Non-coding RNAs (miRNAs and lncRNAs) and their roles in lymphogenesis in all types of lymphomas and lymphoid malignancies (Review)

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Abstract. Contemporary developments in molecular biology have been combined with discoveries on the analysis of the role of all non-coding RNAs (ncRNAs) in human diseases, particularly in cancer, by examining their roles in cells. Currently, included among these common types of cancer, are all the lymphomas and lymphoid malignancies, which represent a diverse group of neoplasms and malignant disorders. Initial data suggest that non-coding RNAs, particularly long ncRNAs (lncRNAs), play key roles in oncogenesis and that lncRNA-mediated biology is an important key pathway to cancer progression. Other non-coding RNAs, termed microRNAs (miRNAs or miRs), are very promising cancer molecular biomarkers. They can be detected in tissues, cell lines, biopsy material and all biological fluids, such as blood. With the number of well-characterized cancer-related lncRNAs and miRNAs increasing, the study of the roles of non-coding RNAs in cancer is bringing forth new hypotheses of the biology of cancerous cells. For the first time, to the best of our knowledge, the present review provides an up-to-date summary of the recent literature referring to all diagnosed ncRNAs that mediate the pathogenesis of all types of lymphomas and lymphoid malignancies.

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1. Introduction

Lymphomas are a heterogeneous group of cancers; more specifically, they consist of a group of blood disorders derived from lymphocytes and are presented with multiple variations in clinical presentation, long-term prognosis and pathogenesis. They represent one of the most common types of cancer worldwide and affect numerous patients. According to the World Health Organization (WHO) classification report, there are approximately 100 different types of lymphoma. The two main categories of lymphomas are non-Hodgkin lymphoma (NHL) (consisting 9 out of 10 of all lymphoma cases) and Hodgkin lymphoma (HL) (consisting 1 out of 10 of all lymphoma cases) (1-3). Furthermore, non-Hodgkin lymphomas can be grouped into B- and T-cell NHLs (TNHLs), which account for approximately 90 and 10% of NHLs, respectively (4,5). According to the WHO, two other categories are also considered as types of lymphoid tissue tumors: Multiple myeloma (MM) and immunoproliferative diseases (3).

Epidemiology. According to the WHO, there are the following lymphoma subtypes (WHO 2016): i) Mature B-cell neoplasms; ii) mature T-cell and natural killer (NK) cell neoplasms; iii) precursor lymphoid neoplasms; iv) HL; and v) immunode-ficiency-associated lymphoproliferative disorders (4,5).

B-cell NHLs (BCNHLs) are tumors of B-cells that exhibit a heterogeneity that is attributed to the fact that these tumors are derived from different stages of mature B-cell differentiation. The main subtypes of BCNHLs are the following: i) diffuse large B-cell lymphoma (DLBCL); ii) chronic lymphocytic leukemia (CLL); iii) follicular lymphoma (FL); iv) mantle cell lymphoma (MCL); v) Burkitt's lymphoma (BL); vi) marginal zone lymphoma (MZL); and vii) mucosa-associated lymphoid tissue (MALT) (6). The majority of BCNHLs, such as DLBCL and FL, have passed the germinal center (GC) reaction, indicating that their immunoglobulin (IG) genes have been

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hypermutated. Other subtypes, such as MCL and CLL, are derived from GC-inexperienced B-cells (7).

The most common subtypes of TNHLs and NK-cell NHLS (NK-NHLs) are the following: i) Cutaneous T-cell lymphomas (mycosis fungoides, Sezary syndrome and others); ii) adult T-cell leukemia/lymphoma; iii) angioimmunoblastic T-cell lymphoma; iv) extranodal NK/T-cell lymphoma; nasal type; vi) enteropathy-associated T-cell lymphoma; and vii) anaplastic large cell lymphoma (ALCL) (4).

Risk factors and diagnosis of lymphomas. The most common risk factors for HL are Epstein-Barr virus (EBV) infection and a family history of the disease (8). The most common risk factors for several types of NHLs include the following: i) Autoimmune diseases, such as Sjögren syndrome, celiac disease, rheumatoid arthritis and systemic lupus erythematosus; ii) HIV/AIDS infection; iii) human T-lymphotropic virus infection; iv) *Helicobacter pylori* infection; v) HHV-8 infection; vi) hepatitis C virus infection; vii) medical treatments (patients who have been previously treated for Hodgkin lymphoma, methotrexate and the tumor necrosis factor-a inhibitors); viii) genetic diseases; and ix) certain chemical agents (benzene and certain herbicides and insecticides; weed- and insect-killing substances) (9-15). Some environmental agents, such as red meat consumption and tobacco smoking may also play a role in increasing the risk of developing NHL (11,12,16).

The diagnosis of lymphomas can be achieved due to the enlargement of lymph nodes, which can be determined by performing a lymph node biopsy (17). A lymph node biopsy commonly is followed by performing immunophenotyping, flow cytometry, fluorescence *in situ* hybridization testing, bone marrow aspiration and bone marrow biopsy (18). Imaging via computed tomography of the chest and upper-lower abdomen may then be performed to determine the possible expansion of the lymphoma throughout the human body (17).

Non-coding RNAs (ncRNAs). ncRNAs are RNAs that are not translated to proteins. Over the past ten years, a number of ncRNAs have been identified. Any of the three RNA polymerases (RNA Pol I, RNA Pol II or RNA Pol III) can perform the transcription of a ncRNA. The ncRNAs are divided into the following two main categories: Small ncRNAs, <200 bp in length and long ncRNAs (lncRNAs), >200 bp in length (19).

In these two categories, several individual categories of ncRNAs also exist. These include housekeeping ncRNAs [transfer RNAs (tRNAs) and some ribosomal RNAs (rRNAs)], which are essential for fundamental principles of cellular biology, small nuclear RNAs (snRNAs), and a number of recently observed RNAs which are associated with the transcription of genes into proteins (20).

MicroRNAs (miRNAs or miRs). To date, miRNAs are the less extensively studied ncRNAs for their roles in cancer. Over the past years, a number of targeted reviews have been published (21-23), which have described a complex basic mechanism through which miRNAs can lead to the silencing of target gene expression; through the formation of a silencing complex induced by RISC-induced RNA, which uses proteins from the Argonaute family (such as AGO2) for the splicing of target mRNAs or for the

suspension of the translation of these mRNAs (21). The patterns of expression of miRNAs in different cancer types have been well-observed, and studies have highlighted numerous miRNAs, such as miR-10b, let-7, miR-101 and miR-15a-16 complex-1, which have oncogenic or tumor-suppressive functions (22,23).

lncRNAs. Recent observations of new species of lncRNAs have led to the development of various possible candidates as lncRNAs. Although a number of RNAs have a length of >200 bp, such as repeat sequence transcripts and pseudogenes (24), the term lncRNA (also referred to as lincRNAs, for long transgenic ncRNAs) is not used in the same manner in all cases.

