Blood and Lymphatic Cancer: Targets and Therapy

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REVIEW

MicroRNA dysregulation in B-cell non-Hodgkin lymphoma

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Abstract: B-cell non-Hodgkin lymphomas (NHLs) are lymphoproliferative disorders that can arise at different stages of B-cell development. Even though molecular classification of NHL has allowed for more accurate recognition of distinct aggressive lymphoma subtypes, many patients still fail to respond to standard therapy. As such, there is a need to identify biomarkers and therapeutic targets that can lead to more specific treatments for each NHL patient's disease. MicroRNAs (miRNAs) are small, 17–25 nt RNA molecules that regulate gene expression at the posttranscriptional level. miRNA expression and function is often coordinately dysregulated in NHL, and consequently results in each NHL disease type harboring a distinct miRNA expression signature. miRNA dysregulation may be a consequence of several mechanisms, ranging from dysregulation of the DNA sequences encoding the miRNA to transcriptional regulation of miRNA loci, to dysregulation of the miRNA biogenesis pathway or dysregulation of messenger RNA (mRNA) targets. This coordinated dysregulation of miRNA expression systematically results in the activation of several oncogenic pathways, and consequently the reprogramming of B-cell NHL transcriptomes. The widespread dysregulation of miRNAs suggests that miRNAs may be used as a diagnostic and prognostic tool, and also as actionable drug targets. In this review, we summarize the miRNA profiles of the most common B-cell NHLs, discuss the causes and consequences of miRNA dysregulation, and consider the prospects of miRNA-based biomarkers and therapeutic targets in NHL.

Keywords: miRNA, non-Hodgkin lymphoma, dysregulation, therapy

Introduction

B-cell non-Hodgkin lymphomas (NHLs) are a group of lymphoproliferative disorders that can arise at different stages of B-cell development.[1] Classification of NHLs has mostly been based on immunohistochemical staining and the presence of particular genomic translocations. More recently, molecular profiling has revealed that some NHL subtypes, which are indistinguishable under the microscope, arise from different B-cell developmental stages and utilize distinct oncogenic programs.[2,3] Even though molecular classification of NHL has allowed for more accurate recognition of distinct lymphoma subtypes, many patients still fail to respond to standard therapy.[4] This is likely due to the inherent molecular heterogeneity within each NHL type and the unclear distinctions between NHL types. As such, the identification of other biomarkers and therapeutic targets can offer a better prognosis for each NHL patient.

One category of putative biomarkers and therapeutic targets for NHL and other cancers is the microRNAs (miRNAs). miRNAs are small, 17–25 nt RNA molecules that regulate gene expression at the posttranscriptional level. They were first discovered

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in the context of regulating developmental gene expression patterns in *Caenorhabditis elegans*.[5] Since then, many miRNA species have been identified; an online repository, mirBase (version 19), lists 25,141 distinct mature miRNAs in 193 species.[6] miRNA genes are transcribed into long primary miRNA transcripts (pri-miRNAs), which are then processed in the nucleus to ~70 nt pre-miRNAs by DGCR8 and the RNase III enzyme Drosha. Pre-miRNAs are then exported to the cytoplasm by exportin 5 and further processed by Dicer to ~22 nt double-stranded miRNA duplexes. Each double-stranded duplex is loaded onto the Argonaute protein of a miRNA-induced silencing complex (miRISC) and rapidly unwound by helicase.[7] The mature miRNA acts by directing the miRISC to complementary miRNA binding sites (MBSs) located on messenger RNAs (mRNAs) in order to induce cleavage or translational repression of these mRNA targets. This posttranscriptional regulatory process is known as miRNA-mediated regulation (MMR) and is reviewed in detail by Krol et al.[8] Perfect complementarity of the miRNA seed region to its mRNA target is typically necessary for mRNA cleavage. In cases where there is imperfect complementarity, only translational repression is achieved (Figure 1). Although it was initially understood that miRNA target the 3′-untranslated regions (UTRs) of mRNA, miRNA can also target the 5′-UTR and coding regions to elicit translational repression[9] or enhancement.[10]

miRNA:mRNA interactions are complex. A given miRNA may have multiple (up to several hundred) gene targets, and 60% of mRNAs have binding sites for multiple miRNAs in their 3′-UTRs.[11] Currently, mirTarBase has enumerated a total of 3576 experimentally verified interactions between 657 miRNAs and 2297 target genes.[12] Not surprisingly, miRNAs have been involved in the regulation of numerous biological processes, including cellular growth, differentiation, and apoptosis, and its dysregulation has been associated with the pathogenesis of diseases such as cancer.[13] Many miRNA signatures in cancers have been identified,[14] some of which comprise genome-wide miRNA profiles that have been shown to be effective at discriminating the differentiation state and developmental lineage of tumors with higher accuracy than

