016)
DLBCL	GCB type DLBCL patients vs. ABC type DLBCL patients Total: 905 patients	SubSigLnc-17 was suitable for subtype classification and prognosis prediction.	GEO database	Zhou et al. (2017)

1043 diffuse large B cell lymphoma(DLBCL) patients were selected from the GEO database to assess the prognostic value of lncRNAs and its clinical characteristics by analyzing the lncRNA expression profiles. In the process, six prognostic lncRNAs in 207 patients came up that were associated with the patients' overall survival (OS) against DLBCL (Sun et al., 2016). Moreover, the expression levels of these six lncRNAs were also associated with the good and poor survival. In addition, these six prognostic lncRNAs positively correlated with the Moreover, the expression levels of these six lncRNAs were also associated with the good and poor survival. In addition, these six prognostic lncRNAs positively correlated with the protein-coding genes (PCGs) in three GO functional clusters (including immune system process, DNA repair and cell cycle) and 12 KEGG pathways. The study indicated that the signature of six-lncRNAs might serve as a composite biomarker for risk stratification of DLBCL patients at diagnosis and play regulatory roles on PCGs involved in these known DLBCL-related biological processes and pathways.

A genome-wide comparative analysis was used to unravel theexpression profiles of lncRNAs in a large number of DLBCL patients from the GEO database, including 3 cohorts, totaling of 905 patients. The study uncovered 17 of the 156 differentially expressed lncRNAs between GCB and ABC subtypes and identified them as a 17-lncRNA signature, termed as SubSigLnc-17. This signature was suitable for classification of subtypes and for prognosis prediction, with a sensitivity of 92.5% and specificity of 89.6% (Zhou et al., 2017). The reproducible predictive power of SubSigLnc-17 was successfully confirmed in the internal validation cohort and 2 other independent cohorts. These findings will improve the understanding of potential molecular heterogeneities and will also provide information underlying lncRNA biomarkers in DLBCL.

3. LncRNAs involved in lymphoma

LncRNAs are implicated in the pathogenesis of lymphoma through different signaling pathways, interconnected with various molecular targets. A clear and in-depth understanding of their expression and mechanism of action will be of great help to our subsequent clinical researches. Accordingly, we then discussed several differentially expressed lncRNAs in lymphoma, using the following aspects: their basic characteristics, the current research status in lymphoma and other cancers, mechanism of action and potential clinical relevance (summarized in Table 2).

3.1. LncRNAs exhibit oncogenic properties

3.1.1. Metastasis associated lung adenocarcinoma transcript 1(MALAT1)

MALAT1 is an evolutionarily conserved lncRNA of length 8.7 kb, transcribed from chromosome 11q13.1, located on the nuclear speckles (a sub-nuclear domain). MALAT1 is proposed to coordinate RNA polymerase II transcription, mRNA export, cell cycle, and regulate the alternative pre-mRNA splicing (Tripathi et al., 2010). It is reported that MALAT1 is a putative oncogene and is overexpressed in several solid tumors. Current research also suggested that its overexpression in these solid tumors is associated with cancer metastasis and recurrence (Gutschner et al., 2013).

It plays a positive role in the maintainance of proliferation of undifferentiated status of early-stage hematopoietic cells (Ma et al., 2015). Compared with the normal cells, human MCL tumors expressed high level of MALAT1 in vitro and in vivo.The upregulated levels of it correlated with higher MCL international prognostic index, reduced overall survival (Wang et al., 2016). A recent study indicated that the expression of MALAT1 was significantly associated with the prognosis of human T and NK lymphoma in vivo (Kim et al., 2017). In present study, we observed MALAT1 could directly bind to EZH2 and SUZ12, suggesting that MALAT1 was a key regulator in the process of PRC2-induced H3K27me3 sustaining. Taken together, MALAT1 might be a potentially prognostic and therapeutic candidate in lymphoma.