A number of common features of lncRNAs have been indicated to confirm their biological identity, such as the following: i) Epigenetic regulation as in a transcripted gene; ii) transcription performed by RNA polymerase II; iii) poly-adenylation to the 3'-untranslated region (3'-UTR); iv) frequent splicing of multiple exons through specific molecular patterns; v) regulation by classic transcription factors; and vi) frequent tissue-specific expression (24) (Fig. 1).

ncRNAs in normal B-cell differentiation and T-cell development. B-cell differentiation in adult humans begins within the bone marrow (BM) and is continued thereafter in the lymph nodes, tonsils and spleen (25). On the other hand, T-cells a derived from bone marrow hematopoietic stem cells (HSCs), whose progenitors migrate to and colonize the thymus (26).

The most common lncRNAs affecting normal B-cells are the following: i) MYB-AS1, SMAD1-AS1 and LEF1-AS1, located on 6q23.3, 4q31.21 and 4q25, respectively, are involved in early B-cell development; ii) CRNDE, located on 16q12.2-involved in mitotic cell cycle related processes; and iii) RP11-132N15.3/lnc-BCL6-3, located on 3q27.3, and involved in the modulation of the GC reaction. However, data on the roles of lncRNAs in normal T-cells are limited (27-31).

miRNAs are also involved in lymphocyte development, as first described in 2004; it was demonstrated that miR-223, miR-181 and miR-142 were highly expressed in B-cells (32). miR-181 can also contribute to the regulation of the levels of CD69, BCL2 and TCR during T-cell development. In addition, miR-155 and miR-181 play key roles in the regulation of GC B-cell differentiation (33).

It is essential knowledge that all ncRNAs may play a vital role as predictive and prognostic biomarkers in the pathogenesis and progression of lymphomas and lymphoid malignancies in general. The main aim of the present review was to provide an up-to-date summary of available information on all the known miRNAs and lncRNAs that participate in the development of all lymphoid disorders, with a main focus on their connection to each lymphoma subtype. Furthermore, these molecular biomarkers may be used, in the near future, in the therapeutic management of the majority of lymphomas. Thus, the present review summarizes all published data to date on ncRNAs, in order to shed light on the future perspectives of lymphoma management.

2. Literature search

A literature search was performed, including studies published up to August, 2020, using the following databases: Medline (PubMed), Science Direct, Web of Science and Google Scholar.
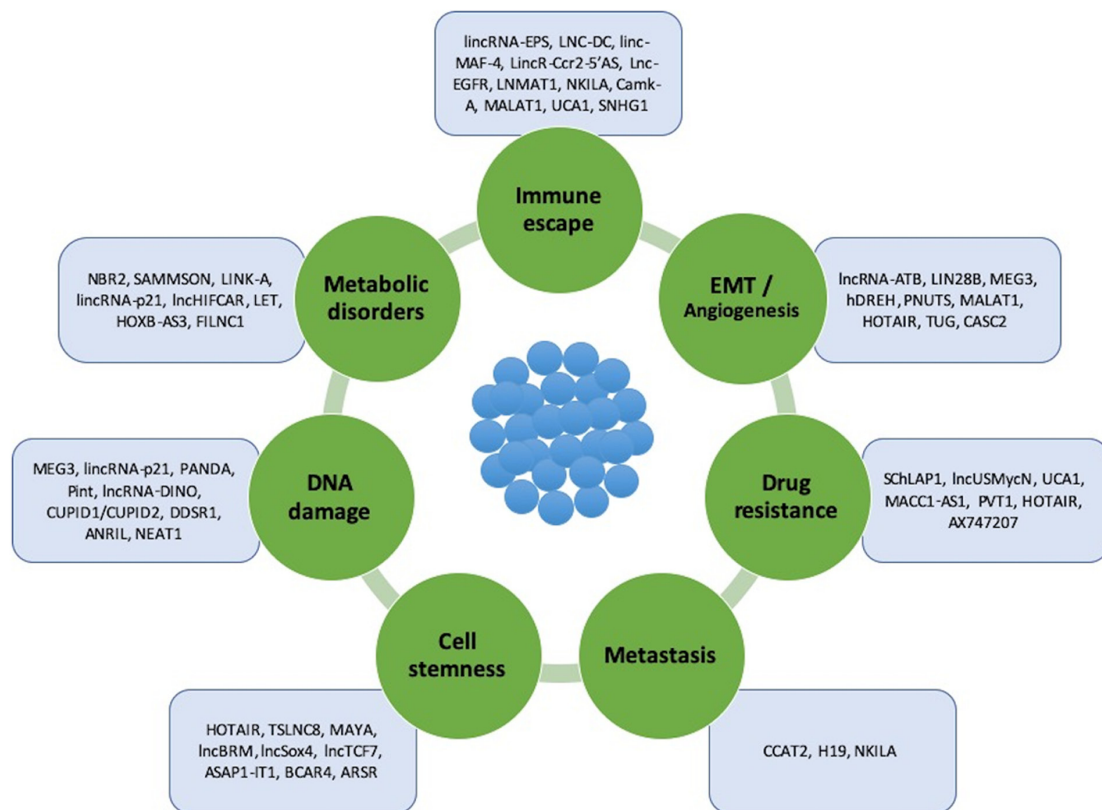
Figure 1. lncRNAs involved in oncogenesis, tumor progression and metastasis. These lncRNAs can be divided into 7 subtypes based on the process/property in which they are involved: Immune system escape, epithelial-mesenchymal transition, and angiogenesis, drug resistance, metastasis, cell stemness, DNA damage and metabolic disorders. lncRNAs, long non-coding RNAs.

Systematic reviews, uncontrolled prospective, retrospective and experimental studies were included for each specific subject (total no. of studies, n=235). The following inclusion criteria were applied: Studies concerning ncRNAs, lncRNAs, miRNAs, cancer and lymphomas: HLs, and BCNHLs and TNHLs. All studies concerning the association of lncRNAs and miRNAs with NHLs and HLs were included.

3. Non-coding RNAs in lymphomas

Over the past years, a number of studies have referred to the significance of lncRNAs and miRNAs in the pathophysiology of lymphomas, particularly B-cell NHLs. There are different non-coding RNAs that play a role in each subtype of lymphoma, and these are referred to the sections and tables below (Figs. 2 and 3).

a) BCNHLs
DLBCL. Diffuse large B-cell lymphoma is the most common form of NHL among adults (34) and it occurs most often in older-aged individuals, with a median age of diagnosis approaching the seventh decade of a patient's life (35). There are 2 different molecular subtypes of DLBCL: GC B-cell like (GC-DLBCL) and activated B-cell like (ABC-DLBCL) (36,37).

Subtypes of DLBCLs with a distinctive morphology or immunophenotype are the following: i) T-cell/histiocyte-rich large B-cell lymphoma; ii) ALK+ large B-cell lymphoma; iii) plasmablastic lymphoma; iv) intravascular large B-cell

lymphoma; and v) large B-cell lymphoma with IRF4 rearrangement (38,39).

Subtypes of DLBCLs with distinctive clinical issues are the following: i) Primary mediastinal large B-cell lymphoma; ii) primary cutaneous DLBCL, leg type; iii) primary DLBCL of the central nervous system; iv) DLBCL associated with chronic inflammation; v) lymphomatoid granulomatosis; and vi) primary effusion lymphoma (38,39).

