MicroRNAs as Biomarkers of B-cell Lymphoma

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ABSTRACT: B-cell lymphomas represent a diverse group of neoplasms classified primarily by histopatholgy and are often challenging to accurately diagnose. Despite having been recognized less than 20 years ago, microRNAs (miRNAs) have emerged as one of the most promising class of cancer molecular biomarkers and are particularly attractive as they can be readily detected in formalin-fixed paraffin-embedded biopsy material and biological fluids such as blood. Many of the identified B-cell lymphoma miRNA biomarkers also play crucial regulatory roles in normal B-cell development. Below we consider the identity, function, and biomarker potential of miRNAs in B-cell lymphoma and most importantly the barriers that remain to be overcome if they are really to become part of routine clinical practice.

KEYWORDS: microRNA, B-cell lymphoma, non-Hodgkin lymphoma, Hodgkin lymphoma, biomarker, liquid biopsies

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Introduction

The first discovery of what we now know as microRNAs (miRNAs) came in 1993 from the laboratories of Victor Ambros in Dartmouth College and Gary Ruvkun in Harvard. They simultaneously published a description of *lin-4*, a previously identified locus in *Caenorhabditis elegans* involved in developmental timing, that appeared to have a direct function without encoding for a protein.[1,2] Things went quiet for the next 7 years, until the Ruvkun lab identified, *let-7a*, a second sequence from *C elegans*, with similar properties to *lin-4*.[3] Unlike *lin-4*, however, the sequence of *let-7* was found to be highly conserved in eukaryotic genomes and it was realized that many similar sequences were present in the genomes of higher species. The first use of the term miRNA was made in 2001 by Lee and Ambros in a publication where they identified a further 15 *C elegans* miRNAs.[4] Since that time, there have been more than 25 000 miRNAs identified in over 200 different species (http://www.mirbase.org), including more than 2500 human miRNAs.[5,6]

MicroRNAs are short non-coding (nc)RNAs of 18 to 24 nucleotides in length that bind to regions of complementarity generally located in the 3′-UTR (untranslated region) of target genes. They primarily act as inhibitor molecules causing post-transcriptional inhibition or degradation, although in some instances, they may also act as gene activators.[7] It is estimated that two-thirds of human genes are directly regulated by miRNAs,[8] and as a consequence, miRNAs are involved in most, if not all, cellular processes under physiological conditions. Moreover, dysfunctional expression of miRNAs appears to be a hallmark of all cancer types,[9,10] including B-cell lymphomas that are the focus of this review.

Lymphoma is a cancer of the lymphatic system arising from B cells or T cells that represents the fifth most common cancer type worldwide, affecting more than a million people. Lymphomas are a heterogeneous group of cancers that vary in presentation, prognosis, and pathogenesis. In the latest version of World Health Organization (WHO) classification, there were more than 100 different lymphoma types listed, most of which were B-cell lymphomas, but which can have very different clinical characteristics and treatment regimens.[11] As a consequence, correct classification of a given lymphoma is often challenging, and therefore there is a clear clinical need for better biomarkers for these diseases. MicroRNAs are particularly attractive candidates as biomarkers, as their expression can classify different tumours according to their diagnosis, subtype, and stage more accurately than messenger RNA expression profiles.[12] Moreover, due to their intrinsic stability, they can be reliably detected in routinely prepared formalin-fixed paraffin-embedded (FFPE) tissue. This stability also means they are readily detected in biological fluids such as blood, which has led to a great deal of interest in the use of miRNAs as biomarkers in liquid biopsies discussed below.

MiRNAs as lymphoma liquid biopsy biomarkers

Currently, the gold standard of B-cell lymphoma diagnosis depends on the histopathologic examination of surgically excised biopsy material. This procedure, however, is expensive, invasive, uncomfortable, and can be risky for patients. Therefore, there has been a great interest in the development of non-invasive cancer biomarkers, also known as liquid biopsies. MicroRNAs hold a great promise in this area, as not only can they be extracted from frozen and paraffin-embedded tissue but also from many different body fluids including blood,[13,14] urine,[15] saliva,[16,17] sputum,[18,19] amniotic fluid, and even from tears.[20]

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Most of the attention has been focused circulating miRNAs in blood, either in whole plasma or within circulating extracellular vesicles such as exosomes.[21,22] The first report of miRNAs in the blood of B-cell lymphomas, or indeed any cancer, came in 2007.[23] We found that levels of *miR-21, miR-155*, and *miR-210* in the serum samples of patients with diffuse large B-cell lymphoma (DLBCL) compared with healthy controls were higher suggesting their usefulness as biomarkers.[24] Since this time, there have been many follow-up studies in blood of patients with lymphoma as described below and in Table 1.