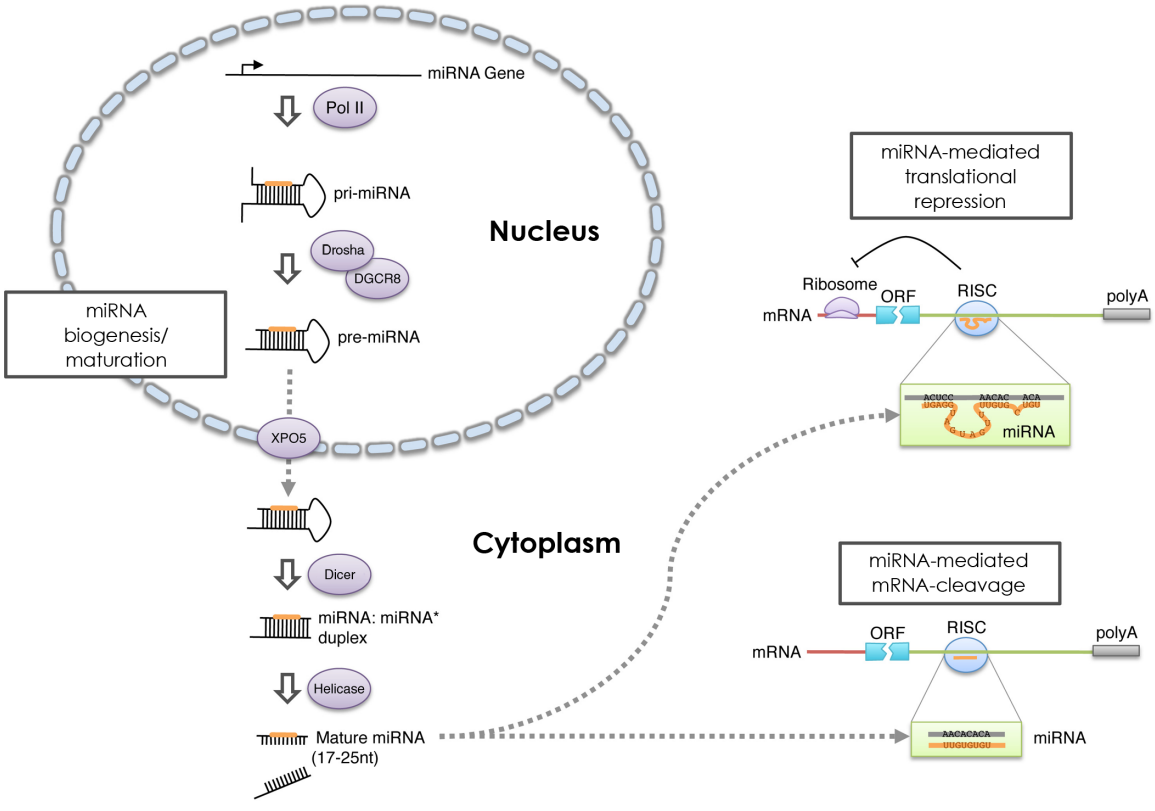

Figure 1 miRNA biogenesis and function.
Notes: miRNA are transcribed in the nucleus into pri-miRNA, which are processed by the Drosha and DGRC8 complex. The premiRNA are then exported to the cytoplasm by XPO5 and further processed by Dicer into miRNA:miRNA* duplexes. Helicase unwinds the duplex, leaving the mature miRNA strands free to associate with the RISC complex to direct mRNA targeting. miRNA:mRNA interacting pairs with perfectly complementary sequences result in the cleavage of target mRNA, whereas partial complementarity achieves translational repression.
Abbreviations: DGRC8, DiGeorge syndrome critical region gene 8; ORF, open reading frame; PolII, RNA polymerase II; polyA, polyadenylic acid tail; RISC, RNA-induced silencing complex; XPO5, Exportin 5.

mRNA profiles.[15] The role of miRNAs in B-cell lineage and development has been reviewed by Fernando et al[16] and Sandhu et al.[17]

Underlying the aberrant expression of miRNA are various mechanisms of miRNA dysregulation, including structural alterations, chromatin remodeling, aberrant transcription factor activity, and disruptions to the miRNA biogenesis pathway. In 2002, Calin et al[18] provided the first evidence of the involvement of miRNA dysregulation in the pathogenesis of B-cell cancers, where they revealed that a genomic deletion at chromosome 13q14 resulted in the loss of miR-15 and miR-16 expression in 68% of B-cell chronic lymphocytic leukemia cases. Since then, NHL molecular profiling efforts have begun to examine the causes and consequences of miRNA dysregulation, and these efforts were first reviewed by Lawrie.[19] Specific miRNAs have been found to characterize various subtypes of NHL and have essential roles in B-cell differentiation and lymphomagenesis,[20–22] and their associations with the pathogenesis of NHL has recently been reviewed by Auer[23] and Di Lisio et al.[24] The frequency of aberrant expression of miRNA NHL subtypes suggests that drug therapy aimed at correcting the expression of these dysregulated miRNA, whether by directly modulating miRNA levels or by targeting the dysregulated miRNA regulatory mechanism, could improve patient survival. In this review, we summarize the miRNA profiling efforts that have identified dysregulated miRNA in the most common B-cell NHLs (Table 1). We then focus our discussion on the causes and consequences of miRNA dysregulation. Finally, we conclude with future prospects of miRNA-based biomarkers and therapeutic targets in NHL.

NHL types have distinct miRNA expression profiles

Diffuse large B-cell lymphoma (DLBCL)

DLBCL is the most common kind of NHL, accounting for almost 30%–40% of newly diagnosed lymphomas.[1] DLBCL tumors are characterized by upregulated expression of miR-150, miR-17-5p, miR-145, and miR-328 when compared with samples from normal lymph nodes and follicular lymphoma (FL).[25] Since miRNA expression tends to be tissue specific, miRNA expression profiles differ based on the primary tumor site. When miRNA expression was compared between central nervous system, testicular, and nodal DLBCL samples, miR-17 was upregulated in DLBCL

Table 1 miRNA expression signatures of the most common NHLs

Disease	Subtype	Upregulated miRNA	Downregulated miRNA	Reference
DLBCL	ABC and GCB	miR-150, miR-17-5p, miR-145, and miR-328	–	25
	ABC vs GCB	miR-155, miR-21, miR-221	–	29
	GCB	miR-17-92 Cluster	–	27
	ABC vs GCB	miR-146a, miR-146b, miR-21, miR-155, miR-500, miR-22, miR-363, miR-574	–	21
	ABC vs GCB	miR-17, miR-19b, miR-20a, miR-29a, miR-92a, miR-106a, miR-720, miR-1260, miR-1280	–	28
	Central nervous system	miR-17	–	26
	Testicular	miR-127	–	26
	Transformed from FL	miR-223, miR-217, miR-222, miR-221, let-7i, let-7b	–	31
FL		miR-9, miR-9*, miR-301, miR-338, miR-213	–	25
		miR-193a, miR-193b, miR-345, miR-513b, miR-574, miR-54, miR-663, miR-1287, miR-1295, miR-1471	miR-17, miR-30a, miR-33a, miR-106a, miR-141, miR-202, miR-205, miR-222, miR-301b, miR-431, miR-570	30
BL	eBL and sBL vs DLBCL	miR-371, miR-185, miR-93, miR-326, miR-497, miR-26b, miR-339, miR-485, miR-9, miR-193a, miR-448, miR-202, miR-483, miR-26a, miR-328, miR-192, miR-429, miR-324, miR-340, miR-105, miR-124	miR-221, miR-155, miR-146a, miR-146b, miR-26b, miR-23a, miR-30d, miR-107, miR-103, miR-222, miR-26a, miR-30a, miR-142, miR-23b, miR-342, miR-29b, miR-34b	33
MCL		miR-17-92, miR-106b, miR-93 and miR-25, miR-617, miR-370, miR-654, mrR-124a, miR-155, miR-302c, miR-345, miR-373* and miR-210	miR-150 and miR-142, miR-31, miR-148a, miR-27b	101
CLL			miR-15, miR-16	18

Notes: The subtype column indicates which subgroups within the disease were compared against when observing for differential expression of miRNA. If no comparator is stated, the disease type was compared against an equivalent of normal B-cells.

