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MicroRNA profiles in B-cell non-Hodgkin lymphoma

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ABSTRACT

B-cell non-Hodgkin's lymphomas are tumors of B-cells that arise following clonal expansion and consequent invasion of immune organs by B-cells blocked at a certain step of the differentiation process. Genetic abnormalities with altered gene expression are common in the transformed state of B-cells at any stage of B-cell development. These stages are regulated by a combination of transcription factors, epigenetic modifications, microRNAs, and extrinsic signals. MicroRNAs are a class of short non-coding single-stranded RNAs implicated in the regulation of mRNA function and translation. Each microRNA can regulate multiple transcripts; and a transcript is under potential control by multiple microRNAs. Their dysregulation can contribute to the pathogenesis of B-cell non-Hodgkin lymphomas, and they could be used as a potential target for diagnosis, evaluation of prognosis and therapy monitoring. The mechanisms of microRNA dysregulation range from dysregulation of the DNA sequences encoding the microRNAs to transcriptional regulation of microRNA loci. In this review, we summarized the microRNA profiles of the

most common B-cell Non-Hodgkin Lymphomas for the pathogenesis, diagnosis and their potential therapeutic implications.

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INTRODUCTION

Lymphomas represent a heterogeneous group of cancers that vary in presentation, prognosis, and pathogenesis. According to the World Health Organization (WHO) classification report, more than 100 different lymphoma types have been identified. Non-Hodgkin's lymphoma (NHL) is a heterogeneous group of disorders that arises in lymphoid hematopoietic tissue and that can be grouped into B- and T-cell lymphomas which account for about 90% and 10% NHLs, respectively (1, 2). B-cells Non-Hodgkin Lymphomas (BCNHL) are tumors of B-cells that arise following clonal expansion and consequent invasion of immune organs by B-cells blocked at a certain step of the differentiation process (3, 4). B-cell lymphomas (BCLs) are a complex and heterogeneous group of tumors with different cellular origin, genetics and pathology. Patients diagnosed with these diseases show extremely variable clinical courses, ranging from very indolent to highly aggressive types, receive various types of treatment modalities, respond differently to therapy, and have extremely variable clinical outcomes (5).

This heterogeneity is partly reflective of the fact that these tumors are derived from different stages of mature B-cell differentiation. It encompasses a wide variety of disease subtypes in which the incidence pattern greatly varied. Diffuse large B cell lymphoma (DLBCL), Mantle cell Lymphoma (MCL), Follicular Lymphoma (FL), Burkitt's lymphoma (BL), Chronic Lymphocytic Leukaemia (CLL), Mucosa-Associated Lymphoid Tissue (MALT) and Marginal zone lymphoma (MZL) are the main subtypes (4). Majority of NHL B-cells have passed the germinal centre (GC) reaction and thus their immunoglobulin (IG) genes have undergone somatic hypermutation (SHM) and heavy chain class-switching. FL and DLBL are good examples of this lymphoma. Other subtypes like MCL and CLL are derived from GC-inexperienced B cells in at least a proportion of cases, or other cell types are marginal zone B cells e.g. MZL (6). The pathophysiology of these lymphomas come from intrinsic cellular aberrations like B-cell receptor (BCR) and NF-kB signaling defect affecting pathways of particular importance and the fact that the tumor cells are reliant on the microenvironment through cell-extrinsic communication and activation via different cell surface receptors (7-9).

Chromosomal translocations involving an oncogene and one of the immunoglobulin genes are a common phenomenon in BCNHLs (10). Three BCNHLs have characteristic genetic abnormalities that are important in determining their biologic features and are useful for differential diagnosis. These include: t(14;18) in FL, t(11;14) in MCL and t(8;14) in BL. Characteristic for these translocations is that a cellular proto-oncogene is placed under the control of the Ig promoter on chromosome 14q, resulting in constitutive activation of the gene which in turn gives to the cell survival or proliferative advantage. In FL, t(14;18) translocation results in overexpression of an anti-apoptosis gene called B cell lymphoma-2 (BCL-2). In MCL and BL, the translocations result in over-expression of cell cycle genes associated with proliferation of Cyclin D1 (CCND1) or Myc, respectively (11, 12). These lymphomas are influenced by aberrant genetic alterations, epigenetic dysregulation, aberrant pathway activation, and complex tumor–microenvironment interactions (13). Diagnosis and classification modalities of these multi-subclass of BCNHLs are challenging. Moreover, the molecular heterogeneity of these disease makes the treatment modalities difficult, accordingly patients who are treated similarly have variable

outcomes (14). However, the advancement of recent technologies in the use of effective and practical detection techniques, and identifications of novel biomarkers at the genetic, epigenetic, and protein level as well as at the tumor microenvironment enables and improves the diagnostic process, sub-typing, outcome stratification, and personalized therapy for lymphoma patients (15).

Among these biomarkers micro ribonucleic acids (miRNAs) are the most important one. Individual miRNA expression and miRNA signatures analysis allow specific cell differentiation stages to be easily identified in the pathogenesis of BCNHL (16). As a result, it can be taken as a powerful player in the pathogenesis, diagnosis and prognosis these diseases (17). In this review, the authors summarize the miRNA profiles and the implications of miRNA dysregulation in the pathogenesis, diagnosis and prognosis of BCNHL, as these molecules appear to be cell type and disease specific, unlike most other biomarkers currently available.