Additionally, there are DLBCLs driven by viruses, such as the following: i) EBV-positive DLBCL, not otherwise specified; and ii) HHV8-positive DLBCL, NOS (Not otherwise specified). There are also DLBCLs driven by disorders related to DLBCL, such as: i) *Helicobactor pylori*-associated DLBCL; and ii) EBV-positive mucocutaneous ulcer (40,41).

In order for a B-cell to be developed or to progress into a DLBCL type, changes in the following genes need to occur: BCL2 (42), BCL6 (42), MYC (36), EZH2 (43), MYD88 (42), CREBBP (44), CD79A and CD79B (44) and PAX5 (44). Therefore, the neoplastic cells in DLBCL exhibit a pathologically overactivation of the nuclear factor (NF)-κB, phosphoinositide 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR), Janus kinase (JAK)/signal transducer and activator of transcription (STAT), mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK), B-cell receptor and Toll-like receptor pathways (42).

Concerning miRNAs in DLBCLs, it has been shown than in ABC-type DLBCL lymphoma, there is a high expression of miR-21, miR-146a, miR155, miR-221 and miR-363, while in GCB-type DLBCL, there is a high expression of miR-421 and
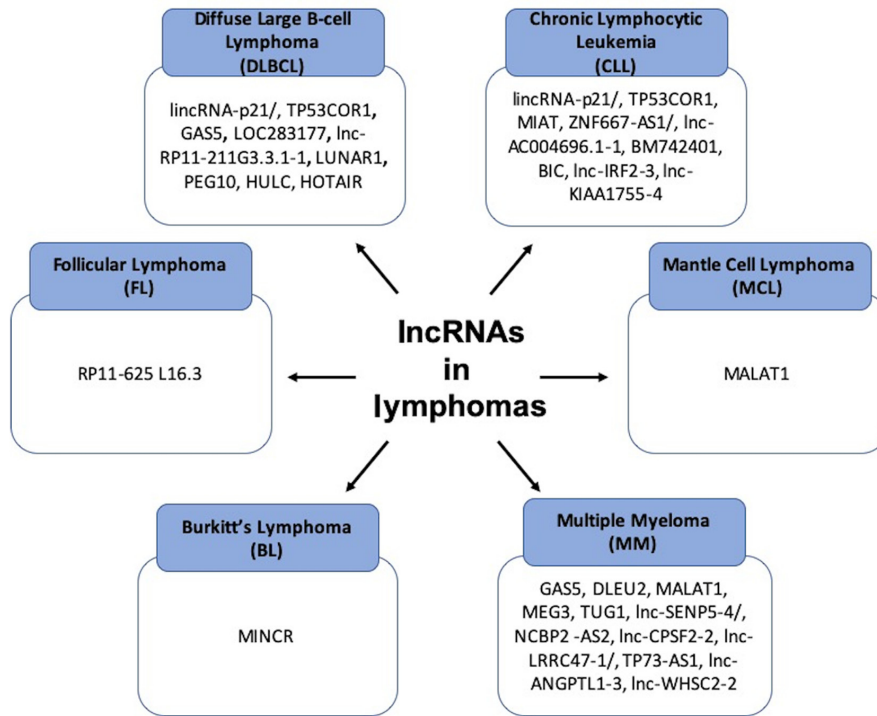
Diffuse Large B-cell Lymphoma (DLBCL)

lincRNA-p21/, TP53COR1, GAS5, LOC283177, lnc-RP11-211G3.3.1-1, LUNAR1, PEG10, HULC, HOTAIR

Chronic Lymphocytic Leukemia (CLL)

lincRNA-p21/, TP53COR1, MIAT, ZNF667-AS1/, lnc-AC004696.1-1, BM742401, BIC, lnc-IRF2-3, lnc-KIAA1755-4

Follicular Lymphoma (FL)

RP11-625 L16.3

lncRNAs in lymphomas

Mantle Cell Lymphoma (MCL)

MALAT1

Burkitt's Lymphoma (BL)

MINCR

Multiple Myeloma (MM)

GAS5, DLEU2, MALAT1, MEG3, TUG1, lnc-SENP5-4/, NCBP2 -AS2, lnc-CPSF2-2, lnc-LRRC47-1/, TP73-AS1, lnc-ANGPTL1-3, lnc-WHSC2-2

Figure 2. Summary of the major lncRNAs that are involved in different types of lymphomas. lncRNAs, long non-coding RNAs.

Diffuse Large B-cell Lymphoma (DLBCL)

miR-20a, -21, -22, -23a, -27a, -27b, -30d, -33a, -34a, -122, -124, -125b, -128, -130a, -141, -142, -145, -146a, -155, -181a, -197, -199a, -199b, -210, -221, -222, -224, -302, -323b, -324, -330, -345, -363, -370, -381, -409, -421, -424, -425, -431, -455, -497, -518a, -519, -520d, -532, -590, -1236, miR-17/92 cluster, 12-miRNA signature, 15-miRNA signature, 27-miRNA signature

Chronic Lymphocytic Leukemia (CLL)

miR-7, -15a, -21, -29, -29a, -31, -34a, -148a, -150, -151, -155, -181b, -182, -192, -320c, -320d, -708, miR-222, miR-15a/16 cluster, miR-17/92 cluster, 13-miRNA signature

Follicular Lymphoma (FL)

miR-9, -17, -31, -155, -217, -221, -222, -223, -494, let-7b, let-7i, 17-miRNA signature, 23-miRNA signature, 44-miRNA signature

miRNAs in lymphomas

Mantle Cell Lymphoma (MCL)

miR-15b, -17, -18a, -18b, -19b, -29, -92a, -129, -135, -146a, -20b, -222, -223, -424, -450, miR-15/16 cluster, miR-17/92 cluster, 95-miRNA signature

Burkitt's Lymphoma (BL)

miR-9, -23a, -26a, -29b, -30d, -34b, -146a, -146b, -155, -181b, -221, -513a, -628, miR-29 family, 19-miRNA signature, 39-miRNA signature, 49-miRNA signature, 22-miRNA signature

Hodgkin Lymphoma (HL)

miR-21, -92b, -135a, -9-2 (methylation), -124a (methylation), miR-30e/dmiR-155, 23-miRNA signature, 25-miRNA signature, 100-miRNA signature, 134-miRNA signature

Splenic Marginal Zone Lymphoma (SMZL)

miR-29a, 29b-1, -96,-127, -129, -139, -182, -183, -335, -411, -451, -486, -593

Mucosa-Associated Lymphoid Tissue (MALT)