Abbreviations: ABC, activated B-cell-like subtype; BL, Burkitt's lymphoma; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; eBL endemic BL subtype; FL, follicular lymphoma; GCB, germinal center B-cell-like subtype; MCL, mantle-cell lymphoma; sBL, sporadic BL subtype.

tumors arising from within the central nervous system, while miR-127 was upregulated in DLBCL tumors arising from within the testis.[26] Although DLBCL cases have a common morphology, they are noted for their striking clinical and molecular variability. Gene expression profiling has revealed at least three DLBCL subtypes that have different genetic aberrations and clinical outcome.[3] Activated B-cell-like (ABC) subtype tumors arise from plasmablasts, while germinal center B-cell-like (GCB) subtype tumors arise from germinal center B-cells. These two subtypes can be distinguished not only by gene expression profiles but also by distinct miRNA expression profiles. In particular, the miR-17-92 cluster of miRNAs are significantly upregulated in GCB-DLBCL tumors compared with ABC-DLBCL and B-cell controls.[27,28] As well, miR-155, miR-221, and miR-21 are more highly expressed in ABC-DLBCL when compared with GCB-DLBCL.[21,29]

Follicular lymphoma (FL)

FL is another NHL that is also derived from germinal center B-cells. A comparison between miRNA expression profiles of FL and DLBCL revealed several miRNA that are overexpressed in both cancers (miR-155, miR-210, miR-106a, miR-149, and miR-139) when compared with normal lymph nodes. This suggests that these frequently overexpressed miRNAs could play significant roles in lymphomagenesis.[25] However, despite this similarity, FLs still have a miRNA signature that is distinct from DLBCL – one that is related to cell proliferation and tumor response. When comparing FL tumor cells with normal germinal center B-cells, miR-20a/b and miR-194 are overexpressed in FL and they target cell proliferation inhibitors *CDKN1A* and *SOCS2*, respectively.[30] Although considered an indolent disease, a significant proportion of FL cases may undergo a transformation to an aggressive DLBCL with a poorer outcome. A miRNA signature consisting of four upregulated miRNAs (let-7b, let-7i, miR-221, and miR-222), and two downregulated miRNAs (miR-223 and miR-217), when comparing transformed DLBCL cases to normal DLBCL cases, can predict this transformation.[31]

Burkitt's lymphoma (BL)

BL is an aggressive NHL characterized by a high degree of proliferation of the malignant cells. Most BL tumors demonstrate dysregulation of the *Myc* gene as a consequence of chromosome 8q24 translocations that place *Myc* under the regulation of immunoglobulin gene regulatory elements.[32] There are three BL subtypes: a sporadic subtype that is diagnosed in developed countries, the Epstein–Barr virus (EBV)-associated endemic subtype, and an HIV-associated subtype. Despite differences in their geographical occurrence and incidence of viral infection, these BL subtypes represent a uniform biological entity: molecular profiling revealed that sporadic and endemic subtypes only differ marginally by the expression of six miRNA and that the viral-induced nature of BL tumors had no significant impact on miRNA expression.[33] However, just as BL tumors and DLBCL tumors differ in their protein-coding gene expression profiles,[34] BL tumors also have a miRNA signature that is distinct from that of DLBCL. Unlike DLBCL, BL tumors underexpress miR-155 compared to normal B-cells.[35]

Mantle-cell lymphoma (MCL)

MCL tumors are relatively more homogeneous and more resistant to chemotherapy than tumors of other lymphomas. MCL tumors harbor the chromosomal translocation t(11;14)(q13;q32), which results in aberrant expression of *CCND1*, a key regulator of the cell cycle. Since MCL is characterized by deregulation of several survival signaling pathways,[36] this translocation alone does not explain all the dysregulation in MCL tumors. At the miRNA level, MCL is characterized by a downregulation of miR-29,[37] miR-15a, and miR-16-1,[38] and an upregulation of the miR-17-92 cluster[39] when compared with normal B-cells.

miRNA dysregulation contributes to tumorigenesis

Dysregulation of miRNA may result in the aberrant expression of miRNA target genes (Figure 2; Table 2), and, in many instances, this disruption of gene expression results in the acceleration of lymphomagenesis. In agreement with this, several miRNAs have expression patterns that have been found to be associated with NHL patient prognosis (Table 3).

miRNA as tumor suppressors

miRNAs that are responsible for repression of genes that would otherwise contribute to tumorigenesis can be classified as tumor suppressors. These tumor-suppressive miRNAs are typically repressed or lost in malignancy. In some instances, this loss results in the miRNA exacerbating the aberrant expression of target genes that may have already been dysregulated by other mechanisms, such as copy number alterations or translocations. For instance, miR-34a is downregulated by Myc, in DLBCL, and the result of this is increased cell proliferation through a FOXP1-dependent

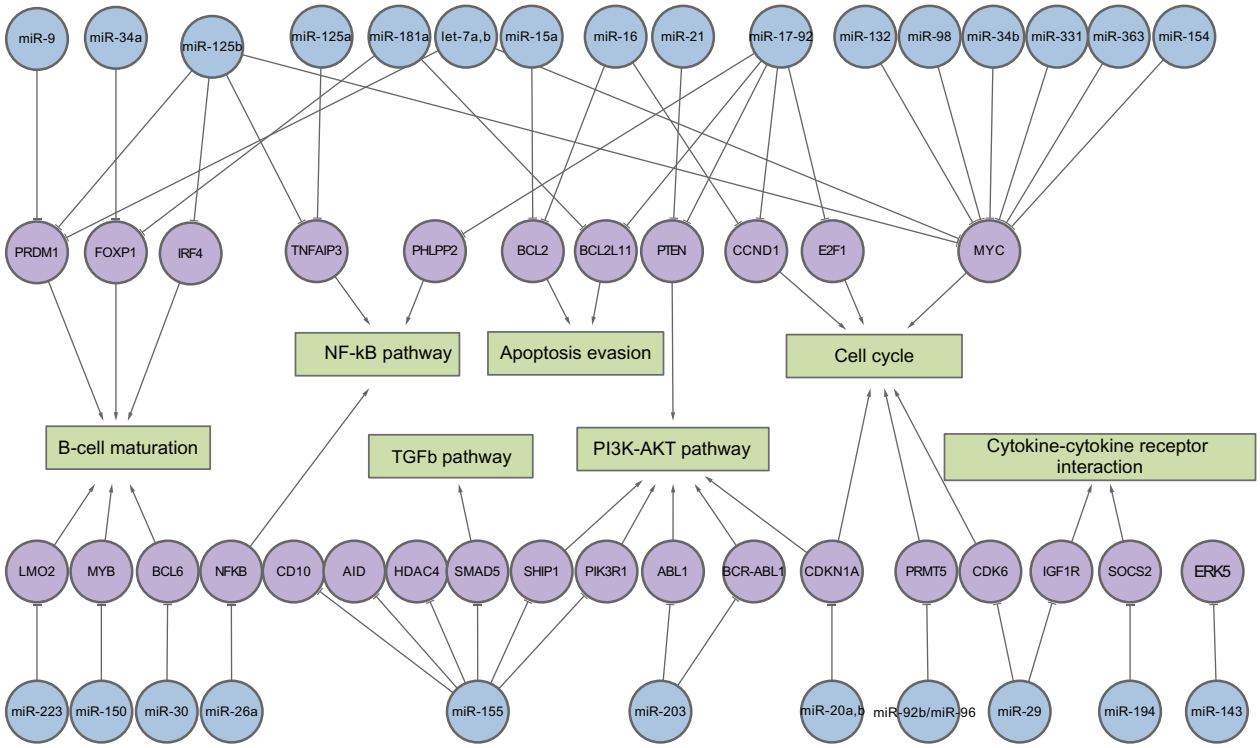

Figure 2 Validated miRNA:mRNA interactions in B-cell non-Hodgkin lymphoma.
Notes: Experimentally determined miRNA:mRNA interactions in B-cell non-Hodgkin lymphoma contexts. Blue circles represent miRNA, purple circles represent genes, and green boxes represent oncogenic pathways or processes affected by the targeted genes.
Abbreviations: AKT, Protein Kinase B; miRNA, microRNA; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; PI3K, Phosphatidylinositide 3-kinase; TGF-b, Transforming growth factor beta.

