OncoTargets and Therapy

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REVIEW

Non-Coding RNAs in Diffuse Large B-Cell Lymphoma

This article was published in the following Dove Press journal:
OncoTargets and Therapy

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Abstract: Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma worldwide. The molecular mechanisms underlying DLBCL have not been fully elucidated, and approximately 40% of patients who undergo standard chemoimmunotherapy still present with primary refractory disease or relapse. Non-coding RNAs (ncRNAs), a group of biomolecules functioning at the RNA level, are increasingly recognized as vital components of molecular biology. With the development of RNA-sequencing (RNA-Seq) technology, accumulating evidence shows that ncRNAs are important mediators of diverse biological processes such as cell proliferation, differentiation, and apoptosis. They are also considered promising biomarkers and better candidates than proteins and genes for the early recognition of disease onset, as they are associated with relative stability, specificity, and reproducibility. In this review, we provide the first comprehensive description of the current knowledge regarding three groups of ncRNAs—microRNAs (miRNAs), circular RNAs (circRNAs), and long non-coding RNAs (lncRNAs)—focusing on their characteristics, molecular functions, as well as diagnostic and therapeutic potential in DLBCL. This review provides an exhaustive account for researchers to explore novel biomarkers for the diagnosis and prognosis of DLBCL and therapeutic targets.

Keywords: diffuse large B-cell lymphoma, microRNA, circRNA, long non-coding RNA

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma worldwide, accounting for approximately 30–40% of all cases in different geographical regions.[1] Patients most often present with a heterogeneous group of tumors, characterized by a high degree of genetic abnormalities, different clinical features, responses to treatment, and prognoses.[2] Although standard therapy for patients with DLBCL has been established, a proportion of patients still relapse despite standard chemoimmunotherapy treatment with rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone (R-CHOP).[3] Allogeneic hematopoietic stem cell transplantation (allo-HSCT) and chimeric antigen receptor (CAR) T cell therapy for relapsed/refractory DLBCL patients have been unsuccessful in achieving durable remission.[4,5] Hence, identifying novel biomarkers for diagnosis and prognosis and therapeutic targets for DLBCL are needed.

Non-coding RNAs (ncRNAs) are functional small RNA molecules that are not translated into proteins.[6] RNA transcripts without protein-coding potential have been reported to represent more than 90% of the human genome.[7] Based on their

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DovePress
http://doi.org/10.2147/OTT.S281810

functions, these ncRNAs can be separated into housekeeping and regulatory transcripts. The regulatory ncRNAs, mainly including microRNAs (miRNAs), circular RNAs (circRNAs), and long non-coding RNAs (lncRNAs), extensively participate in the regulation of gene expression, associated biochemical pathways, and cellular functions. This regulation is necessary to maintain homeostasis, and its dysregulation is often associated with disease development.[8] With the advent of novel high-throughput techniques, an increasing number of ncRNAs have been recognized to be involved in the pathogenesis of hematological malignancies, including leukemia, lymphoma, and multiple myeloma (MM).[9] This review focuses on the roles of miRNAs, circRNAs, and lncRNAs in DLBCL and illustrates their diagnostic and prognostic potential for this disease.

miRNAs

miRNAs are short ncRNAs, approximately 22 nucleotides long, that negatively regulate the expression of their target genes at the transcriptional level by binding to the 3′-untranslated region (3′-UTR) within the target messenger RNA (mRNA).[10] miRNAs affect critical cell processes, such as proliferation, the cell cycle, and apoptosis.[11] Growing evidence indicates that miRNAs have essential functions in malignant B-cell development.[12–17] In addition to coding genes, some non-coding genes, especially miRNAs, are considered to be among the most critical targets for regulating DLBCL development.[18]

Aberrant Expression of miRNAs in DLBCL

Abnormal expression of miRNAs is common in B-cell neoplasms, including B-cell lymphoma. The expression of individual miRNAs and miRNA signatures can help identify specific cell differentiation stages, which is a powerful diagnostic and prognostic method.[16] Jardin et al demonstrated distinct changes in the expression of stage-specific miRNAs in B-cell differentiation, from the naïve B-cell stage (upregulated: miR-181, miR-34a, and miR-223), through germinal center (GC) maturation (upregulated: miR-17-5p, miR-181-b, miR-125b, and miR-155; downregulated: miR-223 and miR-150), to the final stage, leading to either memory B cells (upregulated: miR-223 and miR-181-b; downregulated: miR-17-5p) or plasma cells (downregulated: miR-181-b, miR-17-5p, and miR-30).[16] Interestingly, DLBCL shows the most heterogeneous miRNA profiles of all lymphoma types analyzed.[17] Lim et al conducted the first in-depth sequencing analysis of the DLBCL miRNome (global miRNA expression levels). They noted that 63 and 39 miRNAs exhibited increased and decreased abundance, respectively, in DLBCL.[19] miR-155 and miR-146a were significantly overexpressed in de novo DLBCL patients, and their expression was distinct from that in reactive hyperplasia lymphoid nodes.[20] Besides, several studies have analyzed the association between miRNA expression and the clinicopathological features of patients with DLBCL. miR-214 was found to be downregulated in DLBCL patients, and low miR-214 expression was positively associated with tumor size, clinical stage, and International Prognostic Index (IPI) score.[21] High miR-155 expression was also significantly associated with adverse clinicopathological features, including activated B-cell (ABC)-type DLBCL, the presence of B symptoms, the involvement of extranodal sites, higher IPI, and Eastern Cooperative Oncology Group (ECOG) score.[22,23]

Functions and Mechanisms of miRNAs in DLBCL

Several studies have confirmed that miRNAs can affect important cellular processes, including proliferation, the cell cycle, and apoptosis in DLBCL. For example, as an oncogenic miRNA, miR-155 is reportedly overexpressed in DLBCL tissue compared to control tissue, and it increases cell proliferation and directly or indirectly enhances the G1/S phase transition.[24] Similarly, Li et al showed that miR-155 downregulation inhibits lymphoma cell progression by arresting the cell cycle in the G0/G1 phase and promoting apoptosis. A subsequent tumor formation study in nude mice indicated that miR-155 downregulation delays the progress of tumor formation.[25] Another study reported that miR-34a delivery induces apoptosis and suppresses the growth of DLBCL cells in vivo.[26]

