

# Long Noncoding RNAs in Diffuse Large B-Cell Lymphoma: Current Advances and Perspectives

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**Abstract:** Diffuse large B-cell lymphoma (DLBCL) is a complex and aggressive malignancy originating from B lymphocytes and characterized by extensive clinical, phenotypic and molecular heterogeneity. Although research conducted over the past decades has substantially improved our understanding of DLBCL, its pathogenesis has not yet been fully elucidated. The development of RNA sequencing technology has allowed the identification of numerous long noncoding RNAs (lncRNAs) that exhibit aberrant expression in DLBCL. These lncRNAs play crucial roles in DLBCL development and pathogenesis and are thus good candidates for use as diagnostic biomarkers or therapeutic targets. In this review, we describe the lncRNAs associated with DLBCL, summarize their characteristics and molecular functions, and discuss their relationships with clinical practice.

**Keywords:** diffuse large B-cell lymphoma, long noncoding RNA, biomarkers

## Introduction

Diffuse large B-cell lymphoma (DLBCL), which is a highly aggressive lymphoid malignancy characterized by large B lymphoid cells exhibiting a diffuse growth pattern,<sup>1</sup> is the most prevalent subtype of non-Hodgkin lymphoma (NHL), accounting for 25–35% of all NHL cases globally.<sup>2</sup> The standard-of-care chemoimmunotherapeutic regimen, which consists of R-CHOP, typically leads to a complete response in 50–70% of patients.<sup>3</sup> Unfortunately, 30–40% of patients are either refractory to the current treatment regimen or experience disease relapse after complete response, and thus, these patients exhibit a dismal prognosis.<sup>4,5</sup> Therefore, a better understanding of the molecular mechanism, the exploration of new biomarkers for the diagnosis of DLBCL and prognosis prediction, and the discovery of novel therapeutic targets of DLBCL would be helpful for improving the curative effect of the developed treatments and the prognosis of patients with this disease.

The discovery of noncoding RNAs (ncRNAs) in recent decades has revealed new prospects for tumor research. ncRNAs, including long noncoding RNAs (lncRNAs), microRNAs (miRNAs) and circular RNAs, are RNA transcripts of variable length that are not translated into proteins.<sup>6</sup> The rapid development of next-generation sequencing and bioinformatic approaches has revealed that these functional RNA molecules are greatly relevant to cancer biology.<sup>7</sup> lncRNAs, which are defined as ncRNAs containing more than 200 nucleotides located within intergenic, intronic, or antisense stretches within or overlap with protein-coding genes,<sup>8</sup> are one of the most studied types of ncRNAs and perform important functions in the modulation of gene expression at multiple levels. Emerging lines of evidence indicate that lncRNAs are critical

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regulators and actively participate in the physiological and pathological processes of human cancers, including hematological malignancies.<sup>9</sup> To date, the roles and mechanisms of abnormally expressed lncRNAs in DLBCL have not been fully clarified. In this review, the PubMed database was searched for articles written in the English language that include combinations of the Medical Subject Headings terms long noncoding RNA, lncRNA, lymphoma, diffuse large B cell lymphoma and DLBCL. We aim to provide a comprehensive summary of the recent advances in the study of lncRNAs associated with DLBCL and discuss the clinical relevance of these lncRNAs.

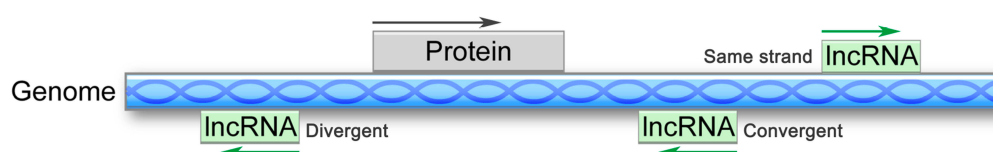
## Overview of lncRNAs

lncRNAs comprise a large and heterogeneous class of transcripts that are greater than 200 nucleotides in length and lack protein-coding capacity. These ncRNAs are generally transcribed and capped by RNA polymerase II, contain introns, are often polyadenylated, and can undergo common posttranscriptional modifications.<sup>10</sup> lncRNAs are frequently evolutionarily conserved, intricately regulated and functionally important.<sup>11,12</sup> So far, tens of thousands of lncRNAs have been annotated in different databases, such as the NONCODE database (<http://www.noncode.org>) and LncRBase (<http://bicre.sources.jcbose.ac.in/zhumur/lncrbase/>), and the number