tumorigenesis pathway.[40] Similarly, miR-15a and miR-16-1 loci are lost in DLBCL[41] and MCL,[42] and this loss contributes to tumorigenesis through the de-repression of their oncogenic targets, including anti-apoptotic *BCL2*, and the cell cycle regulator *CCND1*.[43] In addition, the combinatorial loss of multiple miRNAs could synergistically contribute to tumorigenesis. For instance, a protein that is required for CCND1 activity, CDK6, is also upregulated (amongst other miRNAs) due to the loss of miR-29.[44] Another example is that of the miRNAs that target Myc. In BL, Myc is only successfully de-repressed in the absence of abundant let-7a/b, miR-125b, miR-132, miR-154, miR-331, and miR-363. Interestingly, the expression of these miRNAs is repressed by Myc, suggesting a Myc–miRNA feed-forward loop that may drive tumorigenesis.[45]

miRNA as oncogenes

miRNAs that are overexpressed or amplified in malignancy can result in the repression of tumor-suppressor genes. These miRNAs can be classified as oncogenic miRNA or oncomiRs. For instance, miRNAs from the miR-17-92 cluster are frequently upregulated in NHLs when compared with normal B-cells. Their overexpression facilitates cell proliferation and inhibits apoptosis in B-cells by exerting translational repression on multiple target genes including proapoptotic *BCL2L11* and tumor suppressor *PTEN*.[46] miR-17-92 may also contribute to tumorigenesis by activating members of the PI3K/AKT pathway. In addition, the increased repressive effects of miR-17-92 on its target genes in vivo compared with in vitro suggests that miR-17-92 also regulates the tumor microenvironment, thus accelerating tumorigenesis. In particular, miR-17-92 promotes angiogenesis through suppressing the anti-angiogenic thrombospondin (THBS)-1 and connective tissue growth factor (CTGF), or by inhibiting members of the transforming growth factor (TGF)β pathway.[47]

Since a single miRNA species can regulate the expression of multiple genes, miRNA expression levels must be carefully regulated to ensure cellular homeostasis. Despite its oncogenic effects when overexpressed, miR-17-92 expression is essential for B-cell development – its deletion in mice results in neonatal lethality, congenital cardiac malformations, and improper B-cell development.[48] The same is true of miR-155, where either overexpression or underexpression compared with normal B-cells results in tumorigenesis: underexpression of miR-155 is characteristic

Table 2 Experimentally determined miRNA:mRNA interactions

miRNA	Gene	Context/disease	Comments	Reference
let-7a,b	*MYC*	BL	Cell cycle	45
let-7b	*PRDM1*	DLBCL	B-cell maturation	102,103
miR-125a	*TNFAIP3*	DLBCL	NF-kB pathway	104
miR-125b	*MYC*	BL	Cell cycle	45
miR-125b	*TNFAIP3*	DLBCL	NF-kB pathway	104
miR-125b	*IRF4*	GCB cells	B-cell maturation	21
miR-125b	*PRDM1*	GCB cells	B-cell maturation	21
miR-132	*MYC*	BL	Cell cycle	45
miR-143	*ERK5*	B-cell NHL		105
miR-150	*MYB*	B-cell differentiation	B-cell maturation	106
miR-154	*MYC*	BL	Cell cycle	45
miR-155	*AID*	B-cell		107
miR-155	*AID*	BL	AID induces MYC-IGH translocation	50
miR-155	*CD10*	BL		108
miR-155	*PIK3R1*	DLBCL	PI3K-AKT pathway	51
miR-155	*SHIP1*	DLBCL	PI3K-AKT pathway	109
miR-155	*SMAD5*	DLBCL	TGFβ pathway	52
miR-155	*CD10*	DLBCL		108
miR-155	*HDAC4*	B-cell NHL	Targets BCL6	53
miR-15a	*BCL2*	CLL	Apoptosis evasion	110
miR-16	*BCL2*	CLL	Apoptosis evasion	110
miR-16	*CCND1*	MCL	Cell cycle	43
miR-17-92	*E2F1*	B-cell NHL	Cell cycle	64
miR-17-92	*BCL2L11*	B-cell NHL	Apoptosis evasion	46
miR-17-92	*CCND1*	MCL	Cell cycle	43,81
miR-17-92	*PTEN*	MCL	PI3K-AKT pathway	111
miR-17-92	*PHLPP2*	MCL	NF-kB pathway	47,111
miR-181a	*FOXP1*	DLBCL	B-cell maturation	112
miR-181a	*BCL2L11*	MCL	Apoptosis evasion	113
miR-194	*SOCS2*	FL	Cytokine–cytokine receptor interaction	30
miR-203	*ABL1*	Hematopoietic malignancies	PI3K-AKT pathway	114,115
miR-20a/b	*CDKN1A*	FL	Cell cycle; PI3K-AKT pathway	30
miR-21	*PTEN*	DLBCL	Impacts the PI3K-AKT pathway, thereby affecting cellular sensitivity to the CHOP chemotherapeutic regimen	99
miR-223	*LMO2*	Memory B-cells	B-cell maturation	21
miR-26a	*NFKB*	MCL	NF-kB pathway	101
miR-29	*IGF1R*	MCL	Cytokine–cytokine receptor interaction	37
miR-29	*CDK6*	MCL	Cell cycle	44
miR-30	*BCL6*	B-cell NHL	B-cell maturation	103
miR-331	*MYC*	BL	Cell cycle	45
miR-34a	*FOXP1*	MALT/DLBCL	B-cell maturation	40
miR-34b	*MYC*	BL	Cell cycle	116
miR-363	*MYC*	BL	Cell cycle	45
miR-9	*PRDM1*	B-cell NHL	B-cell maturation	103
miR-92b	*PRMT5*	MCL	Cell cycle	117
miR-96	*PRMT5*	MCL	Cell cycle	117
miR-98	*MYC*	BL	Cell cycle	118

Abbreviations: BL, Burkitt's lymphoma; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; GCB, germinal center B-cell-like subtype; MALT, mucosa-associated lymphoid tissue type; MCL, mantle-cell lymphoma; NHL, non-Hodgkin lymphoma.

of BL, while its overexpression is frequent in DLBCL.[49] The loss of miR-155 in BL results in an overabundance of activation-induced deaminase (AID), which is involved in the deamination of cytosine residues and introduction of U:G mismatches in DNA and consequently results in DNA instability. As such, an abundance of AID typically results in increase of Myc-IGH translocations and thus the aberrant expression of oncogenic Myc.[50] On the other hand, an overabundance of miR-155 contributes to tumorigenesis by dysregulating the expression of members