The most common mechanism of action of miRNAs is binding to complementary sequences on the target mRNA to negatively regulate target genes at the translational and post-transcriptional level. Some miRNAs might play an oncogenic role by regulating the expression of target genes. In DLBCL, miR-155 is a topic of active investigation. The identified targets of miR155 include suppressor of cytokine signaling 3 (*SOCS3*),[27] *p85α* (*PIK3R1*),[28] SH2 domain-containing inositol-5-phosphatase (*SHIP1*),[29] bone morphogenetic protein (BMP)-responsive transcriptional

factor (*SMAD5*),[30] *PU.1*,[31] *Wee1*.[32] Li et al showed that miR-155 could enhance cell proliferation and inhibit apoptosis by targeting the downregulated *SOCS3* expression to activate the Janus kinase (JAK)/signal transducer and activator of transcription 3 (STAT3) signaling pathway.[27] Huang et al showed that miR-155 activates the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) pathway by targeting *p85α* (*PIK3R1*) and indirectly enhances the phosphorylation of AKT, critical for cellular transformation.[28] Another study identified that oncogenic miR-155 targets *SHIP1* to promote tumor necrosis factor-α (TNF-α)-dependent growth of DLBCL.[29] Further, the targeting of *SMAD5* by miR-155 results in sustained phosphorylation of retinoblastoma protein (RB) and decreased abundance of free E2F transcription factor 1 (E2F1), limiting G0/G1 arrest.[30] miRNA-21, an oncogenic agent, is significantly overexpressed in DLBCL tissues; moreover, it might increase DLBCL cell viability and decrease their apoptosis via anti-apoptotic effects by upregulating B-cell lymphoma 2 (*BCL-2*) gene expression.[33] This miRNA could downregulate phosphatase and tensin homolog deleted on chromosome ten (*PTEN*) to inhibit DLBCL cell apoptosis.[34] Likewise, Go et al demonstrated that miR-21 downregulates forkhead box protein O1 (*FOXO1*), a direct target of miR-21, in both direct and indirect manners, by binding to the 3′-UTR of *FOXO1* and activating the PI3K/AKT/mammalian target of rapamycin (mTOR) pathway to increase the cell proliferation in DLBCL.[23] The upregulation of miR-125a/b directly acts on TNF-α-induced protein 3 (*TNFAIP3*) to promote the activation of the NF-κB pathway, which is associated with aggressiveness in human DLBCL cell lines.[35] Some studies support the contribution of miRNA let-7, particularly let-7b, to specific interactions with the PR domain zinc finger protein 1 (*PRDM1*) 3′-UTR and the downregulation of gene expression, thereby representing one of the mechanisms promoting tumorigenesis of DLCBL.[36]

Meanwhile, research on tumor suppressor miRNAs has yielded important results. The *BCL6* gene is a proto-oncogene that is often expressed in DLBCL. Fan et al showed that miR-10a, which is reportedly downregulated in DLBCL, might inhibit proliferation and promote apoptosis by directly binding to the 3′-UTR of the *BCL6* mRNA transcript.[37] Moreover, *BCL6* is a target of miR-187, with miR-187 indirectly promoting lymphoma cell apoptosis and enhancing multidrug (doxorubicin, bortezomib, and vincristine) sensitivity by targeting its 3′-UTR.[38] miR-26a, as a tumor suppressor, suppresses the proliferation and cell cycle progression of DLBCL cells by regulating *p35* expression and inhibiting cyclin-dependent kinase 5 (CDK5)/STAT3 signaling.[39] Another study reported that miR-27b suppressed proliferation and promoted apoptosis by directly targeting the mesenchymal-epithelial transition factor (*MET*) and repressing the oncogenic MET/PI3K/AKT pathway.[40] Moreover, miR-101 downregulation significantly promoted cell proliferation and suppressed cell apoptosis by targeting lysine-specific histone demethylase 1A (*KDM1A*).[41] The overexpression of miR-214 significantly attenuates the malignant phenotype of DLBCL OCI-Ly3 cells in vitro and restricts tumor growth in a xenograft mouse model by targeting programmed death-ligand 1 (*PD-L1*).[21] At the post-transcriptional level, miR-224 was determined to regulate CD59 expression and influence cell proliferation, invasion, and apoptosis.[42] In addition, in ABC-type DLBCL cell lines, miR-181a overexpression could result in G0/G1 cell cycle arrest, increased apoptosis, and decreased invasion via the inhibition of caspase activation and recruitment domain 11 (*CARD11*).[43]

In addition to regulating the expression of target genes, other miRNA-related functions and mechanisms have been reported in DLBCL. Several single-nucleotide polymorphisms (SNPs) or mutations occurring in the miRNA gene region can affect miRNA properties and expression. Zhuang et al suggested that the miR-146a rs2910164 polymorphism can functionally affect the expression of miR-146a, which might explain the risk and pathogenesis of DLBCL in a *Chinese Han* population.[44] Li et al pointed out that the miR-196a2 polymorphism might increase the risk of DLBCL by altering the expression of mature miR-196a2.[45] Indeed, several variants in miRNA genes or target sites have been shown to contribute to the development of DLBCL by affecting miRNA-mediated transcriptional regulatory functions. Kwanhian et al reported somatic mutations in miR-142 that might result in growth stimulation in DLBCL.[46]

miRNAs Serve as Biomarkers in DLBCL

Potential Biomarkers for Diagnosis

There is ample evidence that a distinct miRNA signature characterizes DLBCL. For example, DLBCL cells were shown to have 10- to 30-fold higher miR-155 copy numbers than those in normal circulating B cells.[47] Di Lisio et al proposed a model of 128 miRNAs enabling the discrimination of various lymphoid malignancies, including DLBCL, Burkitt lymphoma (BL), follicular lymphoma (FL), marginal zone lymphoma (MZL), mantle cell