Table 2
lncRNAs involved in lymphoma.

lncRNAs	Lymphoma subtype	Location	Target genes/ Signalings	Potential clinical relevance	References
MALAT1	MCL, DLBCL, T/NK cell lymphoma	11q13.1	EZH2/ autophagy-related signaling pathway	Prognostic marker/ Therapeutic target	Wang et al. (2016) and Kim et al. (2017)
HOTAIR	DLBCL	12q13.13	PI3K/AKT/NF-κB pathway	Prognostic marker/ Diagnostic marker/ Therapeutic target	Yan et al. (2016)
LUNAR1	DLBCL	15q26.3	E2F1, cyclin D1 and p21	Diagnostic marker/ Therapeutic target	Peng and Feng (2016)
HULC	DLBCL	6p24.3	Cyclin D1 and Bcl-2	Therapeutic target	Peng et al. (2016a)
PEG10	DLBCL	7q21.3	Activated by c-MYC	Prognostic marker/ Diagnostic marker/ Therapeutic target	Peng et al. (2016b)
FAS-AS1	B-cell lymphoma	10q23.31	RBM5, EZH2, DZNeP	Therapeutic target	Niitsu et al. (1999), Sehgal et al. (2014) and Beguelin et al. (2013)
MINCR	BL	8q24.3	Induced by MYC	Therapeutic target	Doose et al. (2015)
LINC01013	ALCL	6q23.2	EMT/the snail pathway	Metastasis marker	Chung et al. (2017)
DLEU1/DLEU2	MCL	13q14.3	miR-15a/16-1, BCL2, NF-κB pathway	Tumor suppressor	Kohlhammer et al. (2004)
GAS5	MCL	1q25.1	The mTOR pathway	Tumor suppressor	Mourtada-Maarabouni and Williams(2014) and Nakamura et al. (2008)
LincRNA-p21	DLBCL	Not annotated in human	cyclin D1, CDK4 and p21	Tumor suppressor/ Prognostic biomarker	Peng et al. (2017), Notari et al. (2006) and Du et al. (2010)
H19	TCL	11p15.5	MYC, p53	Therapeutic target/ Tumor suppressor	Takeuchi et al. (2007)
PVT1	BL,HL	8q24.21	host of miR-1204	Therapeutic target	Tsutsumi et al. (2013)
BIC	HL, BL, DLBCL, PMBL	21q21.3	miR-155 host gene	Biomarker	Kluiver et al. (2005), Metzler et al. (2004) and van den Berg et al. (2003)
C13orf25	B-cell lymphoma, MCL	13q31.3	miR-17-92 host gene	Not mentioned	Rinaldi et al. (2007) and Ji et al. (2011)
MIR503HG	ALK-negative ALCL	Xq26	miR-503 / Smurf2 / TGFBR	Therapeutic target	Huang et al. (2018)
SNHG5	DLBCL	6q14.3	snoRNA host	Not mentioned	Tanaka et al. (2000)
RMRP	NHL	9p13.3	Not mentioned	Not mentioned	Taskinen et al. (2008)
LOC283177	DLBCL	11q25	Not mentioned	Not mentioned	Conde et al. (2014)

3.1.2. HOX antisense intergenic RNA (HOTAIR)

HOTAIR is a lncRNA with a length of 2.2 kb, transcribed from the antisense strand of HOXC cluster in chromosome (Rinn et al., 2007). Accumulating evidences have confirmed that it played an oncogenic role in several types of tumors and HOTAIR deregulation is associated with multiple solid cancers. HOTAIR recruits PRC2 to specific target genes, resulting in H3K27 trimethylation and epigenetic silencing of metastatic suppressor genes (Rinn et al., 2007; Gupta et al., 2010). Knockdown of HOTAIR by RNAi technology induces cell cycle arrest, promotes apoptosis and inhibits the proliferation and invasion of tumor cells, possibly through the PI3K/AKT/NF-κB signaling pathway. Furthermore, the inhibition of HOTAIR can also suppress tumor formation in the xenograft model in vivo (Wu et al., 2014). A recent study has shown that HOTAIR was upregulated in diffuse large B-cell lymphoma (DLBCL), correlated with an invasive phenotype that predicted a worse prognosis and therefore, might be a critical element in metastatic progression (Yan et al., 2016).

3.1.3. Leukemia-Associated Non-coding IGF1R Activator RNA 1 (LUNAR1)

LUNAR1 is a 491 nucleotide lncRNA located at 15q26.3, containing 4 exons and a poly (A) tail. Previous studies demonstrated that LUNAR1 is a specific NOTCH1-regulated lncRNA, originally identified in NOTCH1 mutated human primary T-ALL (Trimarchi et al., 2014). LUNAR1 has been considered an oncogene in lymphoma. Through promoting the expression of IGF-1R and sustaining IGF1 signaling, LUNAR1 could efficiently enhance the growth of T-ALL (Medyouf et al., 2011). The upregulated expression of LUNAR1 in DLBCL resulted in cyclic progression and proliferation of lymphoma cells. Downregulation of LUNAR1 suppressed cell proliferation by modulating E2F1, cyclin D1 and p21 (Peng and Feng, 2016). Therefore, LUNAR1 might be considered as a specific diagnostic biomarker and a potential therapeutic target for DLBCL.