Aberrant Expression of miRNAs in B-cell Lymphoma

Many of the miRNAs that have been identified as lymphoma biomarkers (Figure 1 and Table 1) also play key roles in normal B-cell lymphopoiesis. Frequently, these aberrantly expressed biomarker miRNAs also appear to be key drivers of lymphomagenesis.[100,101] For example, *miR-155* controls germinal centre (GC) development by controlling immunoglobulin production, after activation of the B-cell receptor (BCR), and is a requirement for high-affinity antibody formation.[102,103] However, when overexpressed in a transgenic mouse model, the mice developed a high-grade lymphoma similar to DLBCL.[104] In a similar manner, the *miR-17~92* controls pro–B-cell to pre–B-cell development via targeting of the proapoptotic protein BIM,[105] but when overexpressed in a murine MYC model, increased the aggressiveness of B-cell lymphomas.[106,107] *MiR-21* that targets tumour suppressor molecules including PTEN and PDCD4,[108,109] when overexpressed in mice resulted in formation of B-cell lymphomas.[110] *MiR-34a* controls the transition of pro- to pre-B cell in haematopoietic stem cells via FOXP1 and SIRT1 targeting,[111,112] and overexpression of this miRNA in mice abrogated lymphoma formation in a xenotransplant model.

In addition to the miRNAs mentioned above, *miR-181* has long been recognized as a key regulator of GC B-cell differentiation,[113,114] along with *miR-150* that inhibits MYB downregulation.[115] The GC B cells are characterized by expression of markers BCL6, CD10, HGAL, and LMO2, as well as the absence of activated B-cell markers such as IRF4, PRDM1/BLIMP1, and XBP1. These transcription factors are also regulated at the level of miRNAs. For example, *BCL6* is regulated by *miR-30* family, *miR-9* and *let-7a*,[116] whereas *miR-155* regulates expression of HGAL and CD10 protein expression,[117,118] and *miR-223* regulates expression of LMO2.[119] In contrast, *miR-125b* and *miR-155* regulate expression of the activated B-cell markers, IRF4 and PRDM1.[116,120]

The cause of aberrant miRNA expression in lymphoma (and other cancers) can result from many genomic events, such as chromosomal aberrations, epigenetic modifications, mutations in the sequence of miRNAs or their promoter regions, or factors that regulate synthesis or function of miRNAs (for further details see the work by Croce[121]). Below, we discuss the aberrantly expressed miRNAs in different B-cell lymphoproliferative diseases that could facilitate the diagnosis, prognosis, and prediction of treatment response.

Chronic lymphocytic leukaemia

Chronic lymphocytic leukaemia (CLL) is the most common haematologic malignancy worldwide[122] and was the first haematologic malignancy, or indeed any cancer to be associated with aberrant miRNA expression when in 2002, George Calin and colleagues reported that the frequently (55%) deleted locus, 13q14, encodes for the *miR-15a/16-1* cluster, and that these miRNAs were downregulated in most of the patients with 13q(del) CLL.[33] These miRNAs act as tumour suppressors in CLL through targeting of the anti-apoptotic BCL2 protein[123] and the tumour suppressor *TP53*.[124] In contrast, *miR-7-5p, miR-182-5p*, and *miR-320c/d* are regulated by p53 in CLL.[34] Epigenetic silencing of the *miR-15a/16-1* cluster is observed in 30% to 35% of patients with CLL, a feature mediated through HDAC1-3 overexpression,[125] suggesting that these patients might benefit from HDAC-inhibitor–based therapies. However, murine models of the 13q14 deletion suggest that other factors also contribute to the aggressiveness of the disease.[126] Furthermore, the closely related *miR-15b/16-2* cluster also appears to modulate genes involved in proliferation and anti-apoptotic pathways.[127]

Similar to *miR-15a/16-1, miR-181b* is also typically downregulated in CLL, and low expression of this miRNA has been related to poor prognostic outcome.[39] Consistent with this phenotype, levels of *miR-181b* correlate with treatment-free survival in CLL.[40]

In contrast, *miR-155* is overexpressed in CLL but was found to be lower in patients who responded to therapy compared with refractory patients,[47] suggesting its usefulness as a predictive biomarker for CLL. *MiR-29* is also overexpressed in both indolent and aggressive CLL, when compared with normal counterpart, but its expression was found to be lower in aggressive CLL.[35] When *miR-29* was overexpressed in murine B cells, the animals developed an indolent-type form of CLL.[128]

MicroRNA expression profiling has been used to distinguish between aggressive and indolent CLLs, with high levels of *miR-21* and *miR-155* being associated with a higher mortality rate.[40,41] In contrast, upregulation of *miR-708* has been associated with a favourable prognostic outcome for patients with CLL that was shown to be linked to a reduction in the nuclear factor κB signalling pathway.[42] The proliferation status of a subset of peripheral blood cells–unmutated patients with CLL was linked with *miR-22* overexpression via inhibition of PTEN and PI3K/AKT activation.[129]

Recently, it has been described that low levels of *miR-150* in tumour cells or alternatively high levels of this miRNA in (circulating) serum are related to poor prognosis in CLL.[43] In another study, levels of both *miR-150* and *miR-155* in the blood were associated with the prognostic outcome of CLL.[44]

Table 1. List of major miRNAs identified as biomarkers in B-cell malignancies.