lymphoma (MCL), and chronic lymphocytic leukemia (CLL).[48] To discriminate between DLBCL and BL, a specific set of 19 miRNAs differentially expressed between the two lymphoma types was obtained.[48] Similarly, Lenze et al analyzed the miRNA expression of 64 BL and 86 DLBCL samples using analysis of variance, showing that 38 mature miRNAs may distinguish BL from DLBCL,[49] and five of the described miRNAs (miR-155, miR-146a, miR-26a, miR-29b, and miR-34b) are in accordance with Di Lisio's data, among which miR-155 is the most significantly downregulated miRNA in BL. Gebauer et al concluded that the 10 miRNA signatures, which yielded independent biological characterizations of DLBCL and transformed nodal marginal zone lymphoma (NMZL), may be a valuable aid in discriminating between NMZL and DLBCL.[50] Moreover, four miRNAs, including miR-330, miR17-5p, miR-106a, and miR-210, were found to discriminate DLBCL, FL, and lymph nodes (LNs) with an overall accuracy of 98%.[51] Regarding the differentiation between DLBCL and FL, one study identified that the expression levels of miR-20b, miR-26a, miR-92b, and miR-487b were lower in DLBCL than in FL.[52] Fassina et al highlighted the miR-17-92 cluster as a useful tool to differentiate GC B-cell (GCB) DLBCL and high-grade FL.[53] Yet another study showed that miR-4284 and miR-4484 could serve as putative diagnostic biomarkers to help distinguish between DLBCL and reactive LN (RLN) hyperplasia.[54]

Potential Biomarkers for Subtype Classification

Abundant findings have confirmed specific miRNA signatures to distinguish the molecular subtypes of DLBCL. Lawrie et al showed that the expression levels of miR-21, miR-155, and miR-221 are 4.1-, 2.6-, and 1.5-fold higher in ABC- than in GCB-type cell lines, respectively.[55] Montes-Moreno et al determined that miR-331, miR-151, miR-28, and miR-454-3p were upregulated in GCB-type DLBCL, while the expression levels of miR-222, miR-144, miR-451, and miR-221 were higher in ABC-type DLBCL.[56] miR-21 expression levels in non-GCB-type DLBCL tissues are also higher than those in GCB-type DLBCL tissues.[33] Different expression levels of miR-155 between DLBCL subtypes have been reported, with significantly higher levels in the non-GCB subtype[22,32,57] and lower levels in the GCB subtype.[55] The expression level of miR-146a was higher in ABC-type DLBCL patients than in GCB-type DLBCL patients, whereas miR-16 did not significantly differ between the two groups.[20] Culpin et al suggested a nine-miRNA signature (miR-17-92 cluster, miR-29a, miR-106a, miR-720, miR-1260, and miR-1280), all miRNAs of which are expressed at higher levels in ABC-like cell lines. However, this has not been verified at a clinical pathology level.[52] Moreover, Fassina et al showed that miR-17-92 cluster miRNAs (miR-18b, miR-19b, miR-20a, miR-92, miR-93, and miR-106a) are significantly overexpressed in GCB-type DLBCL.[53] Wu et al showed that miR-320d is expressed at remarkably higher levels in DLBCLs of the GCB-type than in those of the ABC-type, suggesting that miR-320d might be useful a marker for subtype classification.[58] Further, Zhu et al observed reduced miR-181a expression in ABC-type DLBCL cells, whereas miR-181b expression was similar between the ABC- and GCB-like DLBCL cell lines.[43]

Potential Biomarkers for Prognosis

Although the IPI score is currently the most widely used predictive indicator for DLBCL, it has some limitations.[59] Wu et al showed miR-155 overexpression to be associated with shorter progression-free survival (PFS), while a high IPI score indicated poor overall survival (OS).[60] A higher expression level of this miRNA correlates with aggressive forms of DLBCL,[57] and predicts lower event-free survival (EFS).[22] The overexpression of miR-146a in DLBCL tends to be associated with more unfavorable prognoses and is reportedly associated with a lower complete remission (CR) rate, lower OS, and shorter PFS.[20] Berglund et al demonstrated that high miR-200c expression was associated with a lower OS in DLBCL R-CHOP-treated patients.[61] The univariate analysis by Alencar et al argued that miR-18a overexpression predicts a shorter OS, whereas increased expression of miR-222 and lower expression of miR-181a are associated with shorter PFS in DLBCL.[62]

In contrast, many other miRNAs tend to indicate more favorable prognoses. The high miR-21 expression in de novo DLBCL is associated with longer PFS and might serve as an independent predictive factor.[55] DLBCL patients expressing a higher level of miR-224 have longer 5-year PFS and OS compared to those with lower miR-224 expression.[63] Using univariate Cox regression, a significant correlation between high miR-34a expression and improved OS was observed by Marques et al.[64] As a favorable biomarker, low expression of miR-27b was associated with poor OS of patients with DLBCL.[40] Likewise, Zhong et al presented evidence that miR-146b-5p and miR-320d were expressed at lower levels in DLBCLs with poor prognosis by analyzing 106 primary

nodal DLBCL samples from patients with the standard CHOP regimen.[58] The lower expression of miR-197 was determined to be associated with frequent progression and reduced PFS in DLBCL after standard R-CHOP therapy, especially with the ABC subtype.[65] Troppan et al indicated that miR-199a and miR-497 were upregulated in DLBCL compared to normal germinal cells. However, elevated miR-199a and miR-497 levels are associated with improved survival in DLBCL patients, most likely increasing drug (doxorubicin, rituximab and, vincristine) sensitivity.[66]