Table 3 miRNA associated with patient prognosis

miRNA	Disease	Clinical variability	Reference
miR-148a	DLBCL	High expression after R-CHOP chemotherapy correlates with poor outcome	123
miR-151	DLBCL	High expression after R-CHOP chemotherapy correlates with poor outcome	123
miR-155	DLBCL	High expression correlates with poor outcome, and indicates a better response to rituximab treatment	124
miR-181a	DLBCL	High expression after R-CHOP chemotherapy correlates with poor progression-free survival	112
miR-18a	DLBCL	High expression after R-CHOP chemotherapy correlates with poor overall survival	112
miR-200c	DLBCL	High expression correlates with poor outcome	125
miR-20b	MCL	High expression correlates with poor outcome	101
miR-21	DLBCL	High expression correlates with poor outcome	29
miR-221	DLBCL	High expression after R-CHOP chemotherapy correlates with poor outcome	123
miR-222	DLBCL	High expression after R-CHOP chemotherapy correlates with poor outcome	21,123
miR-222	DLBCL	High expression after R-CHOP chemotherapy correlates with poor progression-free survival	112
miR-222	DLBCL	High expression after R-CHOP chemotherapy correlates with poor outcome	123
miR-28	DLBCL	High expression after R-CHOP chemotherapy correlates with poor outcome	123
miR-29	MCL	High expression correlates with poor outcome	44
miR-331	DLBCL	High expression after R-CHOP chemotherapy correlates with poor outcome	123
miR-451	DLBCL	High expression after R-CHOP chemotherapy correlates with poor outcome	123
miR-491	DLBCL	High expression after R-CHOP chemotherapy correlates with poor outcome	123
miR-93	DLBCL	High expression after R-CHOP chemotherapy correlates with poor outcome	123
Profile of miRNA	FL	High expression correlates with poor outcome	30

Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle-cell lymphoma; NHL, non-Hodgkin lymphoma.

of the PI3K-AKT pathway,[51] the TGFβ pathway,[52] and other transcriptional regulators.[53] These findings illustrate the prevalence of miRNA dysregulation in NHLs and emphasize the importance of maintaining specific levels of miRNA expression within the cell.

Causes of miRNA dysregulation

Copy number alterations

miRNA dysregulation may result from a variety of causes (Table 4). miRNAs can be dysregulated due to changes in the underlying DNA that encodes them. One category of such genetic alterations is DNA copy number alterations. Due to the nature of copy number alterations affecting large segments of genomic DNA, the same aberration may affect clusters of several miRNAs. A genome-wide study of miRNA expression and copy number in DLBCL identified 63 individual miRNAs, including 28 miRNA clusters, that displayed recurrent copy number changes. One-third of these miRNAs were also found to be part of a tumor-driven classifier, suggesting the significance of copy number alterations in miRNA dysregulation in DLBCL.[41]

Since copy number alterations tend to be NHL subtype-specific, miRNA dysregulation due to copy number alterations vary across B-cell NHL types. In BL, the deletion at chromosome 14q32 results in the downregulation of miR-203, miR-134, and miR-154 when compared with normal lymph nodes.[45] In DLBCL, the amplification at chromosome 11 results in the upregulation of miR-100, miR-125b-1, and miR-130a.[41] Disruption of chromosome X copy number is common in DLBCL,[54] and this results in several miRNAs encoded on chromosome X being frequently amplified (miR-513, miR-223, miR-424).[41] This suggests that tumors with chromosome X disruption may acquire a growth advantage through miRNA dysregulation.

There are particular copy number alterations that are more frequent in particular subtypes of DLBCL. All DLBCL tumors have ten- to 30-fold higher copy numbers of miR-155 when compared with normal circulating B-cells, but ABC-DLBCL two- to three-fold higher levels of miR-155 than GCB-DLBCL. Not surprisingly, upregulation of miR-155 in ABC-DLBCL is attributed to the amplification of chromosome 21q21, which has been associated with inferior outcome in NHL patients.[49] Similarly, gains of chromosome 12q are more frequently associated with tumors classified as the GCB-DLBCL[54] or MCL.[47]

Translocations

miRNAs are frequently located at fragile sites and genomic regions involved in cancers,[55] and may be a cause of miRNA loss or gain. In DLBCL, the t(3;7)(q27;q32) translocation fuses *BCL6* to a noncoding region at *FRA7H* near miR-29, thereby downregulating the expression of miR-29.[56,57] Similarly, a complex *BCL6* rearrangement t(3;13)(q27;q31)t(12;13)(p11;q31) in DLBCL cells results in a ITPR2-BCL6 chimeric fusion gene rearrangements and places the miR-17-92 cluster antisense within this fusion.

Table 4 Causes of miRNA dysregulation

miRNA	Cause of dysregulation	Disease	Reference
let-7e, miR-15a, miR-16, miR-22, miR-23a, miR-23b, miR-24, miR-26a, miR-26b, miR-29a, miR-29b, miR-29c, miR-30c, miR-30e, miR-34a, miR-99b, miR-101a, miR-125b, miR-134, miR-139, miR-140, miR-142-3p, miR-144, miR-146a, miR-150, miR-195, miR-207, miR-210, miR-215, miR-223, miR-342, miR-451, miR-466, miR-467, miR-489, miR-494, let-7a, miR-124, miR-148, miR-155, miR-196, miR-346	Transcription factor dysregulation (MYC)	BL	63
miR-1204	Fragile DNA (translocation) (8q24)	BL	60
miR-124a	DNA hypermethylation	B-cell NHL	68
miR-143, miR-145	Copy number deletion (5q32)	Multiple cancers	119
miR-155	Copy number amplification (21q21)	DLBCL	49
miR-155	Transcription factor dysregulation (PKC and NF-kB) and biogenesis	BL	70
miR-155, miR-20b, miR-221, miR-151-3p, miR-222, miR-29b/c, miR-106a	Viral infection	DLBCL	74
miR-15a/16-1	Copy number deletion (13q14)	DLBCL	41,42
miR-15a/16-1	Transcription factor dysregulation (MYC) through epigenetic modifier (HDAC3)	MCL	38
miR-17-92 cluster	miRNA biogenesis machinery dysregulation	B-cell NHL	78
miR-17-92 cluster	Copy number amplification (12q) (13q31)	Multiple cancers; DLBCL; MCL; BL	39,41, 119,120
miR-17-92 cluster	Fragile DNA (translocation)	DLBCL	58
miR-17-92 cluster	Transcription factor dysregulation (MYC)	DLBCL	64
miR-18a (part of miR-17-92 cluster)	miRNA biogenesis machinery dysregulation	B-cell NHL	121
miR-203	DNA hypermethylation	B-cell NHL	69
miR-203, miR-134, miR-154	Copy number deletion (14q32)	BL	45
miR-22, miR-26a, miR-30e/c, miR-146a, miR-150, let-7, miR-195, miR-26b,miR-29a/c	Transcription factor dysregulation (MYC)	B-cell NHL	62
miR-223	Copy number amplification (Xq12)	DLBCL	41
miR-29	Transcription factor dysregulation (MYC) through epigenetic modifier (EZH2 + HDAC3)	MCL	37
miR-29a, miR-29b-1	Fragile DNA (translocation)	DLBCL	56
miR-34a	Transcription factor dysregulation (MYC)	DLBCL	40
miR-424	Copy number amplification (Xq25)	DLBCL	41
miR-424, miR-223, miR-199a-3p, miR-199a-5p, miR-27b, miR-378, miR-26b, miR-23a, miR-23b	Viral infection	DLBCL	74
miR-513	Copy number amplification (Xq27)	DLBCL	41
miR-7, miR-17, miR-18a, miR-19a, miR-19b, miR-20a, miR-20b, miR-92, miR-106a, miR-128b, miR-130b, miR-206, miR-213, miR-370, miR-422a, miR-468	Transcription factor dysregulation (MYC)	BL	63
miR-9	DNA hypermethylation	BL	32
miR-96, miR-182, miR-589, miR-25	Copy number amplification (7q)	DLBCL	122
ebv-miR-BART3, ebv-miR-BART9 and ebv-miR-BART17-5p	Viral infection	DLBCL	73
ebv-miR-BART7, ebv-miR-BART22, ebv-miR-BART10, ebv-miR-BART11-5, ebv-miR-BART16	Viral infection	DLBCL	74
ebv-miR-BHRF1-3	Viral infection	DLBCL	72