LYMPHOMA	BIOMARKER	MIRNA	SAMPLE	REFERENCES
HL	Diagnostic	*miR-155*	Cell lines	van den berg et al[25] and Metzler et al[26]
		23-miRNA signature	Cell lines	Gibcus et al[27]
		25-miRNA signature	Tissue	Navarro et al[28]
		134- and 100-miRNA signature	Cell lines and tissue	Sanchez-Espiridion et al[29]
		miR-9-2 (methylation)	Tissue	Ben Dhiab et al[30]
	Prognostic	*miR-135a*	Tissue and cell lines	Navarro et al[31]
		miR-21, miR-30e/d, and *miR-92b*	Tissue	Sanchez-Espiridion et al[29]
		miR-124a (methylation)	Tissue	Ben Dhiab et al[32]
CLL	Diagnostic	*miR-15a/16* cluster	PBMCs and cell lines	Calin et al[33]
		miR-7, miR-182, and *miR-320c/d*	PBMCs and cell lines	Blume et al[34]
		miR-29	PBMCs and cell lines	Pekarsky et al[35]
		miR-151	Serum (EV)	Caivano et al[36]
		miR-34a, miR-31, miR-155, miR-150, miR-15a, miR-29a	Serum	Filip et al[37]
		miR-192	PBMCs	Fathullahzadeh et al[38]
	Prognostic	*miR-181b*	PBMCs	Visone et al[39]
		miR-21	PBMCs	Rossi et al[40]
		miR-155	PBMCs	Cui et al[41]
		miR-708	PBMCs and cell lines	Baer et al[42]
		miR-150	Cell lines and serum	Stamatopoulos et al[43]
		miR-150 and *miR-155*	Blood cells	Georgiadis et al[44]
		miR-17~92 cluster	PBMCs	Bomben et al[45]
		13-miRNA signature	PBMCs and cell lines	Calin et al[46]
	Predictive	*miR-181b*	PBMCs	Rossi et al[40]
		miR-155	PBMCs	Ferrajoli et al[47]
		miR-21, miR-148a*, and *miR-222*	PBMCs and cell lines	Ferracin et al[48]
DLBCL	Diagnostic	*miR-21, miR-155*, and *miR-210*	Serum	Lawrie et al[24]
		12-miRNA signature	Tissue	Roehle et al[49]
		15-miRNA signature	Tissue	Lawrie et al[50]
		12-miRNA signature	Tissue	Caramuta et al[51]
		miR-155, miR-221, miR-222, miR-21, miR-363, miR-518a, miR-181a, miR-590, miR-421, and *miR-324*	Cell lines	Lawrie et al[52]
		miR-155 and *miR-146a*	Tissue	Zhong et al[53]
		27-miRNA signature	Tissue and cell lines	Iqbal et al[54]
		miR-124, miR-532, miR-122, miR-128, miR-141, miR-145, miR-197, miR-345, miR-424, and *miR-425*	Plasma and exosomes	Khare et al[55]
		miR-34a, miR-323b, and *miR-431*	Serum	Meng et al[56]

(Continued)

Table 1. (Continued)