3.1.4. Highly upregulated in liver Cancer (HULC)

Another lncRNA dysregulated in lymphoma is HULC. It is a conserved lncRNA with a length of about 500 nucleotides, located at human chromosome locus 6p24.3 (Du et al., 2012). High level of HULC was is originally found in human hepatic carcinoma tissue. Previous studies have characterized HULC to be upregulated in pancreatic cancer and gastric cancer as well (Peng et al., 2014). Lately, its expression level was found upregulated in DLBCL tissues and in cell lines as compared to that in healthy controls. Through suppressing the function of cyclin D1 and Bcl-2, knockdown of HULC efficiently arrested cell growth and promoted cell death in DLBCL cell lines (Peng et al., 2016a). In addition, HULC acts as an oncogenic lncRNA via directly binding with EZH2, thereby inhibiting NKD2 expression. These data suggested that HULC might be a potential candidate for gene therapy in DLBCL.

3.1.5. Paternally expressed 10 (PEG10)

PEG10 is another highly conserved lncRNA located at the human chromosome locus 7q21.3 and it encompasses 763 bp (Ono et al., 2001). Cancer genetics and epigenetics have shown that PEG10 is downstream of a classic proto-oncogene, MYC. Dysregulation of PEG10 is involved in several tumors such as hepatocellular carcinoma, esophageal cancer and B cell chronic lymphocytic leukemia (Hu et al., 2004; Wapinski and Chang, 2011; Kainz et al., 2007). Overexpression of PEG10 could promote cell proliferation, cell cycle, clone formation along with migration and invasion by inducingdegradation of matrix proteases such as, MMP-1, MMP-2, MMP-9 and reducing the expression of cell-to-cell junction molecules such as E-cadherin. Studies have also shown that PEG10 was upregulated in DLBCL tissues and in cell lines that correlated with B symptoms, IPI score, CHOP-like treatment, and Rituximab. In addition, PEG10 knockdown by siRNA could result in growth arrest and cell apoptosis *in vitro* (Peng et al., 2016b). These findings suggested that PEG10 is a progression related biomarker for lymphoma, which could be applied in lymphoma diagnosis and targeting therapy in the future.

3.1.6. FAS-AS1

Sehgal et al. identified FAS-AS1 (a longnon-coding antisense RNA), transcribed from the opposite strand of the intron 1 of the human Fas gene, that acted as a regulator of Fas resistance in lymphoma by alternate splicing of Fas. Serum soluble Fas receptor(sFas) produced by skipping exon 6, repressed cell apoptosis by sequestering the Fas ligand and was associated with a poor prognosis in Non-Hodgkin's lymphoma (NHL) (Niitsu et al., 1999). Compared to healthy lymphocytes, the expression of FAS-AS1 was decreased in primary NHL and B-cell lymphoma cell lines that inversely correlated with the production of sFas. Moreover, experiments showed that FAS-AS1 binded to the RBM5 and inhibited RBM5-mediated exon 6 skipping, corresponding the production of sFas, thereby enhancing Fas-mediated apoptosis in lymphoma (Beguelin et al., 2013). These reports showed that FAS-AS1 lncRNA could negatively regulate Fas-mediated apoptosis by decreasing the expression of sFas, thus revealing a new therapeutic target in lymphoma (Sehgal et al., 2014).

3.1.7. MYC-Induced long non-coding RNA(MINCR)

It is well konwn that the overexpression of the transcription factor MYC is a common imbalance parameter in cancer, and is always associated with poor prognosis, especially in B-cell lymphoma (De Jong et al., 1988). A study focused on MYC-regulated lncRNAs, identified a MYC-regulated lncRNA that they named as MYC-induce long noncoding RNA(MINCR), which is closely associated with MYC expression in MYC-positive lymphoma (Doose et al., 2015). In *in vivo* experiment, MINCR has been shown to promote cell proliferation, increase tumor volumes, reduce cell apoptosis, and induce cell invasion through activating EZH2 expression by targeting miR-26a-5p. Furthermore, knockdown of MINCR by RNAi technology is strongly correlated with an impairment in cell cycle progression. MINCR is now considered as a prognostic marker in malignant lymphoma, and may be a therapeutic target in lymphoma.