Abbreviations: BL, Burkitt's lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; MCL, mantle-cell lymphoma; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; NHL, non-Hodgkin lymphoma; PKC, Protein kinase C.

This translocation results in the upregulated expression of the miR-17-92 cluster.[58] The majority of FL cases (90%) are characterized at the karyotype level by the t(14;18)(q32;q21) translocation – a molecular aberration that is associated with the deregulated expression of miR-16, miR-26a, miR-101, miR-29c, and miR-138.[59] In BL, a translocation often results in the *PVT1* exon 1b region (encoding miR-1204) being fused to the immunoglobulin light chain constant region. This consequently results in the upregulation of miR-1204.[60] Although the consequences of this translocation are unclear, it is of interest as miR-1204 is the miRNA with closest genomic proximity to Myc, and the possible misregulation of both of these genes concurrently may be a synergistic mechanism of lymphomagenesis.

Aberrant transcription factor activity

miRNA dysregulation in NHL can also be a result of a disruption of their expression patterns. Transcription factors are essential in regulating the expression of other genes by binding to transcription factor binding sites that are cis-regulatory elements located in close proximity to the transcription start sites of genes. When the expression of transcription factors that target miRNA loci is dysregulated, the expression of their target miRNA is consequently affected. There are several transcription factors that are dysregulated in lymphomagenesis (Table 4), but the most frequently disrupted is Myc.

Myc is a transcription factor that promotes tumorigenesis by activating and repressing target genes that are involved in cell cycle regulation, cell growth differentiation, metabolism, angiogenesis, and cell adhesion and migration.[61] Given the key role that Myc plays in many pathways of tumorigenesis, it is not surprising that Myc dysregulation is one of the most common abnormalities in cancer. In addition to the regulation of protein-coding genes, a major consequence of Myc upregulation is the extensive reprogramming of miRNA expression patterns in tumors.[62] When comparing the miRNA expression profiles of BL with those of other B-cell lymphomas, BL cases with high expression of Myc displayed a characteristic pattern of Myc-induced miRNA expression: upregulated miRNAs include the miR-17-92 cluster, and downregulated miRNAs include miR-15a and miR-16.[63] Myc as a transcription factor does not only result in the activation of transcription, but also represses the transcription of certain miRNAs. In human and mouse models of B-cell lymphoma, Chang et al[62] observed that overexpression of Myc results in the widespread repression of several miRNAs. Their chromatin immunoprecipitation analysis further identified 11 miRNAs that were repressed by Myc overexpression.

Myc is a transcription factor with many targets, which may sometimes regulate the expression of particular genes through multiple targets. In DLBCL, Myc binds to the promoter of the miR-17-92 cluster on chromosome 13 and activates its transcription. miRNAs from the miR-17-92 cluster then repress the expression of E2F1, a transcription factor that promotes G1-to-S phase progression. Interestingly, Myc also binds to the *E2F1* promoter, thereby directly activating its transcription. The collaborative regulatory action on *E2F1* (upregulation by Myc and downregulation by miR-17-92) suggests that Myc "uses" the miR-17-92 cluster as a means to fine-tune its regulatory mechanism of proliferation.[64] The influence of Myc on miRNA is not limited to the direct binding to its promoters to elicit transcriptional activation or repression. Myc may also affect miRNA expression through the dysregulation of chromatin modifiers that target miRNA loci.

Chromatin modification

Chromatin modification is another mechanism that has a profound effect on the regulation of miRNA expression. Chromatin modification, including DNA methylation, incorporation of histone variants, and posttranslational modifications of histones, imparts epigenetic control of gene expression without disruption to the underlying DNA sequence. These modifications alter the structure of heterochromatin, restricting physical access of nuclear factors, such as transcriptional machinery, to the underlying DNA.[65] DNA methylation refers to the catalyzing of DNA cytosine to methylcytosine by DNA methyltransferase. The presence of additional methyl groups on DNA residues modulates the accessibility of DNA to transcriptional machinery; DNA hypermethylation at gene promoters is associated with the decrease in gene expression.[66] In B-cell NHLs, DNA methylation is dysregulated, and consequently results in the aberrant expression of genes involved in lymphomagenesis.[67] DNA hypermethylation results in the repression of miR-124a expression, which in turn results in the overexpression of oncogenic *CDK6*.[68] Similarly, in several hematological malignancies, DNA hypermethylation results in the repression of miR-203, which enhances the expression of oncogenic *ABL1* and BCR-ABL1 fusion genes.[69] In some instances, DNA hypermethylation could provide an alternative means for Myc activation. In the absence of the Myc-IGH translocation (in BL-translocation-negative cases) miR-9 is hypermethylated, resulting in its downregulation and upregulation of its oncogenic target, Myc.[32]

Histone modifications, unlike DNA methylation, involve the covalent modification of histone residues, rather than of DNA nucleotides. miRNAs may influence histone marks by regulating the expression of histone modifiers. In MCL, miR-15a, miR-16-1, and miR-29 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: Myc binds to and represses HDAC3, an enzyme that is responsible for removing acetyl groups from histone residues. This in turn results in the downregulation of miR-15a/16-1.[38] In a subsequent study by the same group, Myc was observed to work in concert with *EZH2* to repress *HDAC3*, which in turn resulted in the repression of miR-29.[37]