LYMPHOMA	BIOMARKER	MIRNA	SAMPLE	REFERENCES
	Prognostic	*miR-21*	Serum	Lawrie et al[24]
		miR-155 and *miR-146a*	Tissue	Zhong et al[53]
		miR-22	Serum	Marchesi et al[57]
		miR-155	Tissue and cell lines	Iqbal et al[54]
		miR-20a and *miR-30d*	Tissue	Pillar et al[58]
		miR-155	Tissue and cell lines	Zhang et al[59]
		miR-17~92 cluster	Tissue and cell lines	Tagawa et al[60]
		miR-34a	Tissue	He et al[61]
		miR-27b	Tissue	Jia et al[62]
		miR-21	Cell lines	Gu et al[63]
		miR-21	Tissue	Lawrie et al[24] and Zheng et al[64]
	Predictive	*miR-27a, miR-142, miR-199b, miR-222, miR-302, miR-330, miR-425*, and *miR-519*	Tissue	Lawrie et al[50]
		miR-155 and *miR-146a*	Tissue	Zhong et al[53]
		miR-21	Cell lines	Gu et al[63] and Bai et al[65]
		miR-224, miR-455, miR-1236, miR-33a, and *miR-520d*	Serum	Song et al[66]
		miR-125b and *miR-130a*	Tissue and blood	Yuan et al[67]
		miR-199a and miR-497	Tissue and cell lines	Troppan et al[68]
		miR-370, miR-381, and *miR-409*	Tissue and cell lines	Leivonen et al[69]
FL	Diagnostic	*miR-9 and miR-155*	Tissue	Roehle et al[49]
		miR-217, miR-221, miR-222, miR-223, let-7i, and *let-7b*	Tissue	Lawrie et al[50]
		miR-31 and miR-17	Tissue	Thompson et al[70]
		17-miRNA signature	Tissue	Leich et al[71]
		44-miRNA signature	Tissue	Wang et al[72]
		miR-494	Tissue	Arribas et al[73]
		66-miRNA signature	Bone marrow smears	Takei et al[74]
	Predictive	23-miRNA signature	Tissue	Wang et al[72]
BL	Diagnostic	*miR-23a, miR-26a, miR-29b, miR-30d, miR-146a, miR-146b, miR-155*, and *miR-221*	Tissue	Lenze et al[75]
		miR-34b	Cell lines and tissue	Leucci et al[76]
		22-miRNA signature	Tissue	Hezaveh et al[77]
		miR-155, miR-21, and *miR-26a*	Needle aspirates	Zajdel et al[78]
		miR-29 family	Cell lines and tissue	Robaina et al[79] and De Falco et al[80]
		miR-513a	Tissue	De Falco et al[80]
		miR-628	Tissue	De Falco et al[80]

Table 1. (Continued)

LYMPHOMA	BIOMARKER	MIRNA	SAMPLE	REFERENCES
		*miR-9**	Tissue	Onnis et al[81]
		39-miRNA signature	Tissue	Robertus et al[82]
		19-miRNA signature	Tissue	Di Lisio et al[83]
		49-miRNA signature	Tissue	Oduor et al[84]
		miR-181b	Cell lines and tissue	Li et al[85]
MCL	Diagnostic	*miR-15/16 and miR-17~92*	Cell lines	Chen et al[86] and Deshpande et al[87]
		95-miRNA signature	Tissue	Iqbal et al[88]
	Prognostic	*miR-15b*	Tissue	Arakawa et al[89]
		miR-129, miR-135, miR-146a, miR-424, miR-450, and *miR-222*	Tissue	Iqbal et al[88]
		miR-17, miR-18a, miR-19b, and *miR-92a* (*miR-17~92* cluster)	Tissue	Roisman et al[90]
		miR-29	Cell lines and tissue	Zhao et al[91]
		miR-20b	Cell lines and tissue	Di Lisio et al[92]
		miR-18b	Cell lines and tissue	Husby et al[93]
		miR-223	PBMCs and cell lines	Zhou et al[94]
SMZL	Diagnostic	*miR-29a, miR-29b-1, miR-96, miR-129, miR-182, miR-183, miR-335*, and *miR-593*	Tissue	Watkins et al[95]
		miR-127, miR-139, miR-335, miR-411, miR-451, and *miR-486*	Tissue	Bouteloup et al[96]
MALT	Diagnostic	27-miRNA signature	Tissue	Thorns et al[97]
		miR-142, miR-155, and miR-203	Tissue	Fernandez et al[98]
	Prognostic	*miR-142* and *miR-155*	Tissue	Liu et al[99]

Abbreviations: BL, Burkitt lymphoma; CLL, chronic lymphocytic leukaemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HL, Hodgkin lymphoma; miRNA, microRNA; MALT, mucosa-associated lymphoid tissue; MCL, mantle cell lymphoma; PBMCs, peripheral blood mononuclear cells; SMZL, splenic marginal zone lymphoma.
*the minor strand of the mature form of the miRNA

Moreover, high levels of *miR-155* in extracellular vesicles derived from the serum samples of patients with CLL were found compared with healthy controls.[36] Filip et al[37] found that the serum of patients with CLL had higher levels of *miR-34a, miR-31, miR-155, miR-150, miR-15a*, and *miR-29a* than controls. Another study showed that levels of *miR-192* in peripheral blood mononuclear cells (PBMCs) are downregulated in patients with CLL compared with controls, suggesting that this miRNA could be a diagnostic biomarker for early stage of CLL.[38] In CLL, proliferation centres, considered to drive the disease and play a role in progression of disease, had high levels of *miR-155* and *miR-92* and low levels of *miR-150*.[130]