miRNAs Associated with Chemosensitivity and Chemoresistance in DLBCL

miRNAs are increasingly being recognized as novel players in the evaluation of responses to chemotherapy in DLBCL. miR-21 has a vital role in regulating the chemosensitivity of DLBCL cells. Bai et al demonstrated that it impacts the PI3K/AKT signaling pathway by targeting *PTEN*, thus altering cellular sensitivity to the CHOP chemotherapeutic regimen. Furthermore, the knockdown of NF-κB decreases miR-21 expression and increases the cytotoxic effects of the CHOP regimen in the CRL2631 cells of DLBCL.[67] Marques et al observed that miR-34a is highly expressed in doxorubicin-sensitive cell lines and that the downregulation of *FOXP1*, a target of miR-34a, might increase the sensitivity of DLBCL cells to doxorubicin.[68] Another study by Alencar et al revealed that miR-181a indirectly decreases O6-methylguanine DNA methyltransferase (MGMT) protein expression, potentially contributing to better cyclophosphamide chemosensitivity.[62] In vitro, miR-197 shows important functions in doxorubicin chemosensitivity by enhancing doxorubicin-induced apoptosis in SUDHL9 cells of ABC-type DLBCL, providing insights into effective therapeutic strategies.[63] Besides, the overexpression of miR-370-3p, miR-381-3p, and miR-409-3p was found to be involved in DLBCL cell chemosensitivity in vitro because these miRNAs downregulated genes in the phosphatidylinositol, mitogen-activated protein kinase (MAPK), and B-cell antigen receptor (BCR) signaling pathways.[69]

Conversely, abnormalities in diverse, complicated miRNA-related signaling pathways are intertwined with drug resistance. Kim et al reported that miR-124-mediated restoration of glucocorticoid sensitivity is attributed to the inhibition of the AKT/mTOR/myeloid cell leukemia sequence 1 (MCL1) signaling pathway and induction of the glucocorticoid receptor by directly repressing phosphodiesterase 4B (*PDE4B*) expression and boosting cAMP concentrations in DLBCL.[70] Yuan et al showed that DLBCL patients with sustained miR-125b and miR-130a overexpression have a significantly higher probability of chemoresistance mediated by an abnormal NF-κB signaling pathway than those with no or only one highly regulated miRNA.[71] Sun et al indicated that histone deacetylase 6 (HDAC6) inhibits miR-148b by maintaining low acetylation of the histones H3 and H4 in the miR-148b promoter, thus rescuing Ezrin protein expression and stimulating CHOP resistance in DLBCL.[72] The study highlighted that a reduction or knockout of miR-155 affects vincristine resistance in vincristine-sensitive SU-DHL-5 cells (GCB-type DLBCL cell lines). Furthermore, miR-155 functionally induces vincristine sensitivity through the cell cycle checkpoint Wee1 in DLBCL cells of the GCB subclass.[32] Besides, ATP-binding cassette transporter-mediated multidrug resistance was reported in DLBCL. Go et al showed that miR-21 increases the expression and activity of multidrug-resistant protein 1 (MDR1), encoded by ATP-binding cassette subfamily B member 1 (*ABCB1*), to reduce doxorubicin resistance in DLBCL cells by downregulating the activity of the FOXO1/Bim pathway.[23] Nevertheless, exosomal miRNAs have been shown to participate in chemotherapy resistance. Feng et al demonstrated that the expression levels of exosomal miR-99a-5p and miR-125b-5p are significantly higher in multidrug-resistant DLBCL SU-DHL-2/R cells than in SU-DHL-2 cells. Further, the knockdown of miR-99a-5p and miR-125b-5p was found to enhance chemotherapeutic efficacy, resulting in better PFS.[73]

miRNAs Associated with Virus-Related DLBCL

The association between viral infection and DLBCL has been confirmed in numerous studies. Epstein–Barr virus (EBV) infection profoundly influences the cellular miRNA profile in DLBCL. Nine miRNAs (miR-424, miR-223, miR-199a-3p, miR-199a-5p, miR-27b, miR-378, miR-26b, miR-23a, and miR-23b) and seven miRNAs (miR-155, miR-20b, miR-221, miR-151-3p, miR-222, miR-29b/c, and miR-106a) were found to be upregulated and downregulated, respectively, in EBV-positive DLBCL.[74] miR-155 is considered to be the most studied molecular marker

in EBV-positive DLBCL. The expression of miR-155 was observed to be higher in EBV-positive DLBCL according to an in vitro study wherein the EBV-encoded protein, latent membrane protein 1 (LMP1) induced the expression of B-cell integration cluster (BIC), a precursor form of miR-155, in B-lymphoma cells.[75] Likewise, Wood et al showed that the EBV transcription factor, EBV nuclear antigens-2 (EBNA-2), upregulates miR-155 expression by activating an enhancer upstream from the miR-155 host gene (*miR-155HG*), from which miR-155 is derived.[76] Further, EBV-positive patients show higher serum miR-155 levels than those of EBV-negative patients.[77] There are only a few other reports of miRNAs in EBV-positive DLBCL. In one study, miR-424 was the most strongly upregulated miRNA by EBV-infection in primary DLBCL tissue and the cell lines studied; this miRNA upregulated β-catenin protein to promote tumor development by inhibiting tumor suppressor seven in absentia homolog 1 (SIAH1) expression.[74] In elderly patients, miR-146b and miR-222 show high specificity for identifying EBV-positive DLBCL and are considered potential biomarkers and therapeutic targets.[78]

DLBCL is the most common AIDS-related lymphoma (ARL), which occurs at an advanced stage and with B symptoms and involves extranodal tissue, mainly in severely immunosuppressed patients.[79] miRNAs play pivot in the development and progression of human immunodeficiency virus (HIV)-associated DLBCL. Thapa et al showed that miRNAs from the miR-17-92 paralog clusters are overexpressed in AIDS-related DLBCL cases, revealing an oncogenic role for these miRNAs owing to their inhibition of p21.[80] Subsequent studies have supported the use of circulating miR-21, miR-122, and miR-223 levels to discriminate between HIV-infected and uninfected individuals, and higher serum levels of miR-222 can also serve as a diagnostic marker for earlier detection of HIV-infected DLBCL.[81]