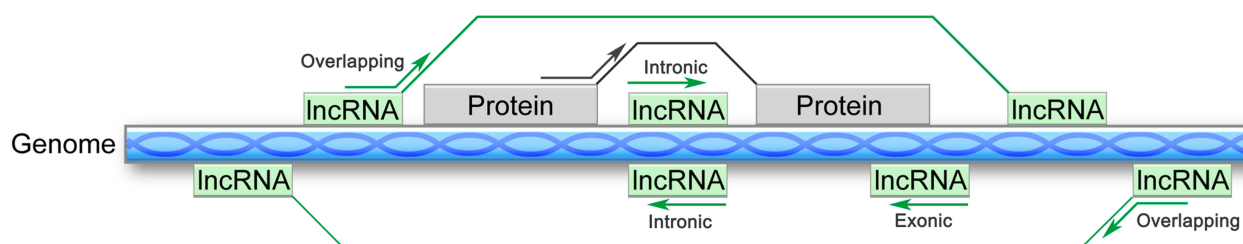
is continuously increasing.<sup>13</sup> The large number and various functions of lncRNAs pose a major challenge to their effective classification. To date, several classification methods have been developed. According to the GENCODE v7 catalog of human lncRNAs, lncRNAs are classified based on their relative positions with respect to protein-coding genes as either 1) intergenic lncRNAs, which are located between two independent genes and can be transcribed from the sense or antisense strand in a divergent or convergent manner, or 2) genic lncRNAs, which can be divided into the following three subtypes: a) exonic lncRNAs, which intersect a protein-coding gene by at least 1 bp; b) intronic lncRNAs, which reside within the intron of a protein-coding gene in either a sense or an antisense orientation; and c) overlapping lncRNAs, which contain a protein-coding gene within an intron in either a sense or an antisense orientation (Figure 1).<sup>14,15</sup> Furthermore, recent studies have recognized that lncRNAs are tightly regulated and are expressed in highly lineage-, spatiotemporal-, tissue- and cell type-specific manners.<sup>13,16,17</sup>

The molecular functions of lncRNAs generally rely on interactions with cellular macromolecules: 1) interactions with chromatin can regulate gene expression by modulating the local chromatin conformation or guiding regulatory molecules to specific loci; 2) interactions with numerous proteins

### A Intergenic



### B Genic



**Figure 1** Classification of lncRNAs according to the GENCODE v7 catalogue. **(A)** Intergenic lncRNAs are located between two coding genes and can be transcribed from either the same strand or antisense in a divergent or convergent manner. **(B)** Genic lncRNAs include three subtypes: exonic lncRNAs, which intersect a protein-coding gene by at least 1 bp; intronic lncRNAs, which reside within the intron of a protein-coding gene in either the sense or antisense direction; and overlapping lncRNAs, which contain a protein-coding gene within an intron in either the sense or antisense direction.