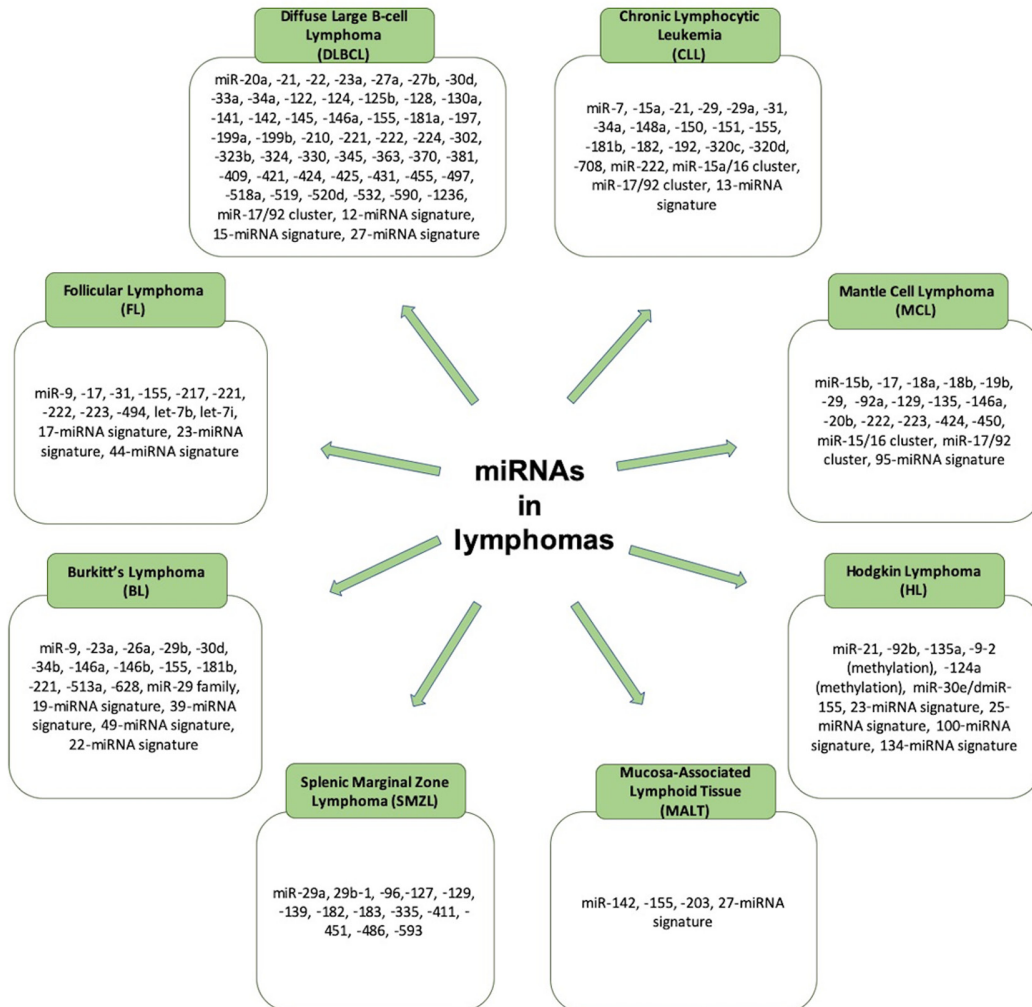miR-142, -155, -203, 27-miRNA signature

Figure 3. Summary of the miRNAs that are involved in different types of lymphomas. miRNAs, microRNAs.

Table I. miRNAs and lncRNAs identified in patients with diffuse large B-cell lymphoma.

miRNA(s)/lncRNA	Genome location (if defined)	Role	Molecular mechanism/sample	(Refs.)
miR-155		Diagnostic biomarker	Presence in serum	(51)
miR-34a		Diagnostic biomarker	Presence in serum	(52)
miR-17/92 cluster		Cell survival, prognostic biomarker	Subtyping	(53)
miR-21, miR-23a, miR-27b, miR-34a		Poor overall survival, diagnostic and prognostic biomarkers	Presence in serum	(54-58)
miR-20a, miR-30d, miR-22, miR-146a		Prognostic biomarkers	Presence in tissues	(59)
miR-21, miR-210		Diagnostic biomarkers	Presence in serum	(60)
12-miRNA signature, 15-miRNA signature, 27-miRNA signature		Diagnostic biomarkers	Presence in tissue	(61-64)
miR-155, miR-221, miR-222, miR-21, miR-363, miR-518a, miR-181a, miR-590, miR-421, miR-324		Diagnostic biomarkers	Presence in cell lines	(65)
miR-124, miR-532, miR-122, miR-128, miR-141, miR-145, miR-197, miR-345, miR-424, miR-425		Diagnostic biomarkers	Presence in plasma and exosomes	(66)
miR-34a, miR-323b, miR-431		Diagnostic biomarkers	Presence in serum	(67)
miR-27a, miR-142, miR-199b, miR-222, miR-302, miR-330, miR-425, miR-519		Predictive biomarkers	Presence in tissue	(46)
miR-224, miR-455, miR-1236, miR-33a, miR-520d		Predictive biomarkers	Presence in serum	(68)
miR-125b, miR-130a, miR-199a, miR-497, miR-370, miR-381, miR-409		Predictive biomarkers	Presence in tissue, blood and cell lines	(69-71)
lincRNA-p21/TP53COR1	17p13.1 (mouse) 6p21.2 (human)	Tumor-suppressor	Link to cyclin D1, CDK4 and p21	(72-76)
GAS5	1q25.1	Tumor-suppressor	Regulation of mTOR pathway	(77-86)
LOC283177	11q25	Uncharacterized	Not described	(87)
lnc-RP11-211G3.3.1-1	3q27.3	Uncharacterized	Not described	(88)
LUNAR1	15q26.3	oncomiR progenitor	NOTCH1 regulation. Enhances IGF1R mRNA expression	(89,90)
PEG10	7q21.3	oncomiR progenitor	Activated by c-MYC	(91-93)
HULC	6p24.3	oncomiR progenitor	Not described	(94-97)
HOTAIR	12q13.13	oncomiR progenitor	Regulation of the PI3K/AKT/NF-κB pathway	(98)

lncRNA, long non-coding RNA; miRNA/miR, microRNA.

the miR-17~92 cluster (45-50) (Table I). In serum samples of patients with DLBCL, increased levels of miR-21, miR-155 and miR-210 have been identified, along with increased levels of miR-124, miR-532-5p miR-15a, miR-16, miR-29c and miR-155. Decreased levels of miR-122, miR-128, miR-141, miR-145, miR-197, miR-345, miR-424 and miR-425 have been also found in the serum of patients with DLBCL. miR-27a, miR-142, miR-199b, miR-222, miR-302, miR-330, miR-425 and miR-519 seem to be associated with the overall survival of patients with DLBCL (50). In any case, miR-155, miR-34a, miRNA-21, miRNA-23a, miRNA-27b, miRNA-34a, 12-miRNA signature, 15-miRNA signature, 27-miRNA signature, miR-363, miR-518a, miR-181a, miR-590, miR-421 and miR-324-either in serum samples, or in tissue or cell line samples of patients with DLBCL, can be used as diagnostic biomarkers in patients with DLBCL (50-71) (Table I and Fig. 3).