3.1.8. LINC01013

A study has found that LINC01013, a novel lncRNA located on chromosome 6q, is highly expressed in human anaplastic large-cell lymphoma (ALCL) specimens and its expression is positively associated with the invasiveness of anaplastic lymphoma kinase(ALK)+ cells. Overexpression of LINC01013 induced ALCL cell invasion by activating the expression of snail and fibronectin. Inversely, LINC01013 knockdown decreased tumor cell invasion ability (Chung et al., 2017). These results indicated that LINC01013 promotes cancer cell invasion by the activation of the snail-fibronectin pathway and may present as a metastatic marker in ALCL.

3.2. LncRNAsexerttumor suppressor properties

3.2.1. Deleted in leukemia 1 (DLEU1) and 2 (DLEU2)

DLEU1 and DLEU2 are two long ncRNA genes, mapped to a critical region at the long arm of chromosome 13(13q14.3), which is recurrently deleted in solid tumors and hematopoietic malignancies (Stilgenbauer et al., 1998; Wolf et al., 2001). It is especially common in patients with chronic lymphocytic leukemia and predicts a poor prognosis (Cimmino et al., 2005). The homozygous loss of the 13q14.3 region has immense effects on the regulation of normal CD5+ B-cells and their homeostasis. Deletion of the chromosome 13q14 region is a usual genetic aberration in MCL (Kohlhammer et al., 2004) and MM (Harrison et al., 2003). Overexpression of DLEU1 repressed cell proliferation and promoted programmed cell death. Conversely, TALEN-mediated DLEU1 knockout inhibited cell apoptosis and induced cell viability in Raji BL cells, when treated with Rituximab (RTX) and/or Cyclophosphamide(CTX). Furthermore, it is suggested that DLEU1 and

DLEU2 might be significant mediators of NF-κB pathway (Garding et al., 2013; Cimmino et al., 2005). In fact, DLEU1 might serve as a tumor suppressor gene in BL, and DLEU2 could exert its inhibitory effect on cell proliferation and clonogenicity in a miR-15a/16-1-dependent manner (Lerner et al., 2009).

3.2.2. Growth arrest specific 5 (GAS5)

The snoRNA encoding gene, GAS5, is an apoptosis-related lncRNA which is necessary for normal growth arrest in human lymphocytes. GAS5 is encoded at the 1q25.1 chromosomal locus, which is associated with DLBCL and results in recurrent breakpoints or duplication events (Mourtada-Maarabouni et al., 2008). GAS5 mRNA binds and sequesters the glucocorticoid receptor(GR), thereby restraining the glucocorticoid-mediated transcription of some antiapoptotic genes such as the cellular inhibitor of apoptosis 2 (cIAP2), thus modulating cell survival and metabolism (Kino et al., 2010). Furthermore, GAS5 expression is regulated by the mammalian target of rapamycin(mTOR) signaling pathway and mediates the effects of rapamycin and its analogues on MCL cells (Mourtada-Maarabouni and Williams, 2014).

3.2.3. LincRNA-p21

LincRNA-p21 is a p53 activated long intergenic ncRNA identified in mouse, located on chromosome17, approximately 15 kb upstream from the p21 gene (Hall et al., 2015). LincRNA-p21 binds to hnRNP-K and guides it to target genes, acting as transcriptional inhibitors that result in the induction of apoptosis (Hall et al., 2015). It has been suggested to regulate the p53 tumor suppressor pathway by acting in cis as a locus-restricted coactivator for p53-mediated p21 expression. Evidence has shown that lincRNA-p21 level was significantly decreased in DLBCL tissues when compared to normal controls, markedly correlated with B symptoms, IPI score, and serum LDH levels. Furthermore, the high levels of lincRNA-p21 expression revealed a prolonged overall and progress-free survival. LincRNA-p21 overexpression arrested cell growth, cell cycle progression, and modulated the expression of cyclinD1, CDK4 and p21 in DLBCL (Notari et al., 2006; Du et al., 2010). In conclusion, lincRNA-p21 could act as a tumor suppressor and as a potential prognostic marker in DLBCL (Peng et al., 2017).