DEFINITION OF miRNAs, BIOGENESIS, MECHANISM OF GENE REGULATION AND THEIR ROLES IN BCNHL PATHOGENESIS

Definition and biogenesis of miRNA

MiRNAs are small, evolutionary highly conserved, 20-24 nucleotides long, single stranded non-coding RNA molecules. They are involved in the regulation of gene expression by binding to target mRNA in plants, animals and viral genome via post-transcriptional degradation or translational repression. Their mechanism of gene regulation is by translational silencing or by impairing the stability of their target messenger RNAs (mRNAs) (18, 19).

It is predicted that miRNA account for 1-5% of the human genome and regulate at least 30% of protein-coding genes (20). Until 2000's, 940 distinct miRNAs molecules have been identified within the human genome (21). Later on, the recent advancement in small RNA deep sequencing technology has now enabled the identification of over 2500 mature human miRNAs (22).

MiRNA precursors are commonly found in clusters through many different regions of the genome, most frequently within intergenic regions and introns of protein coding genes (23). Human miRNA biogenesis is a multistep process that begins in the nucleus where miRNA genes are transcribed by RNA polymerase II into long primary miRNAs (pri-miRNAs) molecules, and subsequently trimmed into smaller, stem-looped, hairpin-like miRNA precursor (pre-miRNA) by RNase III-type enzyme Drosha that form a microprocessor complex with its binding partners DiGeorge Syndrome critical region gene 8 (DGCR8). Then the pre-miRNAs are exported from the nucleus into the cytoplasm via Exportin-5 to be sliced by another RNase III-type enzyme called Dicer and its binding partners called the transactivator RNA-binding protein (TRBP), to generate a 19- to 23-nucleotides RNA duplex that contains both the mature miRNA strand and its complementary strand. The mature miRNA strand is preferentially incorporated into a miRNA-induced silencing complex (miRISC), while the other strand of miRNA is degraded by the RNA-induced silencing complex (RISC). The miRNA strand guides the RISC to its mRNA target, containing complementary sequence to the mature miRNA and subsequently induces the cleavage or silencing of the target mRNA. The complementarity between miRNA and target mRNA is a crucial factor for the post-transcriptional regulatory mechanism (24, 25).

Mechanisms of miRNAs in gene regulation

Normally, miRNAs play a role in heterochromatin formation, histone modification, DNA methylation, and gene silencing which affects the level of target gene expression (26). They generally bind to a specific target mRNA with a complementary

sequence to induce cleavage, or degradation or block translation by a feedback mechanism. MiRNAs also inhibit protein translation from the target mRNA (27). They can also speed up deadenylation, causing mRNAs to be degraded rapidly (28). For example, miRNA-430 in zebrafish, bantam-miRNA and miRNA-9 in Drosophila cultured cells causes translational repression by the disruption of translation initiation (29).

For the ease of understanding, some scholars categorized and summarized the mechanisms of miRNAs actions as follows: Cap-40S initiation inhibition; 60S Ribosomal unit joining inhibition; elongation inhibition; ribosome drop-off (premature termination); co-translational nascent protein degradation; sequestration in P-bodies; mRNA decay (destabilization); mRNA cleavage; and transcriptional inhibition through microRNA mediated chromatin reorganization followed by gene silencing (30).

MiRNAs may influence histone marks by regulating the expression of histone modifiers. For example, in MCL, downregulated expression of miRNA-15a, miRNA-16-1, and miRNA-29 are due to histone hyperacetylation at the promoter sites of their genes. The hyperacetylation is brought about by the overexpression of Myc: Myc binds to and represses Histone Deacetylase 3 (HDAC3), an enzyme that is responsible for removing acetyl groups from histone residues. This in turn results in the downregulation of miRNA-15a/16-1 (31).

MiRNAs virtually regulate all cellular processes including cell cycle, developmental, cell proliferation, apoptosis, differentiation, metabolism, organ development and morphogenesis, hematopoiesis and disease process including cancers (32, 33). MiRNAs regulate gene expression at the post-transcriptional level by binding to short motifs of complementary sites of transcribed target mRNA at the 3'-untranslated regions (3'-UTRs). When it binds to its specific target, it can cause either protein translational repression or transcript degradation of the mRNA molecule (34).

Deregulation of miRNA expression is a type of genetic alterations relevant for lymphomagenesis. The loss of miRNA-15 and miRNA-16 in CLL with deletion of the 13q14 region (35) and upregulation of miRNA-155 and its precursor mRNA BIC in DLBCL and are good examples (36).

MiRNAs usually play a critical role in tumor development since they are often located at fragile sites and genomic regions on chromosomes that are associated with cancer (37). They are important in cancer biology by regulating the expression levels of target mRNAs to assist tumor growth, metastasis, angiogenesis and immune evasion (38). They play an important role in determining cancer behavior since the non-coding regions of the genome are frequently deleted in cancer including BCNHL often contain miRNA genes (18).

Dysregulation of miRNA may result in the aberrant expression of miRNA target genes, and results in the acceleration of lymphomagenesis (39). Dysregulations of miRNAs can be associated with different diseases (40), chronic lymphocytic leukemia (CLL) being the first human disease known to be associated with miRNA dysregulation. In the pathogenesis of B cell malignancies, miRNAs participate in pathways fundamental to cell development like B-cell receptor (BCR) signalling, B-cell migration/adhesion, cell-cell interactions in immune niches and the production and immunoglobulins class-switching. MiRNAs influence B cell maturation, generation of pre-, marginal zone, follicular, B1, plasma and memory B cells. They also regulate B-cell proliferation through inhibiting proteins like E2F1 involved in the process of cell proliferation (41).