Viral infection

In some cases, miRNA dysregulation can be induced by viral infections. Some variants of NHLs involve the presence of EBV, an oncogenic herpes virus that establishes a latent infection in lymphocytes.[2] EBV readily transforms B-cells into permanently growing cells under certain conditions such as immunosuppression. EBV is implicated in 95% of endemic BL cases and 15% of DLBCL cases. EBV-transformed cells include at least 44 mature viral miRNAs that target viral and endogenous genes.[71] For example, three viral miRNAs (ebv-mir-BHRF1-3) are upregulated in EBV-positive tumors, and are responsible for the downregulation of *CXCL11*. This targeted suppression of *CXCL11* by a viral-encoded miRNA may serve as an immunomodulatory mechanism for tumorigenesis.[72] EBV-specific miRNAs, ebv-mir-BART3, ebv-mir-BART9, and ebv-mir-BART17-5p, are upregulated in tumors and target *BCL6*, a transcription factor that typically represses many genes involved in lymphomagenesis. *BCL6* is also disrupted in NHLs by translocations, but their repression by viral miRNA suggests other mechanisms by which BCL6 could be repressed.[73] In addition to introducing viral miRNAs into cells, EBV induces and represses the expression of several endogenous cellular miRNAs. When comparing EBV-positive with EBV-negative DLBCL cases, a distinct miRNA expression profile for EBV-positive DLBCL cases revealed nine upregulated miRNAs and seven downregulated miRNAs.[74] Similarly, in splenic marginal zone lymphoma (SMZL), a less common B-cell lymphoma, tumor-suppressive miR-26 was found to be downregulated in chronic hepatitis C virus (HCV)-positive tumors compared with HCV-negative tumors.[75] These results suggest that the oncogenic potential of viruses could be, in part, mediated by miRNAs.

miRNA-specific mechanisms of dysregulation

The above mechanisms of dysregulation can also affect protein-coding genes; the following, however, is a miRNA-specific dysregulation mechanism. Dysregulation of miRNA expression can also occur posttranscriptionally during miRNA biogenesis.[76] Both Drosha and Dicer are enzymes that play key roles in processing pri- and pre-miRNA, respectively, in the miRNA biogenesis pathway. They are not only required for the biogenesis of endogenous miRNAs in B-cells, but are also essential for the biogenesis of miRNAs introduced by EBV.[77] In particular, the expression level of Dicer is crucial for the maintenance of cellular homeostasis. The loss of one functional allele of Dicer in BL cells[70] and DLBCL tumors[49] results in impaired miRNA biogenesis and, consequently, an accumulation of the pri-miRNA, which cannot be processed into mature miRNA. However, the complete loss of Dicer prevents lymphomagenesis and is selected against in tumors: one functional allele of *Dicer* is required for the tumor survival, whereas deletion of both alleles of *Dicer* in B-cells does not promote tumorigenesis, but instead induces apoptosis.[78]

Specific RNA-binding proteins are also required for the biogenesis of some miRNA. This is illustrated by the biogenesis of miR-18a from the miR-17-92 cluster. Although all six miRNAs from this cluster are transcribed together as a polycistron, miR-18a additionally requires the presence of hnRNP A1 for its maturation.[79] Although the targets of each of the members of this miRNA cluster do overlap because of the high degree of conservation between the miRNA members, this finding suggests that therapeutically targeting miR-18a alone could fine-tune the expression levels of miR-17-92 targets.

More recently, an atypical miRNA biogenesis pathway has been found in germinal center B-cells, where miRNA can be derived from transfer RNA (tRNA) molecules that undergo Dicer cleavage. Of interest is the tRNA-derived miRNA CU1276 that is strongly downregulated in GCB-lymphomas compared with normal germinal center B-cells, and targets *RPA1*, a modulator of DNA damage response in the germinal center.[80] This finding describes a novel pretranslational regulatory potential for tRNA fragments that are abundantly expressed in cells, and suggests that tRNAs may be relevant to miRNA-based therapies.

Synergy of mechanisms of dysregulation

An individual miRNA may be dysregulated by multiple mechanisms, but the co-occurrence (and implied synergy)

of these mechanisms of dysregulation could exacerbate the aberrant expression of the miRNAs. miRNAs from the miR-17-92 cluster are the most frequently overexpressed in B-cell NHLs.[19] This is likely due to the variety of mechanisms that can result in their dysregulation: copy number amplifications, translocations, aberrant transcriptional regulation by Myc, and the presence of specific RNA-binding proteins.[79] Similarly, the characteristic downregulation of miR-155 in BL tumors is achieved by two mechanisms, one at the transcriptional level and one at the post-processing level. At the transcriptional level, repression is mediated by transcription factors Protein kinase C and nuclear factor kappa-light-chain-enhancer of activated B cells, while at the post-processing level, there is an accumulation of the pri-miRNA of miR-155 (*BIC*) due to the inability of BL cells BIC to process mature miRNA.[70] These findings underscore the significance of the dysregulation of these miRNA in lymphomagenesis, but, more importantly, they indicate that therapies can be designed to address their aberrant expression at either the transcriptional or biogenesis levels.

In addition to dysregulation of miRNA expression, miRNA-mediated repression can be disrupted as a consequence of dysregulation and mutation of mRNA targets. For instance, MCL tumors preferentially express an mRNA transcript variant that arises as a consequence of point mutations and genomic deletions. This truncated splice variant lacks the miR-16 binding site, thus escapes MMR, and results in an upregulation of truncated *CCND1*.[81] Sandberg et al[82] and Mayr et al[83] have also demonstrated more generally that proliferating cells tend to produce mRNA transcripts with shorter 3′-UTRs, suggesting that many more such mRNA splice-variant specific miRNA:mRNA interactions still have yet to be discovered.

The therapeutic potential of miRNA

miRNA as a diagnostic tool in NHL

Current NHL classification and diagnostic techniques rely on a combination of morphologic, biologic, and clinical features to distinguish between NHL subtypes, and thus are unable to accurately classify NHL tumors into specific subtypes.[2] Moreover, recent evidence has challenged the idea of a precise separation between NHL subtypes and suggests that each NHL case should be treated based on its genetic and molecular characteristics. For instance, molecular aberrations may be insufficient to differentiate NHL subtypes – DLBCL and high-grade FL share the t(14;18) translocation – but grade 3b FL has a higher relapse rate and may require a different treatment regimen.[84] Likewise, although t(8;14) translocations characterize most cases of BL, there are some translocation-negative BL cases that still display Myc-mediated gene and miRNA dysregulation.[32,59]

miRNAs are a promising new class of biomarkers that may supplement NHL diagnosis. Their suitability as biomarkers stems from their widespread dysregulation and characteristic expression profiles. One group has demonstrated the feasibility of the expression of the six miRNAs from the miR-17-92 cluster in accurately distinguishing between GCB-DLBCL and FL cases.[85] Several studies[33,35,86] have determined that miR-155 expression can distinguish BL from DLBCL cases.