3.3. LncRNAs with dual functions

H19 is an imprinted lncRNA located in chromosome 11p15, close to the insulin-like growth factor2 (IGF2), showing maternal-specific monoallelic expression. Genomic imprinting is an epigenetic gene regulation process and loss of imprinting (LOI) leads to loss of parental origin specific differential allele expression, which results in the activation of the normally silent genes. H19 is expressed viaIGF2 from the paternal and maternal allele (Gabory et al., 2010). Previous studies have found that dysregulation of H19 is associated with the development of various kinds of cancers, and it was considered behaving as an oncogene or a tumor suppressor (Berteaux et al., 2005; Hibi et al., 1996; Takeuchi et al., 2007). Exited studies indicated that the oncogene c-Myc can promote the expression of H19 (Barsyte-Lovejoy et al., 2006) and the tumor suppressor p53 could suppress H19 expression (Dugimont et al., 1998). In the bone marrow specimens ofuntreated patients with chronic myeloproliferative disorders and acute myelocytic leukemia (AML) (Bock et al., 2003), H19 expression was downregulated. In addition, loss of imprinting of H19 resulted in H19 overexpression in adult T-cell leukemia/lymphoma patients and cell lines (Takeuchi et al., 2007), demonstrating that H19 may play different roles in different hematological tumors.

3.4. Host genes of miRNAs

3.4.1. The plasmacytoma variant translocation(PVT1)

PVT1 was discovered in 1984 (De Jong et al., 1988), located at the chromosomal region 8q24.21, near the transcription factor c-Myc. Its functional significance has evaded discovery and still it remains unclear whether its role in lymphoma depends exclusively on being the host gene of a cluster of miRNAs. The PVT1 gene encodes a variety of mature RNAs via alternative splicing including several miRNAs, such as miR-1204, miR-1205, miR-1206, miR-1207-3p, miR-1207-5p, and miR-1208. Among them, miR-1204 has been known to play different roles, either related to cell development and differentiation or in increasing p53 levels causing cell death. In addition, p53 induces transcription of PVT1 ncRNA (exon-containing) by binding canonical response element at PVT1 locus (Huarte et al., 2010).

The importance of the PVT1 locus is derived from the findings that suggest it is the site of retroviral insertions and tumorigenic translocations. In Burkitt's lymphoma, the t(2;8) and t(8;22) 'variant' translocation breakpoints extending 400 kb downstream of MYC, found in about 20% of such tumors, juxtapose immunoglobulin κ, λ, or light-chain genes to the PVT1 locus. On one hand, PVT1 could regulate c-Myc expression, while on the other hand PVT1 may possibly be regulated by c-Myc. The overexpression of c-Myc or PVT1 in healthy cells, generated from translocations within c-Myc or PVT1, are characteristically related to BL, NHL, and multiple myelomas (Tsutsumi et al., 2013). These data suggested that PVT1 might sever as an oncogene and might play a vital role in tumorigenesis.

3.4.2. B-cell integration cluster (BIC)

Some of the lncRNAs that are active in hematological malignancies are host genes for miRNAs that have carcinogenic or tumor suppressive characteristics as in the case of the B-cell receptor inducible gene BIC or host gene miR-155 (MIR155HG). High expression levels of the non-coding BIC gene and miR-155 have been demonstrated in HL, BL, DLBCL, and PMBL, but remains undetected in healthy samples (Metzler et al., 2004; Kluiver et al., 2005). The overexpression of BIC down-regulated miR-155-mediated certain tumor suppressor genes via the transcriptional activation of the transcription factor MYB (Vargova et al., 2011). Evidence suggests that miR-155 may interact with MYC or its related signaling pathways in the transformation of B lymphocytes. Increased expression of miR-155 might also be linked to the TP53 pathway. In addition, the BIC expression in ABC-like DLBCL phenotype is higher than that in the GCB type. NF-κB activity correlates with the ABC-like phenotype (Davis et al., 2001), and supposedly a NF-κB binding site might exist in the promoter region of the BIC gene (van den Berg et al., 2003). BIC plays a crucial part in the regulation of miR-155, which directly participates in lymphoma genesis.