Each NHL subtype has their distinct miRNA signatures resulting from coordinately dysregulated expressions of miRNAs. This miRNA dysregulation

may be due to dysregulation of the DNA sequences encoding the miRNA to transcriptional regulation of miRNA loci, miRNA biogenesis pathway or messenger RNA (mRNA) targets. The activation of oncogenic pathways, and the reprogramming of BCNHL transcriptomes may be due to this abnormal miRNA expression. This widespread dysregulation suggests that miRNAs can be used as a diagnostic and prognostic tool. Profiling of different cell types and tissues indicated that the pattern of expression of miRNAs is cell type and tissue specific, suggesting that the program of expression of miRNAs is neatly cell type dependent and tightly associated with cell differentiation and development (42, 43).

miRNA PROFILE IN BCNHL PATHOGENESIS, DIAGNOSIS AND SUBTYPING

miRNA profile in BCNHL pathogenesis

MiRNAs are very crucial for the regulation of translation in physiological and pathological states, including the sequential differentiation of B-cells and lymphomagenesis (44).

MiRNAs control hematopoiesis through modulating different signaling pathways that are cell type and context specific (45). MiRNAs play an important role in hematopoiesis as it had been confirmed by the deletion of components of these miRNAs biosynthetic pathway in vivo demonstrates the critical role in hematopoiesis. For instance, miRNA miRNA-17-92 cluster, miRNA-34a, miRNA-125b, miRNA-150, miRNA-181a, and miRNA-212/132 are important for a correct early B-cell development process (46). They mainly involved in the regulations of germinal center (GC) B cell differentiation by targeting of activation induced cytidine deaminase (AID) (47, 48). However, miRNA-17-79 cluster, miRNA-24, miRNA-146, miRNA-155, miRNA-128, and miRNA-181b prevent the differentiation of early stage B cell progenitor cells. Other few miRNAs such as miRNA-16, miRNA-103, and miRNA-107 act later on, and miRNA-221, miRNA-222, and miRNA-223 regulate the terminal or end stages of hematopoietic development (49).

Potential regulatory role for miRNAs in discrete stages of mature B-cell differentiation have a direct role for the miRNA-mediated regulation of oncogenes and key transcription factors in B-cell differentiation (50). MiRNAs that play a determinant task in the lineage differentiation decision of B-cells includes the high expression levels of the cluster of miRNA-23a (miR-23a, miRNA-27a, and miRNA-24) and miRNA-125b reduce the differentiation to B-cell lymphocyte lineage in favor of myeloid differentiation (51, 52). Moreover, some miRNAs have an important role in early B-cell development like miRNA-150 up-regulation in hematopoietic progenitors reduces the normal quantity of mature B cells by blocking the maturation process at the pro-B cell stage (53). There is a strong association between changed miRNA expression and oncogenesis. MiRNAs that enhance cellular processes are associated with oncogenesis and tumor progression, with uncontrolled clonal expansion, increased invasiveness, and resistance to apoptosis. Those miRNAs involved in these processes are called 'oncomiRs', and are frequently upregulated. On the other hand, miRNAs that counteract these oncogenic characteristics are called 'tumor-suppressor miRNAs', and are often down regulated in cancer including BCNHL (54).

The importance of miRNAs in cancer has been underlined by the identification of changes in their target binding sites and the miRNA processing machinery of tumor cells (54, 55).

miRNAs influence B-cell maturation, generation of pre-B, marginal zone, follicular, B1, plasma and memory B cells. MiRNA-150, miRNA-155, miRNA-21, miRNA-34a, miRNA-17-92 and miRNA-15-16 are the major miRNAs having essential functions in malignant B-cell development

(56). The levels of miRNA155, miRNA200c, miRNA130a, miRNA125b and miRNA21 were found significantly upregulated whereas miRNA29c, miRNA451 and miRNA145 were found downregulated in BCNHL patients when compared with healthy controls (57).

The miRNA-17-92 cluster is a polycistronic miRNA encoded by chromosome 13 amplified in BCNHLs (58). This cluster of miRNA is the most complex and highly conserved sequence in humans that produces six mature miRNAs, (miRNA-17, miRNA-18a, miRNA-19a, miRNA-20a, miRNA-19b1, and miRNA-92-1) generated from the third exon of the open reading frame C13orf25 at loci 13q31.3. The 13q31.3 gene locus is a frequent site for gene amplification, which explains highly elevated levels of miRNA-17-92 observed within a variety of lymphomas. MiRNA-17-92 can be directly regulated by c-MYC and E2F transcription factors (E2Fs). However, E2F3 is thought to be the predominant regulator in BCNHL pathogenesis (59).

MiRNA-17-92 cluster is recurrently amplified in human B cell malignancies, causing the overexpression of these miRNAs in several lymphoma types, like MCL, FL, BL, GCB-DLBCL, but is never overexpressed in ABC-DLBCL (60). Forced overexpression of miRNA-155 results in the development of DLBCL (61) by suppressing the growth-inhibition of BMP2/4 and TGF-β1 via SMAD5 inhibition (62).