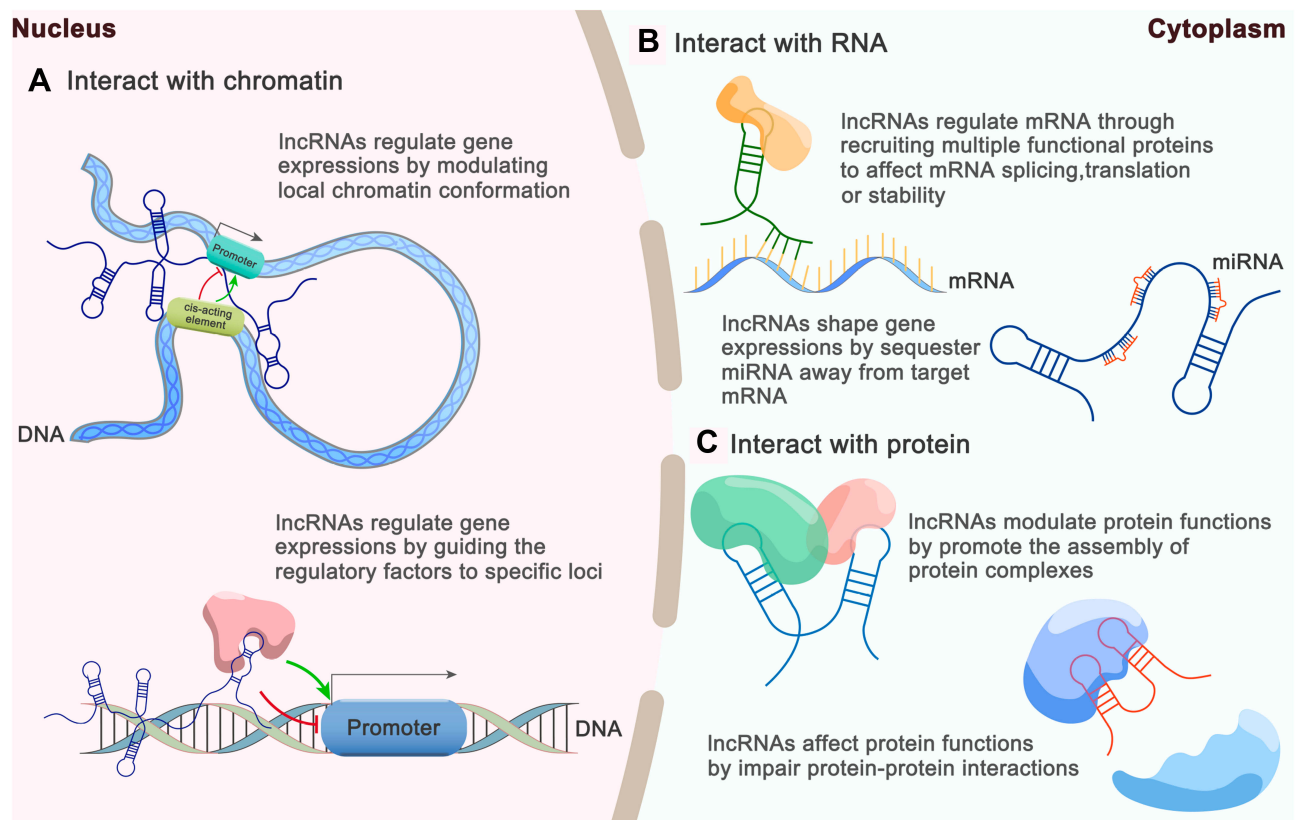
can promote the assembly of protein complexes or impair protein-protein interactions; 3) interactions with mRNAs can affect mRNA splicing, translation or stability through the recruitment of multiple functional proteins; and 4) interactions with miRNAs can shape gene expression by sequestering miRNAs away from their target mRNAs, in agreement with the competing endogenous RNA (ceRNA) hypothesis (Figure 2).<sup>18,19</sup> In other words, lncRNAs can function as 1) decoys by “sponging” intracellular molecules to indirectly block their biological functions with downstream factors, 2) guides by recruiting proteins to access regulatory sites of the relevant gene, 3) signals by acting as molecular signals to modulate transcription in response to various stimuli, 4) scaffolds by forming central platforms for the assembly of other molecules or 5) enhancers by binding with mediator complexes to enhance transcription.<sup>10,20-22</sup> However, the functions of the vast majority of lncRNAs remain unidentified.

## lncRNAs as Candidate Prognostic Biomarkers in DLBCL

Since the development of genomics, numerous methods, including high-throughput sequencing, microarray analysis,

and RT-qPCR, have been developed for the detection of lncRNAs. Numerous studies have suggested that aberrant lncRNA expression is closely related to DLBCL. The International Prognostic Index (IPI), which is the most important predictive model for DLBCL, is considered the strongest prognostic indicator and provides the most robust guidance for individual treatment.<sup>23</sup> Although the IPI score is currently the most widely used predictive model for DLBCL, it has some limitations.<sup>24,25</sup> Numerous studies have attempted to correlate distinct lncRNA expression patterns with clinical diagnoses, subtype classifications, treatment responses and survival outcomes with the aim of highlighting putative prognostic biomarkers for this disease.