Table II. miRNAs and lncRNAs identified in patients with chronic lymphocytic leukemia.

miRNA(s)/lncRNA	Genome location (if defined)	Role/activation	Molecular mechanism/sample	(Refs.)
miR-15a/16 cluster, miR-7, miR-182, miR-320c/d, miR-29, miR-192		Diagnostic biomarkers	Presence in PBMCs and cell lines	(107,108,115,116)
miR-151, miR-34a, miR-31, miR-155, miR-150, miR-15a, miR-29a		Diagnostic biomarkers	Presence in serum	(113-114)
miR-181b, miR-21, miR-155, miR-708, miR-17~92 cluster, 13-miRNA signature, miR-150, miR-155		Prognostic biomarkers	Presence in PBMCs, cell lines, serum, blood cells	(115,133-135)
miR-181b, miR-155, miR-21, miR-148a, miR-222		Predictive biomarkers	Presence in PBMCs and cell lines	(133-135)
DLEU2	13q14.3	Tumor suppressor	NF-κB activation	(117-120)
NEAT1	11q13.1	Tumor-suppressor	Induction by p53	(121,122)
lincRNA-p21/TP53COR1	17p13.1 (mouse) 6p21.2 (human)	Tumor-suppressor	Induction by p53	(72-76)
MIAT	22q12.1	Oncogene	Regulatory loop with OCT4	(123-126)
ZNF667-AS1/lnc-AC004696.1-1	19q13.43	Uncharacterized	Not described	(127,128)
BM742401	18q11.2	Tumor-suppressor	Not described	(129,130)
BIC	21q21	oncomiR progenitor	Host of miR-155-5p and miR-155-3p	(131,132)
lnc-IRF2-3	4q35	Uncharacterized	Not described	(128)
lnc-KIAA1755-4	20q11.23	Uncharacterized	Not described	(128)

lncRNA, long non-coding RNA; miRNA/miR, microRNA; PBMCs, peripheral blood mononuclear cells.

Concerning lncRNAs in patients with DLBCLs, the following have been observed (Table I): i) lincRNA-p21/TP53COR1, located chromosome on 6p21.2 (human), acting as a tumor suppressor by linking to cyclin D1, CDK4 and p21 (72-76); ii) GAS5, located on chromosome 1q25.1, acting as a tumor suppressor by regulating the mTOR pathway (77-86); iii) LOC283177, located on chromosome 11q25, with an uncharacterized mode of action (87); iv) lnc-RP11-211G3.3.1-1, located on chromosome 3q27.3, with an uncharacterized mode of action (88); v) LUNAR1, located on chromosome 15q26.3, acting as an oncomiR progenitor by regulating NOTCH1 and enhancing insulin-like growth factor 1 receptor (IGF1R) mRNA expression (89,90); vi) PEG10, located on chromosome 7q21.3, acting as an oncomiR progenitor, and being activated by c-MYC (91-93); vii) HULC, located on chromosome 6p24.3, acting as an oncomiR progenitor (94-97); viii) HOTAIR, located on chromosome 12q13.13, acting as an oncomiR progenitor, via the regulation the of the PI3K/AKT/NF-κB pathway (98) (Fig. 2).

CLL. CLL is the most common form of leukemia affecting adults (99). In the case that along with CLL, there are enlarged lymph nodes, this clinical condition is referred to as small lymphocytic lymphoma (SLL). The groups of CLL/SLL monoclonal B-cells are the following: Low-count CLL/SLL with a number of monoclonal B-cells <0.5x10^9 cells/liter (i.e. 0.5x10^9/l), and high-count CLL/SLL MBL with monoclonal B-cells ≥0.5x10^9/l but <5x10^9/l (99). A patient is diagnosed as having CLL if the number of monoclonal B-cells are >5x10^9/l (100,101). Classical CLL, according to the Matutes score (102), includes the expression of five different markers in the immunophenotype: These are CD5, CD23, FMC7, CD22 and immunoglobulin light chain (102-104).

Concerning miRNAs in CLL, miR-15a/16-1 acts as a tumor suppressor in patients with CLL and its expression is therefore found to be decreased (105,106), while miR-7-5p, miR-182-5p and miR-320c/d are regulated by p53, and are increased in patients with CLL (107,108). miR-181b expression is also low in patients with CLL (with a poor outcome) (109). miR-155 is overexpressed in patients with CLL and together with miR-21, lead to higher mortality levels in patients with CLL (110) (Table II and Fig. 3).

Additionally, patients with CLL are characterized by higher levels of miR-34a, miR-31, miR-155, miR-150, miR-15a and miR-29a; these can be used as diagnostic biomarkers (110-115). In particular, miR-192 is expressed in low levels in patients with CLL and can be thus used a diagnostic biomarker for CLL (116) (Table II).

Table III. miRNAs and lncRNAs identified in patients with follicular lymphoma.

miRNA(s)/lncRNA	Genome location (if defined)	Role/activation	Molecular mechanism/sample	(Refs.)
RP11-625 L16.3	12	Uncharacterized	Not described	(72)
miR-9, miR-155, miR-31, miR-17		Diagnostic biomarkers	Presence in tissues	(136,137)
miR-217, miR-221, miR-222, miR-223, let-7i, let-7b		Diagnostic biomarkers	Presence in tissues	(138,140)
17-miRNA signature, 44-miRNA signature, miR-494		Diagnostic biomarkers	Presence in tissues	(138,139)
23-miRNA signature		Predictive biomarkers	Presence in tissues	(139)

lncRNA, long non-coding RNA; miRNA/miR, microRNA.

Concerning lncRNAs in patients with CLL, the following have been observed (Table II): i) DLEU2, located on chromosome 13q14.3, acting as tumor suppressor by activating the NF-κB pathway (117-120); ii) NEAT1, located on chromosome 11q13.1, acting as a tumor suppressor via induction by p53 (121,122); iii) lincRNA-p21/TP53COR1, located on chromosome p21.2 (human), acting as a tumor suppressor via induction by p53 (72-76); iv) MIAT, located on chromosome 22q12.1, acting as an oncogene by forming a regulatory loop with OCT4 (123-126); v) ZNF667-AS1/lnc-AC004696.1-1, located on chromosome 19q13.43, with an uncharacterized mode of action (127,128); vi) BM742401, located on chromosome 18q11.2, acting as a tumor suppressor, with an uncharacterized mode of action (129,130); vii) BIC, located on chromosome 21q21, acting as an oncomiR progenitor by being a host of miR-155-5p and miR-155-3p (131,132); viii) lnc-IRF2-3, located on chromosome 4q35 with an uncharacterized mode of action (128); ix) lnc-KIAA1755-4, located on chromosome 20q11.23 with an uncharacterized mode of action (128) (Fig. 2).

Finally, in Table II, references are provided of all the other miRNAs used as predictive and prognostic biomarkers in clinical trials of patients with CLL (133-135).

FLs. FL is the second most common type of NHL, and the most common indolent NHL. It derives from the uncontrolled division of centrocytes and centroblasts of the follicles in the GCs of lymph nodes.

The genomic alterations that can be found in FL include the following: i) the t(14:18)(q32:q21.3) translocation (the majority of the cases); ii) 1p36 deletions (second most common genomic alteration in FL) that lead to the loss of TNFAIP3; iii) mutations in PRDM1; and iv) the same mutations observed in *in situ* FL (ISFL), including KMT2D, CREEBP, BCL2 and EZH2, as well as other mutations (45).

According to the WHO criteria, there are differences, which can be observed under a microscope, which can be used to diagnose and categorize FL into the following 3 grades, with grade 3 comprising A and B subtypes (46): Grade 1, follicles with <5 centroblasts per high-power field (hpf); grade 2, follicles with 6 to 15 centroblasts per hpf; grade 3, follicles with >15 centroblasts per hpf; grade 3A, grade 3 in which the follicles contain predominantly centrocytes; grade 3B, grade 3 in which the follicles consist almost entirely of centroblasts.