Epidemiological studies have shown an increased risk of developing B-cell lymphomas in patients with chronic hepatitis C virus (HCV) infection.[82] Augello et al detected 6 and 14 miRNAs that were upregulated and downregulated, respectively, in HCV-associated DLBCL with respect to non-infected ones. Importantly, these researchers found that decreased expression of miR-138-5p and increased expression of miR-147a, miR-147b, and miR-511-5p were poor prognostic factors for HCV-positive DLBCL patients.[83]

circRNAs

circRNAs, a novel type of ncRNA with a covalently closed loop structure generated by head-to-tail splicing, have attracted great research interest lately.[84] There are four categories of circRNAs, namely exonic circRNAs, circular intronic RNA, exon-intron circRNAs, and intergenic circRNAs.[85] Based on the relevant literature, we can highlight several remarkable characteristics of circRNAs as follows. (1) They exist in high abundance; Jeck et al reported circRNAs to be considerably more abundant (>10-fold) than the corresponding linear mRNAs.[86] (2) They have high stability; the structures lack free ends, which provides high resistance to RNA exonuclease or RNase R activity, conferring higher stability than linear RNAs.[87,88] Some studies have shown that circRNA transcript half-lives exceed 48 h.[86] (3) They are highly conserved; circRNAs show an ancient, evolutionarily conserved feature in different species.[86,89] With the combination of high-throughput sequencing and new computational algorithms, thousands of circRNAs have now been revealed in species spanning from humans to archaea.[86,87,89] (4) They exhibit specific expression; circRNAs often exhibit tissue-/developmental stage-specific expression. For example, Nicolet et al provided the first comprehensive analysis of circRNA expression in human hematopoietic cells, suggesting that their expression increases upon maturation.[90] circRNA functions depend on subcellular localization. Cytoplasmic circRNAs can function as miRNA sponges, binding to proteins and even translating proteins, whereas nuclear circRNAs might participate in the regulation of gene expression by binding to proteins.[91] Extensive studies have confirmed that circRNAs can function as competitive endogenous RNA (ceRNA), reducing their inhibitory effects on target genes by efficiently sponging miRNAs.[92]

circRNAs are known to be related to the occurrence, development, and progression of human diseases, especially cancer.[93] circRNAs might function as oncogenes or tumor suppressors to alter tumor cell proliferation, apoptosis, invasion, and migration.[94] Emerging evidence indicates that circRNAs participate in the oncogenesis of several carcinomas, including breast cancer,[95] lung cancer,[96] and colorectal cancer.[97] However, only a few published studies show that circRNAs participate in the etiology of DLBCL.

Hu et al identified a novel and highly stable DLBCL-related circRNA, circ-APC (hsa_circ_0127621), which was reportedly downregulated in DLBCL tissues, cell lines, and plasma, as evidenced by microarray

analysis.[91] Their study reported that the inhibitory effects of circ-APC on DLBCL cell proliferation depend on its ability to upregulate adenomatous polyposis coli (*APC*). Upregulated *APC* dampens the canonical Wnt/β-catenin signaling pathway to retard DLBCL growth by reducing the nuclear accumulation of β-catenin. Further evidence identified that nuclear circ-APC binds to the *APC* promoter and recruits the DNA demethylase Ten-eleven translocation 1 (TET1), thereby transcriptionally upregulating *APC*. Cytoplasmic circ-APC, acting as a sponge for miR-888, increases *APC* expression by sponging and inhibiting miR-888, thus regulating the Wnt/β-catenin signaling pathway and resulting in the proliferation of DLBCL cells. Notably, the OS is shorter for patients with lower circ-APC levels in DLBCL tissues, and circ-APC expression might serve as an independent prognostic factor for DLBCL patients. Therefore, circ-APC is a novel proliferation inhibitor, and restoring circ-APC expression might be a promising therapeutic approach for DLBCL patients.

Dahl et al applied a new method for the accurate quantification of circRNAs, using NanoString technology with different B-cell malignancies, including DLBCL, BL, MCL, and MM.[98] They elucidated the expression of 52 circRNA candidates, mainly focusing on circRNAs previously implicated in other cancers and those produced from host genes involved in lymphomagenesis. The results showed that circRNA expression profiles could help distinguish different B-cell malignancies. They also found a novel circRNA, derived from the Ikaros family zinc finger 1 (*IKZF3*) gene, which was determined to be highly expressed in MM and DLBCL cell lines.

lncRNAs

lncRNAs are a class of ncRNAs over 200 nucleotides long, which lack or have little protein-coding capacity.[99] Based on their genomic location, lncRNAs are classified into sense lncRNAs, antisense lncRNAs, bidirectional lncRNAs, and intron and intergenic lncRNAs.[100] The aberrant expression of lncRNAs is strongly associated with tumorigenesis, tumor progression, and metastasis, highlighting their clinical applications as diagnostic and prognostic biomarkers, as well as therapeutic targets in different cancer types.

Expression of lncRNAs in DLBCL

lncRNAs, which are expressed in highly tissue- and cell type-specific manners, are functionally critical for the development of human diseases. Lymphoid differentiation-related lncRNAs have been explored in recent years.[101] Tayari et al showed the dynamic regulation of lncRNA expression during B cell transition from naïve B cells to GC-B cells, resulting in memory B cells.[102] One study examined RNA-Seq data sets of DLBCL and identified 2632 novel, multi-exonic candidate lncRNAs expressed in more than one DLBCL tumor, most of which are not expressed in normal B cells.[103] By applying microarray technology, Gao et al revealed 1648 significantly upregulated lncRNAs and 2671 significantly downregulated lncRNAs in two different GCB-type DLBCL cell lines (OCI-ly1 and OCI-ly19) compared to the levels in normal B lymphocytes.[104] Using lncRNA chip array assays, another study reported that 1053 lncRNAs were remarkably differentially expressed in DLBCL cell lines compared with normal B cells, and 416 and 637 of these lncRNAs were upregulated and downregulated, respectively.[105] In an in silico study, among 189 candidate lncRNAs, growth arrest-specific 5 (GAS5), miR-17-92a-1 cluster host gene (*MIR17HG*), highly upregulated in liver cancer (HULC), and prostate cancer antigen 3 (PCA3) were found to be highly altered in DLBCL patients, and abnormal expression of GAS5 was most commonly detected.[106]