MiRNA-19a and miRNA-19b are two miRNAs in this cluster play key roles in the induction of BCNHL progression. Whereas miRNA-17-5p and miRNA-20a are the other two miRNAs which play a key role in controlling cell proliferation by regulating the transcription factor E2F1. As a result, miRNA-17-5p and miRNA-20a are considered as tumor suppressors, highlighting the complexity and versatility of miRNA-mediated regulation in cancer (54, 63).

miRNA profiles in the subtypes of BCNHL

miRNA profiles in Diffused Large B-Cell Lymphoma (DLBCL)

DLBCL is one of the most common, frequent and aggressive kind of BCNHL, accounting for nearly 30–40% of newly diagnosed lymphomas (1). It is a heterogeneous group of diseases with an aggressive clinical course (64) that accounts for approximately one third of patients with NHL. Due to its heterogeneity in genetic abnormalities, clinical features, response to treatment and prognosis (65, 66) and outcome prediction based on clinical and molecular features is difficult. Thus, an assessment of miRNA expression profiling can be used to get important information regarding diagnostic, subtyping and outcome prediction for DLBCL (67).

In light of miRNAs' potential as diagnostic markers for cancer prognostication there is an increasing interest in the possible role for miRNAs as markers for both B-cell differentiation stage and malignant transformation. It has been shown that miRNA expression patterns can characterize the stages of human B-cell differentiation (50, 68, 69). To date, a large number of microRNA signatures in lymphomas were identified, and the role of miRNAs in the development, classification and in the regulation of target genes is under intensive investigation (68).

miRNAs, such as miRNA-17-92, miR-15a/16-1 clusters, miRNA-222 and let-7f are highly expressed in DLBCL pathogenesis and common targets for copy number changes. Among the multiple miRNA loci on 12q that were frequently targeted by copy number gains, miRNA 26a-2 and let-7i were found also highly expressed in the prime tumors. These data suggest that the chromosome 12q miRNAs are more likely to contribute to the pathogenesis of GCB-type DLBCL (70).

The mechanisms of the above miRNAs in the pathogenesis of DLBCL are described below.

The role of miRNA-15a/miRNA-16-1 cluster in the pathogenesis of DLBCL via targeting BCL2 is to reduce apoptosis of lymphoma cells (71). Similarly, the increased expression of miRNA-17-92 cluster leading to increased expression of *MYC* and increases the development and the aggressiveness of lymphomas (72) and by reducing the degree of apoptosis of lymphoma cells (73). The function of miRNA-17–92 is associated with c-MYC, and a negative feedback loop may exist between miRNA-17–92 and c-MYC. This is important in the regulation of cell proliferation and apoptosis as it induces the growth of B-cell lymphoma by reducing apoptosis and promoting the proliferation of lymphoma cells. There are several other potential targets for miR-17–92, including proapoptotic BCL-2 interacting mediator of cell death, PTEN and E2F transcription factor 1, which is a direct target of MYC and promotes cell cycle progression (74).

On the other hand, the let-7f miRNA regulates the expression of the RAS proteins that regulate cell growth and differentiation through MAP kinase signaling. Hence, let-7f indirectly alters the cell proliferation rate through its downstream MAP signaling cascade and regulates the expression of oncogenes (75).

Additionally, miRNA-330, miRNA-17-5p, miRNA-106a, and miRNA-210 were found increasingly expressed DLBCL. The mechanism in the pathogenesis of the disease is that an alteration in miRNA expression levels in DLBCL causes an aberrant expression of miRNA target genes and consequent disruption of the gene expression profile, which can result in cancer development. Multiple mechanisms has been identified like genomic mutation of miRNA loci, epigenetic changes and deregulation of transcription factors contribute to the modulations of miRNA expression levels (76, 77). In the contrary of the above-mentioned miRNAs, miRNA-150, miRNA-145, miRNA-328, miRNA-139, miRNA-99a, miRNA-10a, miRNA-95, miRNA-149, miRNA-320, miRNA-151 and let7e had considerably decreased expression in DLBCL (78). As it had been reported by Fassina *et al.*, miRNA-17-92 cluster, miRNA-150 and miRNA-210 were found to be significantly overexpressed in GCB-DLBCL and allowed correct identification of 97% GCB-DLBCL cases (79).

As it had been reported by Thapa *et al.*, miRNA-17, miRNA-106a and miRNA-106b regulate the proliferation, apoptosis and invasion of DLBCL cells by repressing the expression of cyclin-dependent kinase inhibitor 1. In addition, higher expression level of miRNA-15a, miRNA-16, miRNA-17, miRNA-106, miRNA-21, miRNA-155 and miRNA-34a-5p are specific to DLBCL than in other malignancies. This suggesting that these miRNAs may be used as potential candidate biomarkers for DLBCL diagnosis (80). DLBCL tumors are also characterized by upregulated expression of miRNA-150, miRNA-17-5p, miRNA-145, and miRNA-328 when compared with samples taken from normal lymph nodes and follicular lymphoma (FL) (78).

MiRNA-155 is one of the best recognized miRNAs in lymphomas, particularly in DLBCL usually upregulated in several lymphoma subtypes (54, 61, 74) such as in primary mediastinal BCL (PMBCL) and DLBCL, especially of the ABC type (81, 82). It acts as an onco-miRNA in the pathogenesis and aggressiveness of these lymphoma subtypes. Levels of miRNA-155 expression in ABC- DLBCL subtype were found to be significantly higher than in GC-DLBCL, suggesting that miRNA-155 is diagnostically useful to distinguish ABC-DLBCLs from GC-DLBCL and may explain the poor prognosis of ABC-DLBCL patients (15). For example, forced over-expression of miRNA-155 in mice results in the development of a high grade BCL similar to DLBCL (61, 83) confirmed that the association between this miRNA expression and BCNHL development.