Low-grade FLs are grades 1 and 2, as well as grade 3A. Grade 3B is regarded as a highly aggressive FL, which can be easily transformed into a higher grade (46). The transformation of FL into a more aggressive state or other type of aggressive lymphoma is associated with specific genetic alterations, such as in the following genes: CREEBP, KMT2D, STAT6, CARD11, CD79, TNFAIP3, CD58, CDKN2A or CDKN2B, TNFRSF4 and c-MYC (45,46,136-138).

Concerning miRNAs in FLs, a number of studies have demonstrated that there is an increase in the levels of 6 particular miRNAs: miR-223, miR-217, miR-222, miR221, let-7i and let-7b in patients with FL, in which their lymphoma underwent a transformation. In addition, the miR-17~92 cluster can be used as a useful diagnostic biomarker found in patients with FL, while miR-20a/b and miR-194 can also be found in patients with FL. Other useful diagnostic biomarkers in patients with FL may be the following: miR-9, miR-155, miR-31, miR-17, miR-217, miR-221, miR-222, miR-223, let-7i, let-7b17-miRNA signature, 44-miRNA signature, miR-494 23-miRNA signature (136-140) (Table III and Fig. 3).

Concerning lncRNAs in patients with FL, studies have demonstrated that there are 3-fold as many lncRNAs that are upregulated than lncRNAs that are downregulated in patients with FL3A stage disease, without their biological functions being cleared yet. The only lncRNA that seems to be upregulated in patients with FL3A grade disease is RP11-625 L16.3, located on chromosome 12, with an uncharacterized mode of action (72) (Table III and Fig. 2).

MCLs. MCL is recognizable as an aggressive and incurable small B-cell lymphoma. It predominantly affects older-aged males (>60 years old), and sometimes it may be indolent in some patients. MCLs arise from the mantle zone of early B-cells of the lymph node follicle and they possess the t(11;14)(q13;q32) translocation with an overexpression of cyclin D1.MCL cells also exhibit CD5+ and CD23- and surface IgM/D expression (141,142).

Two types of clinically indolent variants have now been identified (140,141). Classical MCL with IGHV-unmutated or minimally mutated B-cells and SOX11 overexpression; usually presented in lymph nodes and other extranodal sites. Additional molecular/cytogenetic abnormalities may be presented in blastoid or pleomorphic MCL. Leukemic non-nodal MCL

Table IV. miRNAs and lncRNAs observed in patients with mantle-cell lymphoma.

miRNA(s)/lncRNA	Genome location (if defined)	Role/activation	Molecular mechanism/sample	(Refs.)
MALAT1	11q13	Oncogene	Regulation of the bioavailability of TGF-β	(146-152)
miR-15/16, miR-17/92		Diagnostic biomarker	Presence in cell lines	(141,142)
95-miRNA signature		Diagnostic biomarker	Presence in tissues	(143)
miR-15b, miR-129, miR-135, miR-146a, miR-424, miR-450, miR-222, miR-17, miR-18a, miR-19b, miR-92a (miR-17/92 cluster)		Prognostic biomarkers	Presence in tissues	(144,153)
miR-29, miR-20b, miR-18b		Prognostic biomarkers	Presence in cell lines and tissues	(154-156)
miR-223		Prognostic biomarkers	Presence in PBMCs and cell lines	(157)

lncRNA, long non-coding RNA; miRNA/miR, microRNA; PBMCs, peripheral blood mononuclear cells.

Table V. miRNAs and lncRNAs identified in patients with Burkitt's lymphoma.

miRNA(s)/lncRNA	Genome location (if defined)	Role/activation	Molecular mechanism/sample	(Refs.)
MINCR	8q24.3	Uncharacterized	Induction of MYC	(173)
miR-23a, miR-26a, miR-29b, miR-30d, miR-146a, miR-146b, miR-155, miR-221		Diagnostic biomarkers	Presence in tissues	(165)
22-miRNA signature, miR-513a, miR-628, miR-9		Diagnostic biomarkers	Presence in tissues	(166,167)
39-miRNA signature, 19-miRNA signature, 49-miRNA signature		Diagnostic biomarkers	Presence in tissues	(168-171)
miR-34b, miR-29 family, miR-181b		Diagnostic biomarkers	Presence in cell lines and tissues	(167,171-173)

lncRNA, long non-coding RNA; miRNA/miR, microRNA.

develops from IGHV-mutated SOX11 B-cells, and is usually presented in peripheral blood, BM and spleen (142).

Concerning miRNAs in MCLs, a number of studies have demonstrated the overexpression of miR-15/16 and miR-17~92 in MCL and that this is associated with an aggressive form of the disease (143,144). In addition, the inhibition of miR-29 has been demonstrated to lead to the progression of MCL (a potential prognostic marker for MCL) (143-145). Additionally, the 95-miRNA signature can be a diagnostic biomarker for MCL (145) (Table IV and Fig. 3).

Concerning lncRNAs in patients with MCL, it has been demonstrated that MALAT1 is overexpressed in human MCL tissues and cell lines compared to normal B-cells [a high international prognostic index (IPI) is present], and is associated with the lower overall survival of patients with MCL (146). Thus, MALAT1, located on 11q13 chromosome, can act as an oncogene in patients with MCL (regulation of the bioavailability of TGF-β) (146-152) (Table IV and Fig. 2).

Finally, in Table IV, references of all the other miRNAs that have been observed in patients with MCL and used as prognostic biomarkers in clinical trials are presented (153-157).

BL. BL is a type of aggressive B-NHL. It may be presented with any of three main clinical variants: Endemic BL, sporadic BL and the immunodeficiency-associated BL (158). In all types of BL, the dysregulation of the c-myc gene is observed (the gene is found at 8q24), presented with any one of the three known chromosomal translocations (159). The most common variant is t(8;14)(q24;q32), which involves c-myc and IGH (159).

The variant at t(2;8)(p12;q24) involves IGK and c-myc (160). The variant at t(8;22)(q24;q11) involves IGL and c-myc (160). In addition, a last variant of three-way translocation, t(8;14;18) has been identified (161).

Concerning miRNAs in patients with BL, it seems that MYC regulates and is regulated by numerous miRNAs (Table V), the most common of which are the following: miR-23a, miR-26a, miR-29b, miR-30d, miR-146a, miR-146b,

Table VI. miRNAs identified in patients with splenic marginal zone lymphoma B-cell lymphoma and mucosa-associated lymphoid tissue lymphoma.

miRNA(s)	Disease type	Genome location	Role/activation	Molecular mechanism/sample	(Refs.)
miR-29a, miR-29b-1, miR-96, miR-129, miR-182, miR-183, miR-335, miR-593	Splenic marginal zone lymphoma		Diagnostic biomarkers	Presence in tissues	(174)
miR-127, miR-139, miR-335, miR-411, miR-451, miR-486	Splenic marginal zone lymphoma		Diagnostic biomarkers	Presence in tissues	(175)
27-miRNA signature, miR-142, miR-155, miR-203	Mucosa-associated lymphoid tissue		Diagnostic biomarkers	Presence in tissues	(176,177)
miR-142, miR-155	Mucosa-associated lymphoid tissue		Prognostic biomarkers	Presence in tissues	(177)

miRNA/miR, microRNA.

miR-155, and miR-221 (162-165) [widely used as diagnostic biomarkers (166-173)] (Table V and Fig. 3).