Hodgkin lymphoma

Hodgkin lymphoma (HL), first described in 1832 by Thomas Hodgkin,[131] is one of the most frequent lymphomas, accounting for 1% of total cancers worldwide. The defining characteristic of HL is that neoplastic cells typically account for less than 1% of the tumour mass.[132] Tumour cells in classical HL (cHL), known as Hodgkin and Reed-Sternberg (HRS) cells, lack functional BCR expression or typical B-cell markers and instead express CD15 and CD30 cell surface markers.[133,134] Anke van den Berg's lab was the first to identify miRNAs in HL, when they observed in 2003 that the non-coding *BIC* locus, subsequently found to encode for *miR-155*, was overexpressed in HL cell lines.[25,26] Since this time, *miR-155* has been shown to target several genes in HL cells including *DET1* and *NIAM*, among others.[135]

Apart from this miRNA, several others have been implicated in HL including *miR-135a* which was the first miRNA to be associated with survival in HL.[31] The patients with HL with low levels of *miR-135a* had shorter disease-free survival than those with high levels of this miRNA. JAK2 is directly targeted by *miR-135a*, and the overexpression of this miRNA increases apoptotic levels and decreases cell growth via Bcl-xL

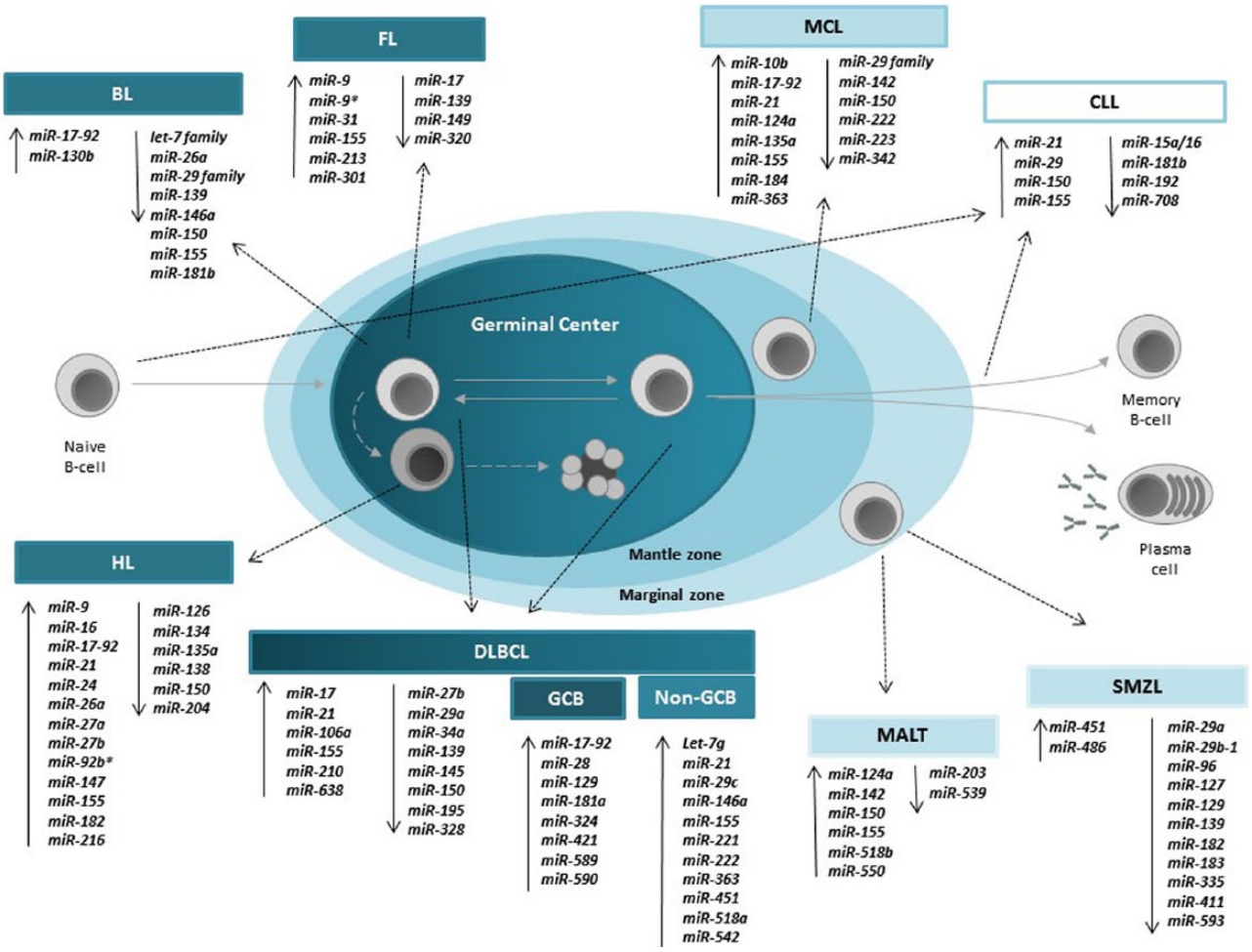

Figure 1. Schematic diagram of the major B-cell lymphoma miRNA biomarkers that have been identified and their relationship to B-cell development. BL indicates Burkitt lymphoma; CLL, chronic lymphocytic leukaemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HL, Hodgkin lymphoma; miRNA, microRNA; MALT, mucosa-associated lymphoid tissue; MCL, mantle cell lymphoma; PBMCs, peripheral blood mononuclear cells; SMZL, splenic marginal zone lymphoma.