Functions and Mechanisms of lncRNAs in DLBCL

The importance of lncRNAs in a variety of biological functions, including cell proliferation, differentiation, and apoptosis, has been established.[107] These lncRNAs are reported to be extensively involved in the biological mechanisms of DLBCL by "sponging" intracellular molecules to indirectly block their biological functions with downstream factors. For instance, Wang et al showed that the lncRNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT-1) is upregulated in DLBCL and sponges miR-195 to enhance DLBCL cell proliferation, migration, and resistance to CD8 + T cell cytotoxicity by inducing the expression of *PD-L1*. Besides, MALAT-1 was also found to promote epithelial-mesenchymal transition (EMT)-like processes by activating the Ras/extracellular signal-regulated kinase (ERK) signaling pathway through the miR-195/PD-L1 axis.[108] The lncRNA small nucleolar RNA host gene 14 (SNHG14) can act as a ceRNA sponge of miR-5590-3p to upregulate the downstream protein zinc finger E-box binding homeobox 1 (ZEB1), which transcriptionally activates SNHG14 and PD-L1 to promote immune evasion of DLBCL cells.[109] Similarly, lncRNA SNHG16 can also promote proliferation and cell cycle progression by directly interacting with miR-

Table 1 miRNAs in Diffuse Large B Cell Lymphoma

miRNAs	Altered Expression	Targets	Pathways	Function	Reference
miR-10a	Downregulated	BCL-6	-	Inhibit cell proliferation and promote apoptosis	37
miR-21	Upregulated	BCL-2	-	Promote proliferation and inhibit apoptosis	33
		PTEN	-	Inhibit apoptosis	34
		FOXO1	PI3K/AKT/mTOR signaling pathway	Increase proliferation, drug resistance and inhibit apoptosis	23
		PTEN	PI3K/AKT signaling pathway	Increase chemoresistance to the CHOP regimen	67
miR-26a	Downregulated	p35	CDK5/STAT3 signaling pathway	Inhibit proliferation and cell cycle progression	39
miR-27b	Downregulated	MET	PI3K/AKT signaling pathway	Inhibit cell viability, proliferation and promote apoptosis	40
miR-34a	Downregulated	FOXP1	-	Increase chemosensitivity to doxorubicin	64
		-	-	Inhibit cell proliferation and promote apoptosis	26
miR-101	Downregulated	KDM1A	-	Inhibit cell proliferation and promote apoptosis	41
miR-124	-	PDE4B	AKT/mTOR/MCL1 signaling pathway	Increase chemosensitivity of glucocorticoid	70
miR-125a/b	-	TNFAIP3	NF-κB signaling pathway	Increase aggressiveness	35
miR-155	Upregulated	TGFBR2	-	Promote proliferation, cell cycle progression and inhibit apoptosis	25
		-	-	Promote cell proliferation and cell cycle progression	24
		SOCS3	JAK/STATsignaling pathway	Promote proliferation and inhibit apoptosis	27
		p85α	PI3K/AKT signaling pathway	Promote proliferation, cellular transformation and inhibit apoptosis	28
		SMAD5	TGF-β signaling pathway	Promote cell cycle progression	30
		SHIP1	-	Promote tumor growth	29
miR-181a	-	CARD11	-	Inhibit invasion, cell cycle progression and promote apoptosis	43
		MGMT	-	Increase cyclophosphamide chemosensitivity	62
miR-187	Downregulated	BCL-6	-	Promote apoptosis and increase chemotherapy sensitivity	38
miR-199a miR-497	Upregulated	-	-	Increase chemosensitivity	66
miR-214	Downregulated	PD-L1	-	Inhibit tumor growth	21

(*Continued*)

Table 1 (Continued).

miRNAs	Altered Expression	Targets	Pathways	Function	Reference
miR-224	Downregulated	CD59	-	Inhibit proliferation, invasion and promote apoptosis	42
miR-146b-5p miR-320d	Downregulated	-	-	Inhibit cell proliferation	58
miR-370-3p miR-381-3p miR-409-3p	Downregulated	-	MAPK/BCR signaling pathway	Increase sensitivity to rituximab and doxorubicin	69
let-7b	Upregulated	PRDM1	-	Promote lymphomagenesis	36

Abbreviation: TGFBR2, transforming growth factor beta receptor 2.

497-5p and inversely increasing the abundance of the downstream proto-oncogene proviral integration site for Moloney murine leukemia virus 1 (*PIM1*) in DLBCL cells.[110] As another member of the same gene family, SNHG12 was recently reported to boost DLCBL tumorigenesis by sponging miR-195.[111]

lncRNAs might interfere with the cell cycle and promote the occurrence and development of DLBCL. Studies have shown that the lncRNA nuclear enriched abundant transcript 1_1 (NEAT1_1) is highly expressed in tumor cells, while its knockdown results in growth inhibition, cell cycle arrest, and apoptosis induction.[112] The lncRNA leukemia-associated noncoding IGF1R activator RNA 1 (LUNAR1) knockdown has been found to significantly repress DLBCL cell proliferation by regulating its functional downstream targets, such as *E2F1*, *cyclin D1*, and *p21*, to alter cell cycle progression.[113] Peng et al demonstrated that lncRNA HULC knockdown might arrest cell proliferation and induce apoptosis by downregulating the expression of cyclin D1 and Bcl-2 proteins in DLBCL cells.[114] Their study further showed that lncRNA long intergenic noncoding RNA-p21 (lincRNA-p21) could inhibit cell proliferation and induce cell cycle arrest by functionally modulating downstream *p21*, *cyclin D1*, and *CDK4* expression.[115] In addition, as a tumor suppressor gene, lncRNA PANDA inhibits cell proliferation and induces G0/G1 cell cycle arrest by silencing the MAPK/ERK signaling pathway in DLBCL cells.[116] Another study showed that knocking down the expression of lncRNA HOTAIR inhibits cell proliferation, arrests the cell cycle in the G2/M phase, and induces cell apoptosis in vitro, partly through the PI3K/AKT/NF-κB pathway.[117]