Verma et al<sup>26</sup> performed a systematic analysis to identify novel lncRNAs from the polyadenylated transcriptome of 116 primary DLBCL samples. These researchers identified 2632 novel lncRNAs expressed in more than one tumor: two-thirds of these were not expressed in normal B cells, and more than one-third of these lncRNAs exhibited differential expression between the two major DLBCL subtypes—activated B-cell (ABC) and germinal center B-cell (GCB). Their study significantly expanded the



**Figure 2** Brief overview of lncRNA functions based on interactions with various intracellular molecules. (A) lncRNA can interact with chromatin. (B) lncRNA can interact with mRNA and miRNA. (C) lncRNA can interact with protein.

DLBCL transcriptome and provides an abundant information source for further research. Gao et al<sup>27</sup> applied microarray technology to profile the expression of lncRNAs in two different GCB-DLBCL cell lines (OCI-ly1 and OCI-ly19) and normal B lymphocytes, and their data revealed that 1648 lncRNAs were upregulated and 2671 lncRNAs were downregulated in GCB-DLBCL cell lines. In addition, this research group detected the expression levels of five lncRNAs that exhibit significant changes in expression (upregulated: *NAALADL2-AS2*, *HOTAIRM1* and *AFAP1-AS1*; downregulated: *RP4-545C24.1* and *OR2A1-AS1*) in clinical samples by RT-qPCR and found that the expression trends were similar to those indicated by the microarray data. Another study showed that 1053 lncRNAs were significantly differentially expressed in DLBCL cell lines compared with normal B cells, and 416 and 637 of these lncRNAs were upregulated and downregulated, respectively. Among the differentially expressed lncRNAs, *NAALADL2-AS2* exhibited the greatest upregulation, and *NONHSAT120161* showed the strongest downregulation.<sup>28</sup> Zhou et al<sup>29</sup> performed a genome-wide comparative analysis of lncRNA expression profiles in a large number of DLBCL patients from the Gene Expression Omnibus (GEO) database, including patients in three cohorts (total number=905). Their study identified 17 of the 156 differentially expressed lncRNAs between the GCB and ABC subtypes as candidate biomarkers and established a 17-lncRNA signature (*ENTPD1-AS1*, *SACS-AS1*, *SH3BP5-AS1*, *RP11-101C11.1*, *AC009892.10*, *RP1-68D18.4*, *MIR600HG*, *RP11-278 J6.4*, *RP11-203B7.2*, *CSMD2-AS1*, *CTC-467 M3.1*, *RP4-788P17.1*, *RP11-553 L6.5*, *CRNDE*, *RP11-519G16.3*, *RP11-21 L19.1* and *MME-AS1*) for subtype classification (GCB and ABC) and prognosis prediction (overall survival (OS) and progression-free survival (PFS)) that showed favorable reproducible predictive power. Sun et al<sup>30</sup> analyzed the lncRNA expression profiles in three cohorts of 1043 DLBCL patients from the GEO database and identified a set of six lncRNAs that were significantly associated with patient OS. The six-lncRNA signature (*SACS-AS1*, *MME-AS1*, *CSMD2-AS1*, *RP11-360F5.1*, *RP1125K19.1*, and *CTC-467M3.1*) can be used as a predictive factor for dividing DLBCL patients with similar IPI scores into a high-risk group and a low-risk group that exhibit significantly different survival outcomes. Another bioinformatic analysis based on available RNA sequencing metadata in cancer biportals revealed that the lncRNAs *GAS5*, *MIR17HG*, *HULC* and *PCA3* were highly altered in DLBCL patients,

and among these lncRNAs, abnormal expression of *GAS5* was most commonly detected.<sup>31</sup> In addition, a meta-analysis conducted by Xu et al demonstrated that lncRNA expression profiling exhibits advantages in the diagnosis and classification of DLBCL. Aberrant expression levels of lncRNAs are also strongly related to worse OS and appear to be promising predictors of DLBCL prognosis.<sup>32</sup>