Down-regulation of the target mRNA is considered the main mechanism by which miRNAs modulate protein expression. MiRNA expression level can aid to distinguish between subtypes of DLBCL (GC-DLBCL and ABC-DLBCL) even though the subtype differentiation is based on validated FFPE technique by using Nanostring testing. For example, the miRNA-21, miRNA-144, miRNA-155, miRNA-221, miRNA-222 and miRNA-451 were found upregulated and more highly expressed in the ABC subtype than in the GCB subtype (69). On the other hand, miRNA-28, miRNA-151, miRNA-331, and miRNA-454-3p were found to be upregulated in the GC-type DLBCL (84). For example, the mechanism by which miRNA-21 upregulated expression influences the pathogenesis of ABC-DLBCL is associated with tumor growth, invasion and metastasis through targeting multiple tumor and metastasis suppressor genes, including programmed cell death 4 (neoplastic transformation inhibitor), tropomyosin 1-α and phosphatase and tensinhomolog (PTEN) (85, 86).

miRNA profiles in Burkitt Lymphoma (BL) diagnosis

Burkitt lymphoma (BL) is another aggressive type of BCL. BL is a highly aggressive type of BCNHL and is the fastest growing human tumor. It has two major subtypes, the endemic one that is predominantly affecting young children and common in equatorial Africa, and the systemic/sporadic type which is affecting adults as well and occurs in worldwide (87). Recent studies using NGS on BL have improved the understanding of the pathogenesis of these tumors. Mutations in the transcription factor 3 (TCF3) or its negative regulator ID3 occur in about 70% of sporadic and immunodeficiency-related BL and 40% of endemic cases. TCF3 promotes survival and proliferation in lymphoid cells by activating the B-cell receptor/phosphatidylinositol 3-kinase signaling pathways and modulating the expression of cyclin D3, which is also mutated in 30% of BL (1). The most frequently mutated genes in Burkitt lymphoma were *MYC* (40%) and Inhibitor of DNA binding 3 (*ID3*) (34%) (88).

It is characterized by a high degree of proliferation of the malignant cells and deregulation of the *c-Myc* gene caused by t(8;14)(q24;q32) leading to the constitutive expression of the Myc oncogene (89). BL is also characterized by the dysregulated expression of *Myc* as a consequence of translocations of immunoglobulin genes. It was found that miRNA-155 expression is highly reduced in BL because miRNA-155 suppresses activation induced cytidine deaminase (AID) mediated Myc-IGH translocation (90). Therefore, BL can be characterized by the unstable interaction between c-Myc and miRNAs like let-7a, miRNA-34b, miRNA-98, miRNA-331 and miRNA-363 (91). Upregulated expressions of miRNA-155 mediated by c-MYC play a role in the lymphomagenesis of pediatric BL (36).

In addition to histological, immunohistochemistry testing in conjunction with BCL2 and c-Myc testing, miRNA profiling can improve the differentiation of BL from DLBCL (1). Moreover, miRNA may have a clear role in pathogenesis, differentiating BL from other, but it is only investigational. For example, the loss of miRNA-155 expression in BL is useful distinctive marker in the differential diagnosis from DLBCL (92).

In BL patient's miRNA expression profiling, miRNA-150 having c-Myb and survivin protein targets had extremely decreased expression levels. Thus, deregulation of miRNA-150 is an important diagnostic biomarker for BL screening and diagnosis (93). In majority of the cases of BL, there is a *c-Myc* translocation, members of the miRNA-17-92 cluster (miRNA-17-3p, miRNA-18a, miRNA-19a, miRNA-19b and miRNA-92) are up regulated and let-7 family miRNAs are down regulated (94). Expressions of miRNA-21 and miRNA-23a are useful molecular

biomarkers in the diagnosis and prognosis for BL in children (95). MiRNA-221/222 is also critical mediator for BL pathogenesis (96).

miRNAs profiles in Follicular Lymphoma (FL)

Follicular lymphoma (FL) is another of the most common forms of B-cell lymphoma derived from germinal center B-cells. It comprises approximately 15–20% of newly diagnosed lymphomas (97).

A specific chromosomal translocations t(14;18)(q32;q21) involving the B-cell lymphoma-2 gene (*BCL2*) and immunoglobulin (Ig) loci is essential for FL development (11). In addition to t(14;18)(q32;q21) as the molecular hallmark of FL, chromosomal rearrangements affecting the *BCL6* locus constitute one of the most common cytogenetic finding (98, 99). FL is the slow growing BCNHLs accounting for about 20–30% of all NHL. It has the tendency to transform into DLBCL, with translocation t(14;18)(q23;q21) in 90% of cases and is associated with BCL2 activation which may lead to accumulation of GCB cells with prolonged lifespan (100).

The comparison study performed on miRNA expression profiles of FL and DLBCL shown that miRNA-155, miRNA-210, miRNA-106a, miRNA-149, and miRNA-139 were found overexpressed in both of these cancers when compared with normal lymph nodes. These overexpressed miRNAs are suggestive of lymphomagenesis (78). Other overexpressed miRNAs distinct to FL are miRNA-20a/b and miRNA-194 and they target cell proliferation inhibitors like *CDKN1A* and *SOCS2*, respectively (101).

The miRNAs that showed significantly decreased expressions in FL patients are miRNA-202, and miRNA-139-5p. However, miRNA-338-5p, miRNA-9, and miRNA-330-3p are significantly up regulated (94, 102).

miRNAs differentially expressed in BL, DLBCL and FL

Rapid and accurate differential diagnosis of BL versus DLBCL is very important for therapeutic decisions and patient prognosis. MiRNA-155 is the most significantly lost miRNA in BL, followed by miRNA-29b and miRNA-146a, whereas the most significantly gone miRNAs in DLBCL are miRNA-17-3p, miRNA-595 and miRNA-663. MiRNA-29b is downregulated in BL cases (103-105). In addition, miRNA-34b is also downregulated in BL (94, 106).