The Wnt/β-catenin signaling pathway is increasingly being implicated in lncRNA-mediated DLBCL development. Zhao et al found that the lncRNA SMAD5 antisense RNA 1 (SMAD5-AS1) can sponge miR-135b-5p to inhibit DLBCL development via the classical Wnt/β-catenin pathway.[118] The lncRNA functional intergenic repeating RNA element (FIRRE) functions as an oncogene and activates the Wnt/β-catenin signaling pathway to facilitate DLBCL cell proliferation and reduce cell apoptosis by translocating β-catenin into the nucleus.[119] Forkhead box M1 (FOXM1), one of the likely transcription factors of the lncRNA olfactory receptor family 3 subfamily A member 4 (OR3A4), positively upregulated the expression of OR3A4 to enhance the occurrence of DLBCL via the Wnt/β-catenin signaling pathway at the transcriptional level.[120]

lncRNAs as Biomarkers in DLBCL

Potential Biomarkers for Diagnosis and Subtype Classification

Mounting studies have analyzed the expression of lncRNAs by comparing DLBCL patients and healthy subjects. For instance, the lncRNAs PEG10 and LUNAR1 were upregulated in DLBCL patients,[113,121] whereas PANDA was significantly downregulated.[116] The area under the curve (AUC) of PEG10, PANDA, and LUNAR1 reached 0.8228, 0.760, and 0.9420, respectively, indicating that these three lncRNAs could be diagnostic markers for distinguishing DLBCL patients from healthy individuals.[113,116,121] Another study showed that the expression of five lncRNAs could help distinguish DLBCL with RLN. Among these differentially expressed lncRNAs, ENST00000424690, ENST00000425358, and NR_026892 were upregulated, and ENST00000464929 and ENST00000475089 were downregulated in DLBCL compared to RLN.[104] Moreover, Deng et al demonstrated that NEAT1_1 could serve as a useful diagnostic tool to differentiate between DLBCL and lymphadenitis.[112]

Table 2 lncRNAs in Diffuse Large B Cell Lymphoma

lncRNAs	Altered Expression	Targets	Pathways	Function	Reference
MALAT-1	Upregulated	miR-195	Ras/ERK signaling pathway	Increase proliferation, migration and immune escape, promote EMT-like process and inhibit apoptosis by regulation of PD-L1	108
SNHG12	Upregulated	miR-195	-	Accelerate tumorigenesis of DLCBL	111
SNHG14	Upregulated	miR-5590-3p	-	Promote cell proliferation, migration, immune evasion and EMT-like processes	109
SNHG16	Upregulated	miR-497-5p	-	Promote cell proliferation and cell cycle progression	110
NEAT1_1	Upregulated	-	-	Promote cell viability and migration	112
LUNAR1	Upregulated	-	-	Promote cell proliferation by regulating E2F1, cyclin D1 and p21 expression	113
HULC	Upregulated	-	-	Promote cell proliferation via regulating cyclin D1 and Bcl-2	114
HOTAIR	Upregulated	-	PI3K/AKT/NF-κB signaling pathway	Promote cell proliferation and cell cycle progression	117
FIRRE	Upregulated	-	Wnt/β-catenin signaling pathway	Facilitate DLBCL cell growth via modulation of the nuclear translocation of β-catenin.	119
OR3A4	Upregulated	-	Wnt/β-catenin signaling pathway	Promote cell proliferation	120
PEG10	Upregulated	-	-	Promote cell proliferation and inhibit apoptosis	121
LincRNA-p21	Downregulated	-	-	Inhibit cell proliferation and cycle progression via regulating cyclin D1, CDK4 and p21 expression	115
PANDA	Downregulated	-	MAPK/ERK signaling pathway	Inhibit cell proliferation and accelerate cell cycle arrest	116
SMAD5-AS1	Downregulated	miR-135b-5p	Wnt/β-catenin signaling pathway	Regulate the expression of APC through binding to miR-135b-5p to inhibit cells proliferation	118
NONHSAG026900	Downregulated	-	-	Inhibit cell cycle activity to limit tumor growth	123
SubSigLnc-17	Upregulated: 6 Downregulated:11	-	-	Discriminate GCB and ABC subtypes with high accuracy	122

Several studies have reported the connection between lncRNA expression patterns and subtype classification. A panel of 17 lncRNA biomarkers (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) was integrated to form a lncRNA-based molecular signature (termed SubSigLnc-17), which could discriminate GCB from ABC subtypes, with high accuracy.[122] Further, Zhao et al indicated that patients with the GCB subtype had significantly higher values of the lncRNA NONHSAG026900 than those

with the non-GCB subtype, suggesting the diagnostic potential of NONHSAG026900.[123] However, relevant studies related to subtype classification remain limited, and the available data are not sufficient for conclusively demonstrating that a single lncRNA can be used in clinical practice as a biomarker.

Potential Biomarkers for Prognosis

Numerous studies have shown that altered levels of lncRNAs are also closely associated with OS and appear to be powerful predictors of prognosis in DLBCL. Sun et al suggested that a six-lncRNA signature (SACS-AS1, MME-AS1, CSMD2-AS1, RP11-360F5.1, RP11-25K19.1, and CTC-467M3.1) could provide additional prognostic information to improve survival prediction for DLBCL at the molecular level beyond the conventional IPI system.[124] Patients with NONHSAG026900 overexpression were found to have longer 5-year OS or PFS than those from the low-expression group. As a favorable biomarker associated with DLBCL prognosis of patients, NONHSAG026900 could also improve the predictive power of IPI as an independent factor.[123] Peng et al showed that HULC could represent a novel indicator of poor prognosis and be an independent factor to forecast the OS and PFS of DLBCL,[114] whereas in a different study, the same authors showed PEG10 to only serve as an independent predictor of poor OS based on multivariate analysis.[121] Increased expression of NEAT1_1 and FIEER and decreased PANDA expression are closely correlated with poorer clinical outcomes and OS in DLBCL patients.[112,116,119] The results from a study by Yan et al revealed that DLBCL patients expressing higher levels of HOTAIR have a poorer prognosis.[117] Besides, patients expressing high levels of lincRNA-p21 tend to have more favorable prognoses than their low-expression counterparts,[105] whereas LUNAR1 overexpression and OR3A4 overexpression were found to be unfavorable prognostic predictors for DLBCL.[113,120]