3.4.3. C13orf25

C13orf25 or host gene miR-17(MIR17HG) encodes a cluster of 6 miRNAs. miR-17-92 expression is increased in MCL (Rinaldi et al., 2007), B-cell lymphoma (Ji et al., 2011), and solid tumors (Hayashita et al., 2005). The gene promoter is regulated by the collaborative activity of certain transcription factors such as MYC and E2F, and most of these transcription factors only have a moderate individual effect. The inhibitory MYC family member was shown to bind to a putative promoter region in the first intron of the gene locus, resulting in mutation of the MYC binding site and an enhanced promoter activity. However, mutation of a putative SP1-binding site reduced the promoter activity by 70%. The miR-17-92 cluster acts as a oncogene, regulating cell proliferation and survival in lymphoma. In addition, C13orf25 locus also encoded miR-17/20a, promoting tumor formation.

3.4.4. MIR503HG

MIR503HG (miR-503 host gene) is a lncRNA that is located on chromosome X (Xq26). A recent study found that MIR503HG is highly expressed in ALK-negative ALCL cell lines as compared to the normal controls. MIR503HG depletion suppressed ALCL cell proliferation both *in vivo* and *in vitro*. Inversely, overexpression of MIR503HG promoted tumor cell growth. They also reported that MIR503HG-induced proliferation was mediated by miR-503/Smurf2/TGFBR axis (Huang et al.,

2018). These results support an insight that MIR503HG might act as an oncogene, a novel proliferation marker, and a potential therapeutic target in ALK-negative ALCL.

3.5. LncRNAs poorly characterized in lymphoma

3.5.1. Small nucleolar RNA host gene 5 (SNHG5)

SNHG5 is a non-coding, multiple, small nucleolar RNA host, located at the breakpoint of the chromosomal translocation t(3;6)(q27;q15). SNHG5 in gastric cancer was upregulated as compared to normal and was closely associated with the metastasis stage (Zhao et al., 2016). It was also upregulated in primary melanoma samples as compared to the normal tissues (Ichigozaki et al., 2016). Moreover, SNHG5 is also involved in the pathogenesis of DLBCL. SNHG5 knockdown induced cell cycle arrest and apoptosis *in vitro* and inhibited tumor outgrowth *in vivo*. These data suggested that SNHG5 plays a certain role in tumor formation and may present as a new tumor marker (Tanaka et al., 2000).

3.5.2. Ribonuclease mitochondrial RNA processing (RMRP)

RMRP is a lncRNA that encodes for the RNA component of the ribonuclease complex, RNase MRP, and is mutated in Cartilage-Hair Hypoplasia (CHH). CHH is an autosomal recessive chondrodysplasia that results in a short physical stature and an increased overall cancer rate in patients as compared to the normal population. NHL was the most prevalent type of cancer found to develop in such cases (Taskinen et al., 2008; Ridanpaa et al., 2001).

3.5.3. LOC283177

A study carried out a copy number variation (CNV) analysis using GWAS(Genome-wide association study) data of 681 NHL patients and 749 controls to explore the relationship between common copy number variants, structural variation, and lymphoma susceptibility. A novel association in 11q25 was observed for DLBCL, which involved the partial duplication of the C-terminus region of the LOC283177 lncRNA that was further verified by quantitative PCR(qPCR). A previous report in a CNV study of AML showed a duplication in the region overlapping LOC283177 (Kuhn et al., 2012). The relative abundance of LOC283177 was higher in the DLBCL cases as compared to the controls. This was the first time LOC283177 linked to DLBCL (Conde et al., 2014).

4. LncRNAs as potential biomarkers and therapeutic targets

LncRNA are valuable biomarkers in liquid biopsy for a variety of pathologies (Qi and Du, 2013; Tong and Lo, 2006). Various techniques, such as qPCR, transcriptome profiling, and hybridization can be used to evaluate the distribution and expression levels of lncRNA, which enables noninvasive diagnosis and help us assess the progression or recovery of the disease. The first FDA approved case of lncRNAs as a diagnostic marker was PCA3 for the detection of prostate cancer (Bussemakers et al., 1999). It could diagnose prostate cancer efficiently and specifically together with the traditional serum marker, prostate-specific antigen (PSA). There also reported potential lncRNA diagnostic markers for hepatocellular carcinoma and gastric cancer (Panzitt et al., 2007; Shao et al., 2014). HOTAIR has been considered as prognostic marker for colorectal cancer. However, it is necessary to confirm the consistency of lncRNA expression in body fluids and tumor tissues via further studies and clinical data for diagnostic accuracy and specificity.