inhibition.[31] In addition, *let-7* and *miR-9* inhibition has been shown to block plasma cell differentiation, by decreasing levels of PRDM1/BLIMP1, as well as targeting Dicer and HuR.[136] In a complementary study, inhibition of *miR-9* was observed to hamper cytokine production and consequent inflammatory cell attraction in HL cell lines.[137]

A 25-miRNA signature that could differentiate between cHL and reactive lymph nodes was identified by Navarro et al[28] using chromogenic in situ hybridization. Gibcus et al[27] compared the expression of miRNAs between different HL cell lines and other B-cell lymphoma cell lines and described a 23-miRNA signature for HL, which included the overexpression of *miR-17~92* cluster, *miR-16, miR-21, miR-24*, and *miR-155* along with the downregulation of *miR-150*. Using microarrays, another group identified 134 differentially expressed miRNAs in HL cell lines and an overlapping signature of 100 miRNAs differentially expressed in tumour samples.[29] Moreover, they observed that the levels of *miR-21, miR-30e, miR-30d*, and *miR-92b* could differentiate patients with HL according to prognostic risk groups. Epigenetic modifications of miRNA sequences have also been associated with HL including hypermethylation of *miR-124a* which was associated with more aggressive HL,[32] and *miR-9-2* methylation which is a common feature of this disease.[30] Navarro et al[138] recently observed that *miR-34a* and *miR-203* are frequently methylated in HL cells. It has been recently found that the alteration of miRNAs related to the regulation of antioxidant enzymes is associated with an aggressive outcome of the disease.[139] In plasma, the levels of *miR-494, miR-1973*, and *miR-21* were higher in patients with HL than controls,[21] and in another study, levels of *miR-24, miR-127, miR-21, miR-155*, and *let-7a* were higher in purified plasma exosomes from patients with HL than disease controls.[22]

Diffuse large B-cell lymphoma

Diffuse large B-cell lymphoma is the most common B-cell lymphoma in Western countries, accounting for around 20% to

30% of cases.[11] Thanks to the routine implementation of R-CHOP therapy, the survival of patients with DLBCL has been greatly improved; however, a third of patients still relapse or have a refractory disease.[140] Diffuse large B-cell lymphoma is a heterogeneous disease both at the clinical and molecular level, with the existence of at least 2 different molecular subtypes: GC B-cell like (GC-DLBCL) and activated B-cell like (ABC-DLBCL).[141] These subtypes are also distinguishable at the miRNA profile level with ABC-type lymphoma being associated with high expression of *miR-21, miR-146a, miR-155, miR-221*, and *miR-363*, and GCB-type DLBCL with high expression of *miR-421* and the *miR-17~92* cluster.[49-53,142] It has been described that miRNAs can predict differences between DLBCL and follicular lymphoma (FL)[49,50] or DLBCL and Burkitt lymphoma (BL).[54,75] Central nervous system (CNS) relapse is a complication of DLBCL that occurs in approximately 5% of patients, associated with low survival, *miR-20a* and *miR-30d* are correlated with CNS relapse in patients with DLBCL and therefore could be used for patient stratification.[58]

As noted above, overexpression of *miR-155* in mice is enough to cause development of a high-grade lymphoma, similar to DLBCL.[143] Indeed, when the same authors used an inducible expression system, removal of the *miR-155* stimulus was sufficient to allow complete recovery of affected mice.[104] *MiR-155* has also been linked with metastasis and prognosis in patients with DLBCL.[59] Apart from *miR-155* overexpression, low expression of both *miR-34a* and *miR-27b* expression has also been linked with a worse prognostic outcome for patients with DLBCL.[61,62] In addition, low levels of *miR-21* have been linked with shorter relapse-free survival in both tumour tissue[50] and in serum from patients.[24,66] As a consequence, levels of this miRNA have been proposed to act as an independent prognostic factor in DLBCL.[64] It has been suggested that *miR-21* may contribute to increase viability and reduce apoptotic levels of tumour cells through targeting BCL2 and PTEN.[144,145] Furthermore, *miR-21* inhibition leads to an increase in the sensitivity of DLBCL cell lines to CHOP treatment and reduces tumour cell proliferation and invasion.[63,65]