Unlike mRNA, miRNAs are stable in vitro and long-lived in vivo, and can be detected in urine, peripheral blood, and formalin-fixed paraffin-embedded (FFPE) tissues.[87] Tissue samples collected during surgery, as well as biopsies, are often fixed in FFP, but extracting nucleic acids from FFPE tissue has been problematic. However, since there are several methods that can reliably profile miRNAs in FFPE tissue, including quantitative polymerase chain reaction, in situ hybridization,[75] and microarrays,[88] miRNA research in archival tissue is rapidly gaining popularity.

Circulating miRNAs have several characteristics that make them suitable noninvasive diagnostic biomarkers: blood serum miRNA are resistant to RNase digestion and other harsh conditions such as extreme pH, boiling, extended storage, and multiple freeze–thaw cycles.[89] When considering the circulating miRNA profiles of serum from DLBCL patients compared with healthy subjects, one study found elevated expression of miR-155, miR-210, and miR-21,[90] and a subsequent study additionally found elevated expression of miR-15a, miR-16-1, and miR-29c and decreased expression of miR-34a.[91] As such, the utility of circulating miRNAs as noninvasive biomarkers in NHL diagnosis is promising.

miRNA as a prognostic tool in NHL

miRNAs may also serve as noninvasive biomarkers at the prognostic level, where they can be used to predict patient outcome and to monitor patients after chemotherapy. Several studies have identified miRNAs that have expression profiles associated with patient outcomes (Table 3). Of note is a study that has found that high miR-21 levels in the serum of DLBCL patients indicates relapse-free survival.[90] Similarly, another group found that the downregulation of miR-92a in blood plasma of complete-response NHL patients indicates an increased probability of disease relapse.[92]

Correcting for aberrantly expressed miRNA

Given the large impact of miRNA on tumorigenesis, miRNA-based cancer therapeutics are being designed to correct the aberrant expression of miRNA. Miravirsen (Santaris Pharma A/S, Hørsholm, Denmark), the first miRNA-based therapeutic tested in humans, is currently undergoing Phase II clinical trials for the treatment of HCV infections.[93] miRNA therapy is advantageous because it is extremely specific in its targeting: a partial complementary base-pairing interaction is required between the miRNA ~7 nt seed sequence and mRNA. Moreover, a single miRNA can act as a "master switch," and thus can concurrently target numerous mRNA targets and may be useful where several oncogenic pathways need to be targeted simultaneously.[94] As such, the majority of currently developed miRNA-based therapeutics take the form of miRNA mimics or miRNA inhibitors that can normalize the expression of their target genes (reviewed in Iorio and Croce[95]). In the context of NHLs, one study has successfully demonstrated Locked nucleic acid-mediated anti-miR-155 silencing in B-cell lymphomas in mice.[96] However, the development of miRNA therapeutics in NHLs is still in its infancy, probably due to the confounding results of miRNA therapeutic experiments. For instance, in testing the tumor-suppressor activity of miR-34a, one study reported that, not only did miR-34a not inhibit cell proliferation, it resulted in proapoptotic activity by dysregulation of the c-MYC/p53 regulatory axis.[97] This suggests that the attribute of miRNA as a master switch could result in many off-target effects, which we currently lack a complete understanding of.

Despite this, therapeutically targeting the causes of miRNA dysregulation in NHL directly can still be considered. For instance, aberrantly expressed transcription factors or epigenetic modifiers that regulate miRNA expression can be directly targeted to reverse dysregulation of miRNA and other targets of the epigenetic modifiers. One specific example would be the therapeutic targeting of collaborative oncogenic partners *HDAC* and *EZH2* to restore the expression of tumor-suppressive miR-29 and other HDAC and EZH2 targets in MCL cell lines. In a recent study, this restoration was achieved by the combined inhibition of HDAC and EZH2 (through vorinostat, DZNep, or their small interfering RNA). As a consequence, a reduction of oncogenic CDK6 and insulin-like growth factor (IGF)-1R and subsequent inhibition of cell survival and colony formation in vitro was observed.[37] In another study, downregulation of miR-17, miR-18, miR-15b, miR-34a, and miR-155 was achieved by dose-dependent vorinostat and trichostatin A treatments in cell lines, and promoted a set of proapoptotic changes.[98]

Personalized medicine

Since miRNA dysregulation is heterogeneous within and between NHL types, treating each NHL patient based on the particular molecular aberrations their disease presents might result in better outcomes. In the age of personalized medicine, it is likely that miRNA genotypes and miRNA and mRNA expression and epigenetic profiles for each patient will be readily available for the identification of molecular aberrations that define a particular patients disease. With this information, clinicians and scientists could move from prescribing a uniform treatment regime to all NHL patients to instead designing patient-specific therapies that may precisely supplement or antagonize the identified dysregulated miRNA in that patient's disease. In addition, if dysregulation of miRNA biogenesis machinery is identified, perhaps therapies could be designed to correct dysregulated expression of Dicer and Drosha. If proper miRNA biogenesis can be restored, it would avoid having the replacement of individual miRNA species, which could result in a myriad of off-target effects.

Drug resistance is a major obstacle to the successful treatment of DLBCL – nearly half of the patients treated with the cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) regimen stop responding to treatment and become drug resistant. At the level of prognosis, certain miRNA have been found to regulate the sensitivity of patients to particular drug regiments. miR-21 expression levels in DLBCL cell lines is relatively high, and miR-21 knockdown can significantly downregulate the expression level of PTEN protein and thereby increase the sensitivity of DLBCL cell lines to the CHOP chemotherapeutic regimen.[99] Similarly, miR-148b levels were upregulated in response to radiation treatment of DLBCL cell lines, and were found to inhibit proliferation and increase radiosensitivity by enhancing radiation-induced apoptosis. Identifying miRNA expression levels of these miRNA that regulate treatment sensitivity would aid in the development of individualized treatment plans for DLBCL patients with abnormal expression of these miRNA, in order to increase the efficacy of treatment regimens.[100]

Conclusion

Recent work has increased our understanding of dysregulation of miRNA expression across diverse types of B-cell NHL. This coordinated dysregulation of miRNA expression

systematically results in the activation of several oncogenic pathways, and consequently the reprogramming of the B-cell NHL transcriptomes. miRNA dysregulation is a consequence of several mechanisms, ranging from dysregulation of the DNA sequences encoding the miRNA, to transcriptional regulation of miRNA loci, to dysregulation of the miRNA biogenesis pathway or dysregulation of mRNA targets. The widespread dysregulation of miRNA suggests that, not only can it be used not only as a diagnostic and prognostic tool, but its mechanisms of dysregulation can be used as actionable drug targets. An understanding of the mechanisms of miRNA dysregulation as summarized here can perhaps better inform the design of miRNA-based therapeutic strategies and lead to better survival for NHL patients.

Disclosure

The authors report no conflicts of interest in this work.

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