Several studies have also demonstrated the prognostic significance of single lncRNAs in DLBCL. The lncRNA *HOX* transcript antisense RNA (*HOTAIR*) has been widely confirmed as a crucial regulator in human cancers.<sup>33</sup> Recent studies verified that *HOTAIR* is overexpressed in DLBCL tumor tissues and cell lines and found that this lncRNA is significantly correlated with the tumor sizes, clinical stages, B symptoms and IPI scores of the patients. A higher expression level of *HOTAIR* is often correlated with a shorter OS time and poorer prognosis and might serve as an independent predictive factor for DLBCL patients.<sup>34–36</sup> Shi et al indicated that the lncRNA functional intergenic repeating RNA element (*FIRRE*) is significantly upregulated in both DLBCL patient samples and cell lines. High *FIRRE* levels are closely associated with poor OS.<sup>37</sup> Another lncRNA, nuclear paraspeckle assembly transcript 1\_1 (*NEAT1\_1*), which usually functions as an oncogene in human malignancies, is highly expressed in DLBCL patients and might serve as a predictive marker of poor prognosis.<sup>38</sup> Tang et al found that increased levels of the lncRNA *RP11-513G11.1* in the peripheral blood of patients with DLBCL predict significantly shortened PFS and OS times.<sup>39</sup> By repurposing 1403 normal and DLBCL samples from seven microarray datasets, Zhao et al found that increased expression of the lncRNA *NONHSAG026900* might be an independent biomarker of favorable prognosis in DLBCL and can improve the predictive power of the IPI scoring system.<sup>40</sup> The results from a study conducted by Wang et al imply that a decreased level of the lncRNA *p21-associated ncRNA DNA damage activated (PANDA)* in serum is strongly correlated with poorer clinical outcomes and lower OS rates in patients with DLBCL.<sup>41</sup> Peng et al found that the lncRNA long intergenic noncoding RNA-*p21* (*lincRNA-p21*) is markedly downregulated in DLBCL and associated with clinical characteristics. Patients with high lncRNA-p21 expression levels exhibit favorable OS and PFS outcomes.<sup>42</sup> In addition, several studies have indicated aberrant expression patterns of the lncRNAs small nucleolar RNA host gene 14 (*SNHG14*), small nucleolar RNA host gene 16 (*SNHG16*), taurine-upregulated gene 1 (*TUG1*), metastasis-associated lung adenocarcinoma transcript 1



(*MALAT1*) and mothers against decapentaplegic homolog 5-antisense RNA 1 (*SMAD5-AS1*) in DLBCL tumor tissues and cell lines; these findings indicate that these lncRNAs can potentially serve as biomarkers for DLBCL, but this possibility needs further study.<sup>43–47</sup>

## Functional Studies of lncRNAs in DLBCL

Functional studies of numerous lncRNAs that are aberrantly expressed in DLBCL have attempted to shed light on their precise involvement in various aspects of tumor cell biology. These lncRNAs are reportedly extensively involved in most biological mechanisms and pathophysiological processes of DLBCL. For instance, the lncRNA *MALAT1* is upregulated in DLBCL and functions as a ceRNA sponge of *miR-195* to activate the expression of the immune checkpoint molecule PD-L1, which results in enhanced cell proliferation, migration and immune escape abilities. In addition, *MALAT1* can promote CD8<sup>+</sup> T cell apoptosis and EMT-like processes (via Ras/ERK signaling).<sup>46</sup> Interestingly, *MALAT1* overexpression is correlated with chemotherapeutic resistance to adriamycin by enhancing protective cell autophagy.<sup>48</sup> The lncRNA *SNHG14* elicits oncogenic functions in multiple types of cancers, including DLBCL.<sup>49</sup> A recent study showed that increased levels of *SNHG14* promote the proliferation, migration and epithelial-to-mesenchymal transition (EMT) of DLBCL cells. Additionally, *SNHG14* can act as a ceRNA sponge of *miR-5590-3p* and subsequently reactivates the downstream protein ZEB1. ZEB1 can transcriptionally activate the inhibitory immunoreceptor PD-L1 to promote tumor cell immune evasion, which suggests that *SNHG14* targeting might be a potential strategy for improving the efficacy of DLBCL immunotherapy.<sup>43</sup> As another member of the same gene family, *SNHG16* can also promote proliferation and cell cycle progression by directly interacting with *miR-497-5p* and inversely increasing the abundance of the downstream oncoprotein PIM1 in DLBCL cells. Thus, *SNHG16* might be a promising therapeutic target in DLBCL.<sup>44</sup> According to a study conducted by Zhao et al, the lncRNA *SMAD5-AS1* is often downregulated and might act as a tumor suppressor in DLBCL. Further studies have shown that *SMAD5-AS1* can inhibit DLBCL cell proliferation by sponging *miR-135b-5p* to upregulate the expression of downstream APC (which negatively regulates the Wnt/ $\beta$ -catenin pathway by promoting  $\beta$ -catenin degradation<sup>50</sup>) and inactivate the