Several studies have looked at the association between miRNA expression and prognostic outcome in R-CHOP-treated patients with DLBCL. Our study found that levels of *miR-27a, miR-142, miR-199b, miR-222, miR-302, miR-330, miR-425*, and *miR-519* were linked with overall survival.[50] More recently, *miR-125b* and *miR-130a* were associated with resistance to R-CHOP in DLBCL,[67] and high expression of m*iR-155* has also been linked to treatment failure.[54] In vitro, overexpression of *miR-199a* and *miR-497* resulted in increased sensitivity to rituximab, vincristine, and doxorubicin, drugs present in R-CHOP regimen.[68] Overexpression of *miR-370-3p, miR-381-3p*, and *miR-409-3p* also increased sensitivity to rituximab and doxorubicin.[69]

Outside of the tumour itself, we observed that levels of *miR-21, miR-155*, and *miR-210* in the serum samples of patients with DLBCL were differentially expressed when compared with serum samples from healthy controls.[24] Subsequent studies using plasma also observed increased levels of *miR-124* and *miR-532-5p* along with decreased levels of *miR-122, miR-128, miR-141, miR-145, miR-197, miR-345, miR-424*, and *miR-425*.[55] Fang et al[146] found that *miR-15a, miR-16, miR-29c*, and *miR-155* were upregulated and *miR-34a* was downregulated in the serum samples of patients with DLBCL, and more recently Yuan et al[67] found a good correlation between circulating levels of 8 miRNAs and their matched FFPE samples. High expression of serum *miR-22* was associated with poor prognostic outcome.[57] Recently, next-generation sequencing (NGS) technology was used to identify 51 miRNAs that were differentially expressed in the serum samples of patients with DLBCL compared with control serum samples.[56] Three of these were validated by quantitative reverse transcription-polymerase chain reaction in a validation cohort. *MiR-34a-5p* was upregulated, whereas *miR-323-3p* and *miR-431-5p* were downregulated.

Follicular lymphoma

Follicular lymphoma is the most common indolent B-cell lymphoma worldwide, and despite being essentially incurable, it has a median overall survival of ~20 years. However, nearly a third of patients with FL will suffer histologic transformation into a high-grade lymphoma often termed transformed FL (tFL), that is morphologically indistinguishable from DLBCL, with a much worse prognosis than the antecedent FL.[147,148] We identified a signature of 6 miRNAs (*miR-223, miR-217, miR-222, miR-221*, and *let-7i* and *let-7b*) that could distinguish between de novo DLBCL and tFL.[50] Subsequently, *miR-31* and *miR-17-5p* have also been identified as being differentially expressed between FL and tFL.[70]

The t(14;18) translocation resulting in the constitutive expression of the anti-apoptotic BCL2 protein is the genetic hallmark of more than 90% of FL cases.[149] Using microarrays, a signature of 17 miRNAs was identified when comparing t(14; 18)-positive and t(14; 18)-negative FL cases. Down regulation of *miR-16, miR-26a, miR-101, miR-29c*, and *miR-138* was associated with changes in the expression of target genes related to cell cycle control, apoptosis, and B-cell differentiation.[71] It has been demonstrated that miRNA expression differs between pathogenic and non-neoplastic tissue, such as *miR-9* and *miR-155*.[49] Another study found a subset of 44 miRNAs which discriminates between FL and follicular hyperplasia, and the same study also described a 23-miRNA signature that was associated with an improved response to chemotherapy.[72] Moreover, *miR-494* was found overexpressed in FL compared with a potentially confounding diagnosis of nodal marginal zone lymphoma.[73]

Finally, one study analysed bone marrow smears from patients with FL and showed that 39 miRNA were decreased and 27 miRNA were increased significantly; among these, *miR-451* showed the greatest decrease and *miR-338-5p* the greatest increase in patients with FL.[74]

Burkitt lymphoma

Burkitt lymphoma most commonly affects children and adolescents and is a highly aggressive lymphoma with a very poor prognosis that often involves extra-nodal sites. Burkitt lymphoma is characterized by overexpression of the MYC oncogene and is associated with the t(8:14) translocation in most of the cases (>90%).[11] However, there are few cases that lack the t(8:14) translocation but have MYC overexpressed.[76] The authors suggest that *miR-34b* could be responsible for MYC overexpression in these cases.[76] In further studies, additional miRNAs have been identified as being differentially expressed between t(8:14)-positive and t(8:14)-negative cases by downregulation of *miR-29* family members,[79,80] *miR-9*[81] and *miR-34b*,[76] and upregulation of *miR-513a-5p* and *miR-628-3p*.[77,80] Furthermore, levels of MYC-regulated miRNAs, such as the *let-7* family, *miR-155, miR-146a, miR-29*, and the *miR-17~92* cluster, can distinguish BL from other B-cell lymphoma types.[75,81-83,150] Recently, NGS was used to identify 49 differentially expressed miRNAs between BL cases and normal GC B cells, many of which can target MYC.[84] Furthermore, *miR-181b* was found downregulated in BL cases, and the authors propose that it may function as a tumour suppressor.[85] In an earlier study, significantly lower expression of *miR-155, miR-21*, and *miR-26a* was observed between classical BL and cases with intermediate features between BL and DLBCL (DLBCL/BL).[78]