MiRNA-155, miRNA-21 and miRNA-26a are potential diagnostic biomarkers to differentiate BL from DLBCL and DLBCL/BL. In both BL and DLBCL/BL cases of lymphoma, miRNA-155, miRNA-21, and miRNA-26a showed considerably reduced level of expression than primary DLBCL (107). In addition to miRNA-155, miRNA-17-5P, miRNA-106A, and miRNA-210 are found significantly expressed at a higher concentration in DLBCL than in normal tissue. In opposite to this, miRNA-10a, miRNA-95, miRNA-99a, miRNA-139, miRNA-145, miRNA-149, miRNA-150, miRNA-151, miRNA-320 and miRNA-328 were found to be expressed at a significantly reduced level. MiRNA-330, miRNA-17-5P, miRNA-106A and miRNA-210 are the most discriminatory miRNAs - for DLBCL and FL diagnosis. Comparing DLBCL and FL with other subtypes, miRNA-17-5P and miRNA-92 were found overexpressed whereas eight miRNAs consisting of miRNA-330, miRNA-338, miRNA-135A, miRNA-150, miRNA-125B, miRNA-301, miRNA-126, and miRNA-213 were found down regulated in DLBCL (78).

miRNA profiles in Mantle Cell Lymphoma (MCL)

MCL constitutes approximately 5% to 10% of all newly diagnosed cases of NHLs (108) having the genetic hallmark of t(11;14)(q13;q32)

translocation that results in overexpression and displaces the cyclin D1(CCND1) gene on chromosome 11 downstream to the enhancer region of the IgH gene on chromosome 14 (109).

MiRNA expression profiling of B cells from MCL patients led to the identification of miRNA expression signature and frequent deregulation of a set of miRNAs. For example, miRNAs such as miRNA-124a, miRNA-155, miRNA-328, miRNA-326, miRNA 302c, miRNA-345, miRNA-373, and miRNA-210 were identified as upregulated in patients with MCL (110). The mechanism of this upregulated miRNA in the pathogenesis of MCL is inhibiting *CDK6* expression as well as phosphorylation of RB1. The good example of this mechanism is that miRNA-124a inhibit *CDK6* expression as well as phosphorylation of RB1, targeting of *CDK6* and *CCND1* prevents the downstream pro-survival signaling of the cyclin/CDK pathway (111).

Several miRNAs have been implicated in MCL pathogenesis. The major downregulated miRNAs include miRNA-29 family (miRNA-29a, -29b, and -29c), miRNA-142-3p/5p, miRNA-150, and miRNA-15a/b were found associated with short overall survival of patients with MCL (110). The pathophysiologic roles of miRNAs such as miRNA-15a, miRNA-16-1, and miRNA-29 are by transcriptional repression and its epigenetic regulation by c-Myc in MCL. They are downregulated due to histone hyperacetylation at the promoters of their genes. In this instance, the hyperacetylation is brought about by the overexpression of *Myc* gene in which the binding of *Myc* on target gene represses HDAC3, an enzyme that is responsible for removing acetyl groups from histone residues. This in turn results in the downregulation of miRNA-15a/16-1 (31). MiRNA-29 indirectly targets the de novo DNA methyltransferases thereby controlling gene expression. Therefore, loss of miRNA-29 may result in elevated MCL1 levels (25). MiRNA-29b is down regulated in malignant cells, consistent with MCL-1 protein up regulation. Enforced miRNA-29b expression reduced MCL-1 cellular protein levels and thus miRNA-29 is an endogenous regulator of MCL-1 protein expression and apoptosis. The miRNA-29 also targets CDK6, expression which is a known prognostic and pathogenetic factor in MCL. Furthermore, downregulation of miRNA-29 is in line with the CCND1 overexpression and the consequent CDK4/CDK6 activation, which is the primary event in MCL pathogenesis (112).

Another study showed that miRNA-31, miRNA-148a and miRNA-27b are also among the down regulated miRNAs in MCL, on the other hand miRNA-617, miRNA-370 and miRNA-654 are among the up regulated miRNAs. Of these, miRNA-31 is the most down regulated miRNA targets MAP3K14 (NIK) gene, which is essential for activation of the alternative NF-κB pathway (113). The miRNA clusters at locus 7q22 including miRNA-106b, miRNA-93 and miRNA-25 are also highly up regulated in MCL. MiRNA-106b specifically promotes cell-cycle progression by targeting cyclin-dependent kinase inhibitors p21/CDKN1a. In addition to this function, miRNA-106b overrides doxorubicin-induced DNA damage checkpoint (114). MiRNR-181a and miRNR-181b are down regulated in lymphoma and acts as a tumor suppressor by targeting the T cell lymphoma 1(TCL1) oncogene and indirectly regulate the levels of the oncogene mantle cell lymphoma1 (MCL1) (112). miRNA-21 overexpression also leads to pre-BCL, which is completely dependent on the continued expression of miRNA-21 (54, 115).

miRNAs profiles in Mucosa-Associated Lymphoid Tissue (MALT) Lymphoma

MALT lymphoma usually presents as localized disease and typically arises from sites such as the stomach but characteristically disseminates, either within the same organ or to other extranodal sites where MALT lymphomas are

known to arise (116). Chromosomal alterations, especially trisomy 3, 12, and 18, are common in MALT lymphomas. Chromosomal translocations associated with MALT lymphomas include t(11:18)(q21: q21), resulting in the production of a chimeric protein (API2- MALT1) (117); and t(1;14)(p22;q32), t(14;18)(q32;q21), and t(3;14)(p14.1;q32), resulting respectively in transcriptional deregulation of BCL10, MALT1, and FOXP1 (118, 119).