classical Wnt/ $\beta$ -catenin pathway.<sup>47</sup> *HOTAIR* is one of most studied lncRNAs, and its expression is correlated with poor prognosis in various types of tumors.<sup>33</sup> *HOTAIR* is involved in epigenetic regulation through chromatin remodeling by recruiting polycomb repressive complex 2 (PRC2) proteins (EZH2, SUZ12, and EED) that induce histone H3 trimethylation at lysine 27 (H3K27me3).<sup>33</sup> Elevated *HOTAIR* expression might be strongly related to aggressive DLBCL, possibly by inducing H3K27me3 via EZH2-related PRC2 activation.<sup>35</sup> Moreover, Yan et al revealed that the knockdown of *HOTAIR* induces growth inhibition, cell cycle arrest and apoptosis induction in DLBCL cells, possibly through the PI3K/AKT/NF- $\kappa$ B pathway.<sup>34</sup> The lncRNA *highly upregulated in liver cancer (HULC)*, which was originally found to be strongly overexpressed in human hepatocellular carcinoma,<sup>51</sup> is also involved in the pathogenesis of DLBCL.<sup>52</sup> Mechanistic data suggest that *HULC* can maintain cell survival and that the targeting of *HULC* by  $\beta$ -elemene (a compound derived from the herb *Curcuma wenyujin*) can effectively suppress cell growth and induce apoptosis in DLBCL.<sup>52</sup> Cheng et al demonstrated that the overexpression of the lncRNA *TUG1* has oncogenic effects in DLBCL, and this effects are mediated via direct interaction with the oncoprotein MET accompanied by inhibition of its subsequent ubiquitination and degradation. The targeting of *TUG1* by gene knockdown can significantly suppress cell proliferation and tumor growth in DLBCL.<sup>45</sup> Shi et al focused on the lncRNA *FIRRE*, which can activate the Wnt/ $\beta$ -catenin signaling pathway to facilitate DLBCL cell growth through the modulation of  $\beta$ -catenin nuclear translocation. This research group also demonstrated that the MYC proto-oncogene, which is often highly expressed in DLBCL, contributes to the transcriptional activation of *FIRRE*.<sup>37</sup> The MAPK/ERK pathway plays an important role in modulating cell proliferation and the cell cycle in tumors, and functional interactions exist between p53 and MAPK/ERK signaling.<sup>53</sup> A study conducted by Wang et al revealed that the lncRNA *PANDA* is activated by p53 and functions as a tumor suppressor gene through the inhibition of cell growth via G0/G1 cell cycle arrest by inactivating the MAPK/ERK pathway in DLBCL cells. In addition, treatment with the MAPK/ERK agonist anisomycin can potentially abolish the antitumor effect of *PANDA*.<sup>41</sup> Previous studies have shown that the lncRNA *NEAT1\_1* is highly expressed and predicts poor prognosis in DLBCL, and the knockdown of *NEAT1\_1* results in

growth inhibition, cell cycle arrest and apoptosis induction in tumor cells.<sup>38</sup> In contrast, the lncRNA *lincRNA-p21* (which is downregulated in DLBCL and acts as a tumor suppressor) can inhibit cell proliferation and induce cell cycle arrest by functionally modulating downstream p21, cyclin D1 and CDK4 expression in DLBCL cells.<sup>42</sup> Moreover, through a bioinformatic analysis, Tian et al revealed that some differentially expressed lncRNAs (protein kinase C theta-antisense RNA 1 (*PRKCQ-AS1*), human leukocyte antigen complex P5 (HCP5), OPA-interacting protein 5-antisense RNA 1 (*OIP5-AS1*), growth arrest-specific 5 (*GAS5*) and *TUG1*) might perform crucial functions in the transformation of DLBCL by regulating a series of biological processes, including antiapoptotic processes, the cell cycle, DNA repair, oxidative stress responses and transcription.<sup>54</sup>

DLBCL-related lncRNAs and their roles in DLBCL are summarized in Table 1.