Most of the endemic BL cases (>90%) are associated with Epstein-Barr virus (EBV) infection[11,151] that has been shown to regulate several miRNAs, including *miR-21, miR*-146a, *miR-155, miR-10a*, and *miR-127* in BL cases.[152–155] In addition, EBV itself encodes for miRNAs that can interfere and compete with endogenous expression of miRNAs.[156,157] In paediatric BL levels of cplasma, *miR-21* and *miR-23a* were associated with both diagnosis and prognosis.[158]

Mantle cell lymphoma

Mantle cell lymphoma (MCL) accounts for 5% to 10% of non-Hodgkin lymphomas[159] and has the worst prognosis of any B-cell lymphoma.[160,161] Nearly all MCL (>90%) cases contain the t(11:14) translocation leading to overexpression of cyclin D1 (CCND1).[162,163] It has been demonstrated that *miR-15/16* and *miR-17~92* are involved in CCND1 deregulation.[86,87] The former miRNA (*miR-15b*) additionally involved in the transformation of classical to aggressive MCL.[89] A miRNA signature of 95 miRNAs was identified that could differentiate between differing clinical subtypes of MCL.[88,90] Low *miR-29* together with high *miR-20b* and *miR-18b* levels; high expression of *miR-129, miR-135, miR-146a, miR-424*, and *miR-450*; and low expression of *miR-222* or low *miR-223* levels have been associated with poor prognosis in MCL.[88,91–94]

Other B-cell lymphomas

Splenic marginal zone lymphoma (SMZL) is a rare indolent B-cell lymphoproliferative disorder characterized by the 7q32 deletion. It has been demonstrated that this chromosomal aberration triggers the downregulation of 8 miRNAs (*miR-29a, miR-29b1, miR-96, miR-129, miR-182, miR-183, miR-335*, and *miR-593*) in SMZL cases.[95] *MiR-127, miR-139, miR-335*, and *miR-411* were also found downregulated in SMZL cases, whereas *miR-451* and *miR-486* were upregulated.[96]

Mucosa-associated lymphoid tissue (MALT) lymphoma is a multifocal disease that involves the MALT, frequently of the stomach, and is frequently associated with chronic inflammation as a result of *Helicobacter pylori* infection.[11] On one hand, a signature of 27 miRNAs has been identified that can distinguish between gastritis and MALT lymphoma cases.[97,98] On the other hand, *miR-142* and *miR-155* were found overexpressed in MALT lymphoma lesions compared with surrounding non-tumour mucosae. The expression levels of *miR-142-5p* and *miR-155* were significantly increased in MALT lymphomas resistant to *H pylori* eradication than in cases showing complete remission after *H pylori* eradication. The expression levels of *miR-142-5p* and *miR-155* were also associated with the clinical courses of gastric MALT lymphoma cases.[99]

Discussion and Future Directions

Despite the rapid growth of literature proposing miRNAs as B-cell lymphoma biomarkers, we are still far from the clinical implementation. Most of the miRNA biomarker studies to date are single centre with a retrospective design, with not enough power in most cases (Table 1). As a consequence, many reports are non-overlapping or even contradictory. These differences are probably due to variation in the handling of the material and the technical methodology used in each study.

The choice of the starting material (whole blood, PBMCs, serum, plasma, fresh of FFPE biopsy material) is of vital importance for the experimental design as it will generate different expression profiles.[164-166] Sample collection and handling procedures are also crucial, and in the case of liquid biopsies, they should be optimized to reduce the time between phlebotomy and processing and to avoid excessive haemolysis which could lead major differences in the levels of miRNAs.[167–169]

It should also be taken into account that differences in the miRNA purification procedure are a source of variability.[170] In addition, miRNA detection technique (qRT-PCR, microarrays, or NGS), along with the lack of a standard approach to normalization or a suitable endogenous reference gene for miRNA studies, can influence results significantly.[13,24,171–175] It

is therefore necessary to establish a standardized approach to miRNA biomarker studies alongside a systematic and comprehensive comparison of these confounding factors to ensure that the potential of these molecules is effectively realized in the clinic and live up to the hyperbole.

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