Tissue and cell type specific expression patterns of lncRNAs position them as highly efficacious therapeutic targets. Unfortunately, there have been no examples of targeting lncRNAs for the treatment of lymphoma. We focus here on the recent therapeutic strategies aimed at targeting cancer-associated lncRNAs, to provide insights for the treatment of lymphoma. LncRNAs can be targeted by multiple approaches including: (i) nucleic acid therapeutics. (ii) CRISPR/Cas genome editing techniques. (iii) small molecule inhibitors and (iv) gene therapy.

4.1. Nucleic acid therapeutics

Double-stranded RNA mediated interference (RNAi) and single-stranded ASO(allele-specific oligonucleotide) are the two major ways employing nucleic acid therapeutics. RNAi primarily includes the use of different agents like small interfering RNAs(siRNAs), miRNAs, and short hairpin RNAs (shRNAs). A synthetic short RNA can be delivered to pathological cells, then the antisense strands are loaded onto the RNA induced silencing complex (RISC), which leads to the degradation of the target lncRNA (Ling et al., 2013). Similar to siRNA, ASO functions by base pairing with mRNA to form RNA-DNA hybrids, resulting in endonucleolytic cleavage of the target RNA by RNase H activity. Each of them serves as a direct approach to selectively induce loss-of-function effect on the highly expressed lncRNAs. For example, siRNA-mediated down regulation of HOTAIR expression inhibited cell growth, invasion, and induced cell apoptosis in human breast, hepatocellular and pancreatic cancers (Yang et al., 2011; Fatima et al., 2015). MALAT1 was knocked down by ASO to prevent tumor growth and metastasis ability in human lung cancer and breast cancer cells (Gutschner et al., 2013).

However, several limitations exist in siRNA and ASO based therapeutic strategies such as the requirement for suitable delivery methods (e.g., lipid-based carriers, polymersomes, biocompatible nanoparticles, or viruses) to increase the intracellular uptake. They are usually subjected to additional chemical modifications in order to enhance their stability. Such modifications include adding 2-nucleotides 30 overhangs to siRNA, 20-O-methyl(20-O-Me) sugar residues to siRNA and ASO, that would lock the nucleic acid to ASO. Also, the subcellular localization of lncRNAs should be kept in mind when considering the siRNA or ASO strategy. For lncRNAs located in the nucleus, ASO would be better than siRNA. These shortcomings still pose a serious challenge to their clinical application (Fatima et al., 2015). Next generation nucleic acid therapeutics have exhibited higher stability and better efficacy and less off-target effects. Currently, several ASOs and RNAi that target different lncRNAs have already entered clinical trials for cancer and other diseases.

4.2. CRISPR/Cas genome editing techniques

With recent advances in genome editing methods, such as transcription activator-like effector nucleases (TALENs), zinc-finger nucleases (ZFNs), and clustered regulatory interspaced short palindromic repeat(CRISPR/) interference (CRISPRi), it is feasible to efficiently target lncRNAs in cancer cells (Thakore et al., 2015; Gilbert et al., 2014). In the CRISPRi genome editing approach, dead-Cas9 is fused to transcriptional repressors, and this fusion protein is targeted to a specific gene promoter by an artificially designed single-guide RNA (sgRNA) to achieve transcriptional silencing of lncRNA-expressing loci. For instance, successful knockouts of lncRNA-21A, UCA1, and AK023948 in human breast cellshave been achieved by CRISPR/Cas9 system (Ho et al., 2015). Nowadays, the novel CRISPR/Cas13 system capable of directly targeting RNA was established (Abudayyeh et al., 2017). This indicates another promising way to specifically konckdown of a lncRNA in mammalian cells. Therefore, lncRNAs involved in hematological malignancies such as PVT1, and LUNAR1 might be targeted easier in this way. While experiments have suggested that transcriptional silencing of lncRNAs by CRISPR-based way is possible, and several preclinical studies are taking advantage of these methods, it still remains to be seen to what extent they will translate into clinical scenarios for lymphomas.