## Conclusions and Perspectives

The study of lncRNAs in human malignancies, including DLBCL, remains in its infancy. However, high-throughput sequencing technologies and bioinformatic analysis approaches are increasing the possibility of identifying lncRNAs that are potentially involved in DLBCL. An increasing body of data indicates that lncRNAs play a critical role in the development and pathogenesis of DLBCL, and the lncRNA expression profiles of DLBCL patients might be used for their diagnosis and classification, the prediction of their prognoses and the establishment of targeted therapies. In this review, we discuss the lncRNAs associated with DLBCL, summarize their characteristics and molecular functions, and describe their potential roles as biomarkers.

Based on published studies, lncRNAs are crucial players in regulating multiple oncogenic genes or signaling pathways across DLBCL through multiple aspects of epigenetic regulation. The specific expression patterns of lncRNAs in DLBCL also make them good candidates as diagnostic biomarkers or therapeutic targets. For instance, the well-studied lncRNAs *HOTAIR* and *MALAT-1* have been shown to play important prognostic roles and might serve as potential targets for therapeutic intervention in DLBCL.<sup>34–36,46,48</sup> However, the relevant studies related to DLBCL remain limited, and the available data are not sufficient for conclusively demonstrating that a single lncRNA is representative, highly sensitive, and highly specific and can be used in clinical practice as

a biomarker. The combination of several lncRNAs might be more effective than a single one, and this finding, although hypothetical, is supported by the studies conducted by Zhou et al and Sun et al, who established 17-lncRNA and six-lncRNA panels.<sup>29,30</sup> Based on the existing studies, we believe that the combination of specific expression patterns of lncRNAs with clinical and genetic prognosticators of DLBCL patients will further improve the accuracy and specificity of individual prognostic assessments. Therefore, more research is needed to obtain further useful information.

Researchers are attempting to develop therapeutic strategies involving the targeting of lncRNAs. As mentioned in our manuscript, many studies have shown favorable in vitro data for targeting aberrantly expressed lncRNAs in DLBCL cells. Additionally, the sensitivity to the conventional standard therapy consisting of R-CHOP might be increased by artificial modulation of lncRNAs expressions. Studies have also attempted to develop small-molecule inhibitors that specifically disrupt lncRNA-protein interactions.<sup>55</sup> However, these therapeutic agents that can be safely used for the treatment of DLBCL patients are only beginning to be established. Further studies aiming to identify the most promising lncRNA targets and design the best therapeutics with appropriate efficacy and safety are urgently needed. In summary, we believe that aberrant regulation of lncRNAs in DLBCL is not simply an epiphenomenon but also has great potential for the identification of biomarkers and therapeutic targets. We anticipate that further in-depth investigation of the roles of lncRNAs in DLBCL might help unravel their intricate regulatory networks and provide important insights into DLBCL treatment.

## Abbreviations

DLBCL, diffuse large B-cell lymphoma; lncRNAs, long noncoding RNAs; NHL, non-Hodgkin lymphoma; ncRNAs, noncoding RNAs; miRNAs, microRNAs; circRNAs, circular RNAs; ceRNA, competing endogenous RNA; IPI, International Prognostic Index; GEO, Gene Expression Omnibus; OS, overall survival; PFS, progression-free survival; EMT, epithelial-to-mesenchymal transition; PRC2, polycomb repressive complex 2; H3K27me3, H3 trimethylation at lysine 27; *HOTAIR*, HOX transcript antisense RNA; *FIRRE*, functional intergenic repeating RNA element; *NEAT1\_1*, nuclear paraspeckle assembly transcript 1\_1; *PANDA*, p21 associated ncRNA DNA damage activated; *HULC*, highly upregulated in liver cancer; *lincRNA-p21*, long intergenic noncoding RNA-p21;