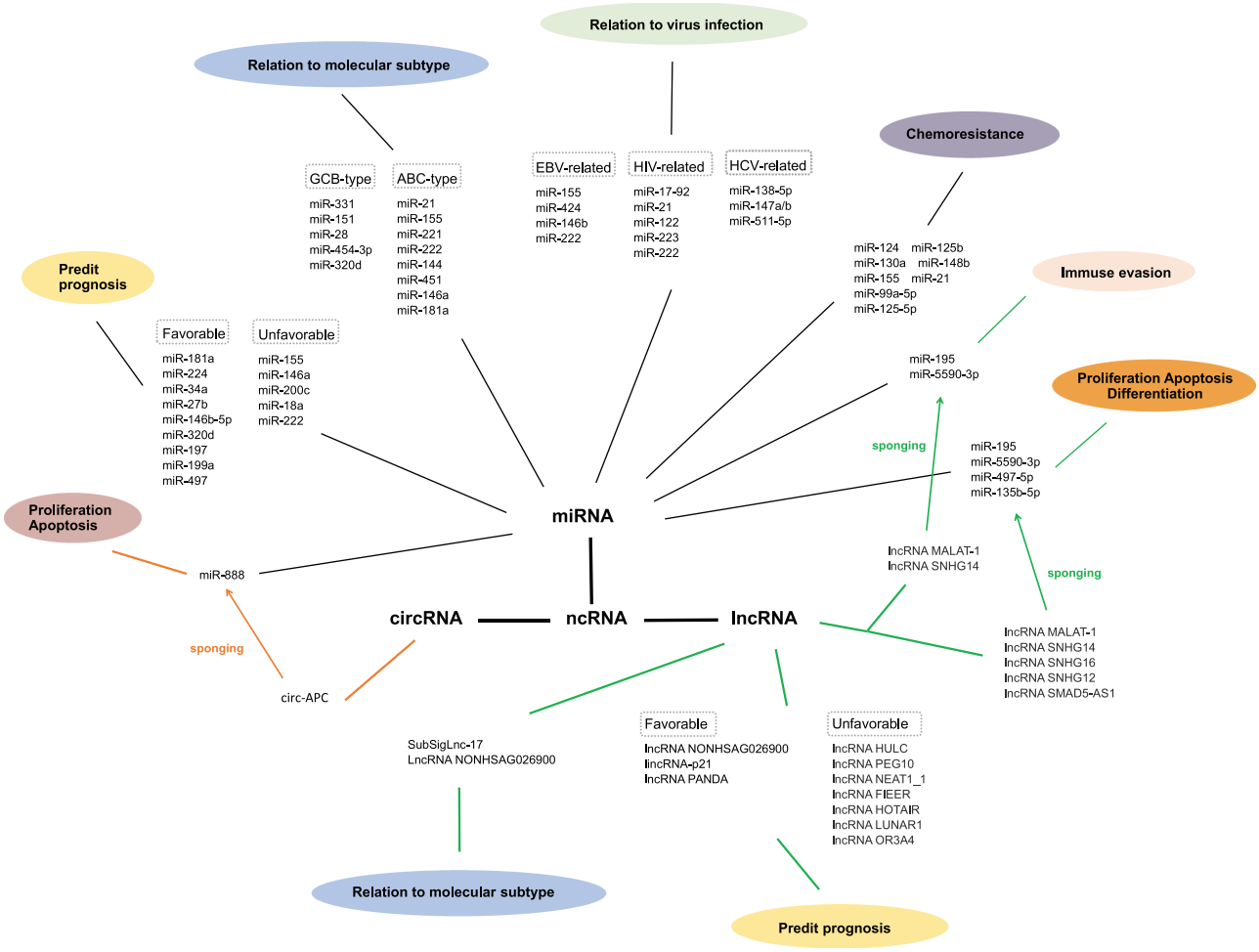

Figure 1 The connections of three groups of ncRNAs involved in diffuse large B cell lymphoma.
Abbreviations: ncRNA, non-coding RNA; miRNA, microRNA; circRNA, circular RNA; lncRNA, long non-coding RNA; GCB, germinal center B-cell; ABC, activated B-cell; EBV, Epstein–Barr virus; HIV, human immunodeficiency virus; HCV, hepatitis C virus.

Conclusion

Abundant evidence suggests the functional role and therapeutic potential of ncRNAs in DLBCL, providing novel insights into the molecular mechanisms of DLBCL and opening clinical avenues toward the development of effective therapies. In this review, we discussed miRNAs, circRNAs, lncRNAs, and their involvement in the subtypes, pathogenesis, chemosensitivity, chemoresistance, and prognosis of DLBCL, as well as interactions with viral infections. The major roles of DLBCL-related miRNAs and lncRNAs are summarized in Tables 1 and 2, respectively. The connections of these three groups of ncRNAs involved in DLBCL is shown in Figure 1. miRNAs are the most extensively studied ncRNAs in DLBCL. Some recent studies have focused on miRNA-targeted therapies, with rewarding treatment outcomes, whereas more research has been dedicated to investigating the therapeutic potential of the highly cell- and tissue-specific lncRNAs and circRNAs in DLBCL. However, there is limited literature on the connections among these three ncRNAs concerning complex regulatory mechanisms. The advent of the post-genomics era calls for discovering additional DLBCL-related ncRNAs to decipher the exact underlying mechanisms. Nevertheless, we intend to explore related aspects and investigate the interactions among the regulatory networks of miRNAs, circRNAs, and lncRNAs in the foreseeable future.

Funding

This work was supported by grants from the Education Department of Jilin Province, P.R.C. (No. JJKH20 190059KJ), the Science and Technology Department of Jilin Province, P.R.C. (No. 20190201050JC), the Science and Technology Department of Jilin Province, P.R.C. (No. 20200201543JC).

Disclosure

The authors declare no competing financial and/or non-financial interests in relation to the work described.

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