Different studies conducted indicated that, there are miRNAs significantly up regulated in MALT lymphoma cases. The miRNA-200 family (miRNA-200a, b and c) is the most common one. The other miRNAs located in these clusters, miRNA-429 and miRNA-141, were also up regulated. The miRNA-200 family inhibits the initiating step of metastasis, the epithelial-mesenchymal transition, by maintaining the epithelial phenotype through directly targeting the transcriptional repressors (120). But miRNA-126 was found down regulated in the case of MALT (94, 120). Additionally, up regulation of miRNA-181c, miRNA-182, miRNA-183, miRNA-200c, miRNA-363, miRNA-654 and miRNA-768-5p were found in this subtype of BCNHL (94).

miRNAs profiles in Nodal Marginal Zone Lymphoma (MZL)

Nodal marginal zone lymphoma (NMZL) is a small B-cell neoplasm whose molecular pathogenesis is still essentially unknown and whose differentiation from other small B-cell lymphomas is hampered by the lack of specific markers (121).

Nodal MZL shows greater expression of miRNA-221, miRNA-223, and let-7f. Expression of these miRNAs is enhanced in nodal MZL, whereas FL strongly expresses miRNA-494. Upregulation of miRNA-223 and miRNA-221, which targets the germinal center-related genes LMO2 and CD10, could be partially responsible for expression of a marginal zone signature. In splenic MZL, the miRNA-29 cluster is commonly lost and its expression silenced (121). (Table 1)

miRNA PROFILES IN BCNHL PROGNOSIS

Best treatment for cancer requires accurately recognizing patients for risk-stratified therapy. Those individuals having a rapid response to initial treatment may benefit from shortened treatment regimens. The role of miRNA in cancers is also implicated in the prognosis

Table 1 A summary of dysregulated miRNAs and their potential implications for diagnosis and subtyping of BCNHL

MiRNA	Expression	B-cell NHL subtype	Potential Role	Reference
miRNA-155, -21, -221	Increased	ABC-DLBCL vs. GCB-DLBCL	Subtyping	(69)
		DLBCL, FL	Diagnosis	
miRNA-155, -21, -210	Increased	DLBCL	Diagnosis	(69, 76, 122)
miRNA-21	Increased	ABC-DLBCL vs. GCB-DLBCL	Subtyping	(122)
miRNA-330, -17-5p, -106a, -210	Dysregulated	DLBCL vs. FL	Subtyping	(78)

miRNA-125b, -143, -451, -145	Increased	DLBCL vs. FL	Subtyping	(123)
miRNA-223, -217, -222, -221,	Dysregulated	DLBCL vs. transformed FL	Subtyping	
miRNA-17-92 cluster, -29a, -106a, -720 , -1260, -1280	Increased	ABC-DLBCL vs. GCB-DLBCL	Subtyping	(124)
miRNA-20b, -26a, -92b, -487b	Increased	DLBCL vs. FL	Subtyping	
miRNA-17-92 cluster, -150, -210	Increased	GCB-DLBCL vs. high grade FL	Subtyping	(79)
miRNA-15a, -16-1, -29c, -155, -34a	Increased	DLBCL	Diagnosis	(85)
miRNA-451	Decreased	FL	Diagnosis	(102)
miRNA-338-5p	Increased	FL	Diagnostic	
miRNA-17-92 cluster (-18b, -20b, -106a	Increased	BL	Diagnostic	(14)
miRNA-155	Decreased	BL vs. DLBCL	Subtype	
		ABC-DLBCL vs. GCB-DLBCL		
miRNA-155, -200c, -130a,-125b, -21	Increased	DLBCL	Diagnostic	(57)
miRNA-451, and -145	Decreased	DLBCL	Diagnostic	
miRNA-9, -301, -338, and -213	Increased	FL	Diagnostic	(78)
miRNA-150, -550, -124a, -518b, -539	Increased	MALT	Diagnostic	(125)

Abbreviations: *miRNA, microRNA; DLBCL, diffuse large B-cell lymphoma; ABC-DLBCL, Activated B-cell like diffuse large B-cell lymphoma; GCB-DLBCL, Germinal center diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle-cell lymphoma; HL, Hodgkin lymphoma; MALT, mucosa-associated lymphoid tissue lymphoma.*

indication. Their expression level is very good indicator for prognoses of lymphomas. For example, low miRNA-324a levels could serve as an indicator of poor survival (126). Circulating miRNAs have the potential to assist clinical decision making because they are highly stable in blood. They are overexpressed in cancer and are quantifiable within the diagnostic laboratory. They can be performed at each consultation to assess disease response and detect relapse.