**Table I** Examples of lncRNAs with Prognostic and/or Functional Impact in DLBCL

lncRNAs	Putative Roles	Expression	Direct Targets	Proposed Functions	Prognostic Impact	References
<i>HOTAIR</i>	Oncogenic	Upregulated	Not assessed	Promotes cell growth and inhibits apoptosis by epigenetic regulating H3K27me3 and activating the PI3K/AKT/NF- $\kappa$ B pathway	Poor	[34–36]
<i>FIRRE</i>	Oncogenic	Upregulated	Not assessed	Is transcriptionally activated by MYC proto-oncogene and activates Wnt/ $\beta$ -catenin signaling to facilitate cell growth via modulation of the nuclear translocation of $\beta$ -catenin	Poor	[37]
<i>NEAT1_1</i>	Oncogenic	Upregulated	Not assessed	Promotes cell proliferation and migration	Poor	[38]
<i>RP11-513G11.1</i>	Oncogenic	Upregulated	Not assessed	Not assessed	Poor	[39]
<i>NONHSAG026900</i>	Tumor suppressor	Downregulated	Not assessed	Not assessed	Favorable	[40]
<i>PANDA</i>	Tumor suppressor	Downregulated	Not assessed	Is transcriptionally activated by p53 and inhibits cell growth by G0/G1 cell cycle arrest through inactivation of the MAPK/ERK pathway in DLBCL cells	Favorable	[41]
<i>lincRNA-p21</i>	Tumor suppressor	Downregulated	Not assessed	Regulates cell growth and cycle by functionally modulating downstream p21, cyclin D1 and CDK4	Favorable	[42]
<i>SHG14</i>	Oncogenic	Upregulated	miR-5590-3p	Promotes cell proliferation, migration, immune evasion and EMT	Not assessed	[43]
<i>SHG16</i>	Oncogenic	Upregulated	miR-497-5p	Promotes cell proliferation and cell cycle progression	Not assessed	[44]
<i>TUG1</i>	Oncogenic	Upregulated	MET	Inhibits the ubiquitination and degradation of MET oncoprotein and promotes cell proliferation and tumor growth	Not assessed	[45]
<i>MALAT1</i>	Oncogenic	Upregulated	miR-195	Enhances cell proliferation, migration and immune escape and EMT-like processes via Ras/ERK signaling and induces adriamycin resistance by triggering protective cell autophagy	Not assessed	[46,48]
<i>SMAD5-AS1</i>	Tumor suppressor	Downregulated	miR-135b-5p	Inhibits tumor cell proliferation by inactivating the classic Wnt/ $\beta$ -catenin pathway	Not assessed	[47]
<i>HULC</i>	Oncogenic	Upregulated	Not assessed	Maintain cell survival and inhibit apoptosis	Not assessed	[52]

**Note:** “Not assessed” denotes that the direct targets or prognostic impacts of the lncRNAs were not assessed in the specific study.

**Abbreviations:** HOTAIR, HOX transcript antisense RNA; FIRRE, functional intergenic repeating RNA element; NEAT1\_1, nuclear paraspeckle assembly transcript 1\_1; PANDA, p21-associated ncRNA DNA damage activated; lincRNA-p21, long intergenic noncoding RNA-p21; SNHG14, small nucleolar RNA host gene 14; SNHG16, small nucleolar RNA host gene 16; TUG1, taurine-upregulated gene 1; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; SMAD5-AS1, mothers against decapentaplegic homolog 5-antisense RNA 1; HULC, highly upregulated in liver cancer; EMT, epithelial-to-mesenchymal transition; H3K27me3, histone H3 trimethylation at lysine 27.

SNHG14, small nucleolar RNA host gene 14; SNHG16, small nucleolar RNA host gene 16; TUG1, taurine-upregulated gene 1; MALAT1, metastasis-associated lung

adenocarcinoma transcript 1; SMAD5-AS1, mothers against decapentaplegic homolog 5-antisense RNA 1; PRKCQ-AS1, protein kinase C theta-antisense RNA 1;

HCP5, human leukocyte antigen complex P5; OIP5-AS1, OPA-interacting protein 5-antisense RNA 1; GAS5, growth arrest-specific 5.

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## Disclosure

The authors declare that they have no competing interests.

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