Concerning lncRNAs in patients with BL, 13 lncRNAs have been identified thus far (173). The most well-identified lncRNA in patients with BL is MINCR, located on chromosome 8q24.3, with an uncharacterized role; but it seems that it causes the induction of myc and modulates its transcriptional program (173).

Other indolent BCNHLs. There are also two other types of BCNHLs which exhibit an indolent course. These are MALT lymphomas and MZL, particularly the splenic type (SMZL).

None of the lncRNAs has been thus far identified as playing a major role in the the activation or progression of a B-cell to transform in any of these types of B-cell lymphomas.

Concerning miRNAs in SMZL, miR-96, miR-129, miR-29a, miR-29b-1, miR-182, miR-183, miR-335 and miR-593 can be used as diagnostic biomarkers, although without sufficient data to date (174) (Table VI and Fig. 3).

As regards miRNAs in MALT lymphomas, miR-203 primarily, and secondly, miR-150, miR550, miR-124a, miR-518b and miR-539, have been widely recognizable as being present in gastric MALT lymphoma (175). Other miRNAs identified in MALT lymphomas are the following: The 27-miRNA signature, miR-142, miR-155, miR-203 miR-142 and miR-155 (176,177) (Table VI and Fig. 3).

b) HLs. There are two main types of HL: Classical Hodgkin lymphoma (9 out of 10 cases) and nodular lymphocyte predominant Hodgkin lymphoma (1 out of 10 cases) (178,179). There is a differentiation in morphology, phenotype and molecular features between both these types. Furthermore, classical HL alone can be subclassified into 4 more pathologic subtypes: i) Nodular sclerosing HL; ii) mixed-cellularity subtype; iii) lymphocyte-rich; and iv) lymphocyte-depleted HL (180-182).

Compared to B-NHLs, only limited data are available on the expression of lncRNAs in HLs. As regards miRNAs in patients with HL Hodgkin, there are studies which show that low miR-135a levels lead to significantly poorer prognostic outcome in Hodgkin patients (183,184). The inhibition of let-7 and miR-9 leads to the prevention of plasma cell differentiation (184). In particular, the inhibition of miR-9 seems to lead to a decrease in cytokine production and a reduced ability in attracting inflammatory cells (185). In addition, miR-155, the 23-miRNA signature and 134- and 100-miRNA signature, 25-miRNA signature and miR-9-2 (methylation) can be used as diagnostic biomarkers in patients with HL (as they are presented in HL cell lines and tissues) (186-193) (Table VII and Fig. 3).

c) T-NHLs and NK-NHLs. T-cell lymphomas affect T-cells and they are divided into 4 major types: i) Extranodal T-cell lymphoma; ii) cutaneous T-cell lymphomas: Sézary syndrome and Mycosis fungoides; iii) anaplastic large cell lymphoma; and iv) angioimmunoblastic T-cell lymphoma. There is also a clinical entity known as aggressive NK-cell leukemia with an aggressive, systemic proliferation of NK cells; it can also be termed aggressive NK-cell lymphoma (194,195).

As regards miRNAs in T-cell and NK-cell lymphomas, very little is known so far. MiRNA-21, miRNA-155, miRNA-150, miRNA-142 and miRNA-494 are present in various forms of cutaneous T-cell lymphomas, compared to related benign disorders (196,197). miRNA-146a and miRNA-155 are also present in patients with cutaneous T-cell lymphomas (1). miRNA-223, miRNA-BART-20, miRNA-BART-8, miRNA-BART-16 and miRNA-BART-9 are EBV-encoded and are associated with the activation of the EBV oncoprotein, LMP-1 (197-204) (Table VIII).

Concerning lncRNAs in various types of T-cell and NK-cell lymphomas, MALAT1, located on chromosome 11q13.1, has been identified as being overexpressed and leads to the induction of BMI1 activation (197); that is the reason why MALAT1 can be used as prognostic marker and therapeutic target in T- and NK-cell lymphomas (195) (Table VIII).

d) Other common B-cell malignancies. MM, also known as plasma cell myeloma, is a fatal malignant hematological disorder which lead to the proliferation of monoclonal antibody-secreting plasma cells; the main criterion is the presence of clonal plasma cells >10% in bone marrow biopsy or in a biopsy from other tissues (plasmacytoma). MM accounts for 10% of all hematological malignancies (205).

Compared to all types of B-cell Lymphomas, very little is known about miRNA expression in patients with MM. As regards lncRNAs in patients with MM, the following have

Table VII. miRNAs identified in patients with Hodgkin lymphoma.

miRNA(s)	Genome location (if defined)	Role/activation	Molecular mechanism/sample	(Refs.)
miR-155		Diagnostic biomarkers	Presence in cell lines	(185,186)
23-miRNA signature, 134-miRNA signature, 100-miRNA signature		Diagnostic biomarkers	Presence in cell lines and tissues	(187,188)
25-miRNA signature and miR-9-2 (methylation)		Diagnostic biomarkers	Presence in tissues	(189,190)
miR-135a		Prognostic biomarkers	Presence in tissues and cell lines	(191)
miR-21, miR-30e/d, miR-92b, miR-124a (methylation)		Prognostic biomarkers	Presence in tissues	(192,193)

miRNA/miR, microRNA.

Table VIII. miRNAs and lncRNAs identified in patients with T-cell and NK-cell lymphomas.

miRNA(s)/lncRNA	Disease type	Genome location (if defined)	Role/activation	Molecular mechanism/sample	(Refs.)
miRNA-21	NK-cell lymphoma-derived cell lines primary NKTCLs		New biomarker or target in thetreatment of NKTCL.	Regulation of apoptosis of NK-cell lymphoma cell lines via the PTEN/AKT signaling pathway	(199)
miRNA-155	NK-cell lymphoma cell lines Primary NKTCL specimens		Potential molecular marker of NKTCL	Regulation of inflammation, immune cells, and the differentiation and maturation of tumor cells	(200)
miRNA-142	Under-expression in NKTCLs lymphomas		Two different forms (miRNA-142-3p and miRNA-412-5p) miRNA-142-3p is a potential target of therapy	Downregulation of RICTOR	(201,202)
miRNA-494	NKTCLs		Potential target of therapy	Downregulation of PTEN	(202)
miRNA-223	NKTCLs		EBV infection	Downregulation of PRDM1	(203)
miRNA-16	NKTCLs		Novel target in NKTCL treatment	Downregulation of CDKN1A	(197)
miRNA-BART-20	NKTCLs		EBV-encoded	Maturation of NK-cells	(204)
miRNA-BART-8	NKTCLs		EBV-encoded	Induction of apoptosis	(204)
miRNA-BART-16	NKTCLs		EBV-encoded	Induction of cell-cell adhesion	(204)
miRNA-BART-9	NKTCLs		EBV-encoded	Induction of cell proliferation	(204)
MALAT1	Various types of T and NK cell lymphomas	11q13.1	Overexpression Prognostic marker and therapeutic target in T and NK cell lymphomas.	Induction of BMI1 activation	(195)

lncRNA, long non-coding RNA; miRNA/miR, microRNA; NKTCL, natural-killer/T cell lymphoma.