4.3. Small molecule inhibitors

LMI070, a small molecule, was found to bind to pre-mRNA of muscular atrophy gene, and its related gene SMN2 is the encode gene of survival motor neuron. The association between them promotes the processing of exons and the translation of protein products to fight the

disease (Palacino et al., 2015). Small molecules can block the interactions between lncRNAs and their associated protein partners, and can also mask the binding sites of their partners. Thus, some of the famous lncRNA-protein interactions such as HOTAIR-PRC2, H19-EZH2 and ANRIL-CBX7 have emerged to be attractive targets. Accordingly, with the help of small molecule inhibitor, 2-PCPA and DZNep, the interaction of HOTAIR with PRC2 or LSD1 can be blocked to reduce metastasis in breast cancer (Tsai et al., 2011). In another approach, small molecule inhibitors can be designed to target the secondary structure or the unique structural elements of lncRNAs, and thus potentially inhibit their interactions with binding partners or destabilize the transcript to confer a therapeutic effect. For lncRNAs mediated regulation of gene expression mainly through their protein partners, targeting lncRNA-protein interactions has an advantage over targeting only RNAs or proteins. Moreover, in comparison with RNAi, ASO, and genome editing methods, this strategy has an advantage that small molecules are easier to be administrated and exhibit a better cellular uptake.

4.4. Gene therapy

Gene therapy is a method that involves the delivery of normal genes or beneficial nucleic acid polymers into target cells, so as to treat certain diseases. BC-819/DTA-H19, a double-stranded DNA plasmid, has been developed which carries a diphtheria toxin subunit under the regulation of the H19 promoter. When the plasmid is injected into the tumor cells, it elicits an antitumor response due to the production of high level of diphtheria toxin in patients with invasive bladder cancer (Amit and Hochberg, 2012). BC-819 is being tested in lung, colon, ovarian and pancreatic cancers as well, and so far has shown encouraging results (Lavie et al., 2017). In addition, some lncRNAs such as MEG3, lincRNA-p21, as mentioned earlier, are down regulated in tumor tissues as compared to normal samples. These tumor suppressor lncRNAs can be delivered by the method of gene therapy.

5. Conclusions

LncRNAs are aberrantly expressed in hematopoietic malignancies. In addition to the above-mentioned studies, GWAS studies indicated that the '*gene deserts*' SNPs may be associated with lncRNAs. The most evident lymphoma associated SNPs are relevant to PVT1 locus (Skibola et al., 2014; Winkle et al., 2017). In a case of DLBCL, the first exons of GAS5 was fused to the BCL6 gene, resulting in an increased expression of BCL6 (Nakamura et al., 2008). These evidences also support the important role for lncRNA transcription in lymphoma.

LncRNAs were found to modulate the key genes in different pathways. The specific expression patterns of lncRNAs in lymphoma make them good candidates as diagnostic biomarkers or therapeutic targets. The first FDA approved lncRNA diagnostic marker, PCA3 has made the diagnosis of prostate cancer more accurate and specific (Tomlins et al., 2015). Moreover, lncRNA profiling suggests that they might not only be helpful diagnostically, but also in subtype classification, and in prognosis prediction of lymphomas.

Accordingly, in the battle against malignant human diseases, the significance of lncRNAs is gaining wider acceptance. Efforts are being made to develop therapeutic strategies aimed at targeting lncRNAs, but there is still long way to go before they are applied to the clinical treatment of lymphomas. Only a few lncRNAs show high sequence conservation across mammalian species (Winkle et al., 2017), such as MALAT1, NEAT1, and H19. The lack of murine models due to poor conservation across species as compared to protein coding genes is an important concern and this impedes further investigation of lncRNAs in human diseases. Useful preclinical models are urgently needed. Genetically Engineered Mouse Models (GEMMs), Patient-Derived Xenograft Models (PDXs), Xenografted Human Cell Lines, Patient-Derived Tumor Organoids, and Zebrafish Models has also gained interest recently (Arun et al., 2018). Another point of concern is that the three-dimensional structures of lncRNAs have been poorly explored, and there has been speculation that functions of lncRNA are independent based on conserved three-dimensional structures. It calls for a thorough understanding of their structures, working mechanism, spatial localization and regulatory networks. Therefore, structure-based drug designing and screening for lncRNAs remains difficult at the moment. Many of the lncRNAs are also dysregulated in certain malignancies as mentioned earlier, therefore, making it difficult to find tissue-specific markers. In the light of therapeutic strategies targeting lncRNAs, how to overcome their limitations, such as delivery vehicles for siRNA, poor cellular uptake of ASOs, nonprogrammable targeting of small molecules will be quite challenging as well. As ASO-based therapies gradually make their way to the clinic, new ways to therapeutically target lymphoma-specific lncRNAs seem just in the near future.

Conflict of interest

We declare that we have no conflict of interest.

Ethical approval

This article does not contain any studies with human participants or animals performed by any of the authors.

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