Currently, there are so many miRNAs having therapeutic roles in BCNHL patients, particularly patients suffering from DLBCL disease have

been identified. A set of miRNAs, consisting of miRNA-222, miRNA-181a, miRNA-129-5p, and miRNA-18a, has been shown to have prognostic value for DLBCL patients (127). On the other hand, eight miRNAs were found to correlate with patient survival. Patients with down regulated miRNA-21, miRNA-23A, miRNA-27A, and miRNA-34A expression had an inferior overall survival (OS), while patients with low levels of miRNA-19A, miRNA-195, and miRNA-LET7G had a shorter event-free survival (EFS). Patients with low expression of miRNA-127 had low OS and

Table 2 Summary of miRNAs having prognostic role in BCNHLs*

MiRNA	Subtype	Expression level	Role	Reference
miRNA-21	de novo DLBCL	Increased	Prognostic-longer relapse-free survival	(69, 76)
miRNA-155	ABC-DLBCL	Increased	Prognostic-treatment failure	(14)
miRNA-125b, -130a	DLBCL	Increased	Prognostic-poor outcome	(57)
miRNA-18a, -181a and -222	DLBCL		Prognostic	(128)
miRNA-106b, -1181, -124, -1299, -25, -33b, -432, -551b, -629, -652, -654-3p, -671-5p, -766, -877, -93, -93	DLBCL	Increased	Prognostic -Predictive of response to treatment	(130)
miRNA-223, -217, -222, -221	FL	Increased	Prognostic	(123)
miRNA-29	MCL	Increased	Prognostic	(110)
miRNA-21, -23a, -27a and -34a	DLBCLs	Down regulated	Poor OS time	(15)
miRNA-19a	DLBCLs	Decreased	Shorter EFS time	(15)
miRNA-195, -let7g	DLBCLs	Decreased	Longer EFS time	(15)
miRNA-92a	DLBCLs	Decreased	A high relapse rate	(69)
miRNA-127	DLBCLs	Decreased	Poor OS and EFS	(15)

**Abbreviations: miRNA, microRNA; DLBCL, diffuse large B-cell lymphoma; GCB, germinal center B-cell; ABC, activated B-cell like; OS, overall survival; EFS, event free survival; RCHOP, rituximab, cyclophosphamide; RFS, relapse free survival*

EFS. Increased expression of miRNA-18a was associated with shorter OS whereas increased expression of miR-181a was seen in patients with longer EFS. In contrast, higher expression of miANA-222 was associated with shorter EFS (128, 129).

MiRNA-21, has been detected in the sera of DLBCL patients and has been suggested as an independent prognostic indicator in primary DLBCL (76, 78). Patients with down regulated miRNA-21, miRNA-23a, miRNA-27a and miRNA-34a expression levels had inferior overall survival (OS). In contrast, event free survival (EFS) was found influenced by low expression levels of miRNA-19a (shorter EFS), miRNA-195 and let-7g (longer EFS, respectively). A poor OS is most strongly correlated with decreased expression of miRNA-21 and miRNA-27a. In addition to miRNA-127, EFS is most strongly influenced by let-7g and miRNA-19a. A reduced expression level of let-7g is contributed to significantly longer EFS whereas a reduced expression level of miRNA-19a correlated with significantly shorter EFS. In conclusion, reduced expression levels of six miRNAs (miRNA-19a, miRNA-21, miRNA-23a, miRNA-27a, miRNA-34a and miRNA-127) identified as poor EFS and/or OS indicators, whereas the opposite is true for miRNA-195 and let-7g. A down-regulated expression level of this miRNA correlates with poor survival prognosis (78). (Table 2)

CONCLUSION AND RECOMMENDATIONS

The importance of miRNAs in cancer biology is through controlling expression of their target mRNAs to facilitate tumor growth, invasion, angiogenesis and immune evasion. MiRNAs are very important molecule in the pathogenesis, diagnosis and prognosis of BCNHL patients since they are easy to detect, are relatively stable during sample handling. They are important determinants of cellular processes controlling pathogenesis, progression, and response to treatment of several types of cancers including B-cell malignancies through translational repression and transcriptional degradation. As such, they can be taken as one of the important diagnostic and prognostic biomarkers available so far. However, integrating these biomarkers into clinical practice effectively and precisely in daily practice is challenging. Despite these challenges, there are many reasons to be optimistic that novel biomarkers will facilitate better algorithms and strategies as we enter a new era of precision medicine to better refine diagnosis, prognostication, and rational treatment design for patients with lymphomas.

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Abbreviations

***ABC**: Activated B-cell*

***AID**: Activation-Induced Cytidine Deaminase*

***BCNHL**: B-Cell Non-Hodgkin Lymphomas*

***BCL**: B-Cell lymphoma; BCR: B-Cell Receptor*

***BL**: Burkitt's lymphoma*

***CCND**: Cyclin D1*

***CSR**: Class Switch Recombination*

***DLBCL**: Diffuse Large B-Cell Lymphoma*

***DNA**: Deoxyribonucleic Acid*

***EFS**: Event free survival*

***FL**: Follicular Lymphoma*

***GC**: Germinal Center*

***HL**: Hodgkin's Lymphoma*

***IgH**: Immunoglobulin Heavy Chain Genes*

***LP**: Lymphocyte-Predominant*

***MCL**: Mantle Cell Lymphoma*

***miRNA**: microRNA*

***miRISC**: miRNA-associated RNA-Induced Silencing Complex*

***MYC**: Myelocytomatosis*

***NMZL**: Marginal Zone Lymphomas*

***NHL**: Non-Hodgkin Lymphoma*

***OS**: Overall survival*

***RNA**: Ribonucleic Acid*

***RAG**: Recombination Activating Gene*

***SHM**: Somatic Hypermutation*

***V(D)J**: Variable, diversity and joining*

***WHO**: World Health Organization*

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Authors' contributions

ZG and MM drafted the manuscript. ZG, FA and MM participated in the design of the study. ZG conceived of the study and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

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