Table IX. lncRNAs identified in patients with multiple myeloma.

lncRNA	Genome location	Role/activation	Molecular mechanism/sample	(Refs.)
GAS5	1q25.1	Tumor-suppressor	Regulation of mTOR pathway	(77-86)
DLEU2	13q14.3	Tumor-suppressor	Host of miR-15a/16-1 cluster and targeting BCL2	(117-120)
MALAT1	11q13	Oncogene	Regulation of the bioavailability of TGF-β	(146-152)
MEG3	14q32.2	Tumor-suppressor	Interaction with p53. Regulation of P53 gene expression	(206-209)
TUG1	22q12.2	Oncogene	Induction by p53	(150,152)
lnc-SENP5-4/NCBP2-AS2	3q29	Uncharacterized	Not described	(85)
lnc-CPSF2-2	14q32	Uncharacterized	Not described	(85)
lnc-LRRC47-1/TP73-AS1	1p36	Uncharacterized	Not described	(85)
lnc-ANGPTL1-3	1q25	Uncharacterized	Not described	(85)
lnc-WHSC2-2	4p16.3	Uncharacterized	Not described	(85)

lncRNA, long non-coding RNA.

been observed (Table IX): i) GAS5, located on chromosome 1q25.1, acting as a tumor-suppressor by regulating the mTOR pathway (77-86); ii) DLEU2, located on chromosome 13q14.3, acting as a tumor-suppressor by being a host of the miR-15a/16-1 cluster and targeting BCL2 (117-120); iii) 3) MALAT1, located on chromosome 11q13, acting as an oncogene by regulating the bioavailability of TGF-β (146-152); iv) MEG3, located on chromosome 14q32.2, acting as a tumor-suppressor by interacting with p53 and regulating p53 gene expression (206-209); v) TUG1, located on chromosome 22q12.2, acting as an oncogene by being induced by p53 (150,152); vi) lnc-SENP5-4/NCBP2-AS2, located on chromosome 3q29, with an uncharacterized mode of action (85); vii) 7) lnc-CPSF2-2, located on chromosome 14q32, with an uncharacterized mode of action (85); viii) lnc-LRRC47-1/TP73-AS1, located on chromosome 1p36, with an uncharacterized mode of action (85); ix) lnc-ANGPTL1-3, located on chromosome 1q25, with an uncharacterized mode of action (85); x) lnc-WHSC2-2, located on chromosome 4p16.3, with an uncharacterized mode of action (85).

4. Anti-ncRNA therapeutic strategies in lymphoid disorders

There are specific strategies that can be used in order to target ncRNAs in tumor management. These are the following: i) Antisense oligonucleotides (ASOs), which can trigger RNaseH-mediated RNA degradation (210); ii) CRISPR/Cas9 genome editing technique which can effectively silence the transcription of the lncRNA-expressing loci (211,212); iii) viral vectors (adenovirus, lentivirus and retrovirus) which can be used as a RNA interference (RNAi) method and can lead to the knockdown of gene expression by neutralizing the targeted RNA through exogenous double-stranded RNA insertion (213-215); and iv) nanomedicine, including lipid-based nanoparticles (liposomes) (216), polymer-based nanoparticles and micelles (217), dendrimers (218), carbon-based nanoparticles (219), and metallic and magnetic nanoparticles, such as gold nanoparticles (220,221).

All these novel therapeutic strategies targeting ncRNAs, have been tested to date in preclinical models with lymphoid disorders. For example, a viral vector carrying miR-28 has been delivered in DLBCL and BL xenografts and in murine models with B-lymphoma, with acceptable prophylactic and therapeutic effects (222).

Furthermore, the ASO strategy, such as LNA-anti-miR-155, has been used in a B-cell lymphoma murine model, exhibiting a significant effect in murine models (223). An anti-miR-155 oligonucleotide with the trademark Cobomarsen is currently being clinically nowadays in patients with cutaneous T-cell lymphoma (224).

Double-stranded RNAi and ASOs are the most commonly used lncRNA-targeted therapies. When the target lncRNA is localized in the nucleus, ASOs are the better therapeutic option (225).

The most important finding, by reviewing the literature, is that either the lncRNA expression signature or miRNA expression may help distinguish between the different lymphoma entities. In addition, as certain ncRNAs may be associated with the progression of lymphoma or drug resistance, these ncRNAs can be used as predictive and prognostic markers (225). However, the ncRNA regulatory network is complex and is not yet fully understood, as the majority of ncRNAs have not yet been thoroughly investigated. Nevertheless, ncRNA-based therapeutics can be combined, in the near future, with other techniques, such as chimeric antigen receptor (CAR) T-cell immunotherapy, the targeting of tumor cells, thus improving their therapeutic efficacy (226,227).

5. Conclusions and future perspectives

Contemporary developments in biology have been combined with insightful discoveries analyzing the role of ncRNAs, either miRNAs or lncRNAs in human tumors, particularly lymphomas, such as: BCNHLs, HLs, T-cell/NK cell NHLs (T-/NK-cell NHLs) and other B-cell malignancies, such as MM.

The present review aimed to provide a thorough summary of the current understanding of ncRNAs in lymphoid malignancies by summarizing, for the first time, to the best of our knowledge, the whole existing ncRNA (and not into different categories), miRNAs and lncRNAs, which are associated with lymphoid disorders.

The initial data suggest that mostly lncRNAs, play key roles in lymphangiogenesis, as a great number of them are deregulated in B-cell malignancies. However, this particular field is still in its infancy, with insufficient data; thus, further studies need to be performed.

Concerning the role of miRNAs as biomarkers in all lymphoid malignancies, ample data are available, although without immediate use in clinical practice. A number of miRNA biomarker studies to date on B-NHLs, HLs, T-/NK-NHLs and MM are not based on multi-center cooperations, and thus, in most cases, a number of reviews are non-overlapping and even contradictory.

For all the above reasons, further multi-center studies are warranted with the establishment of a standardized approach and the use of the same techniques: RT-qPCR, microarrays or next-generation sequencing (NGS). This is mandatory step in order to explore more thoroughly the role and functions of lncRNAs in normal B-cells and malignant B-cells; as well as to perform a more in-depth miRNA biomarker analysis in order to ensure that these molecules can be effectively used in daily practice. These tasks are both compelling and challenging in the next future for the prognosis and potential therapeutic targeting of all lymphoid malignancies; leading to a better treatment plan.

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Availability of data and materials

Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

Authors' contributions

GD developed, planned, supervised the review and wrote the manuscript. MG created the figure and contributed to the writing of the manuscript. VZ supervised the review, contributed to the writing and revisions of the manuscript. DAS and SA collected relevant literature. VZ and GD confirm the authenticity of all the raw data All authors read and approved the final manuscript.

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Not applicable.

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Competing interests

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