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Review Article

Role of microRNA in the pathogenesis of malignant lymphoma

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MicroRNA (miRNA) are non-coding regulatory RNA usually consisting of 20–24 nucleotides. Over the past decade, increases and decreases in miRNA expression have been shown to associate with various types of disease, including cancer. The first two known miRNA aberrations resulted from altered expression of *DLEU2* and *C13orf25* in hematological malignancies. *DLEU2*, which encodes miR-15a and miR-16-1, was discovered from 13q14 deletion in chronic lymphocytic leukemia, while *C13orf25*, which encodes six mature miRNA (miR-17, miR-18, miR-19a, miR-19b, miR-20a and miR-92a), was identified from 13q31 amplification in aggressive B-cell lymphomas. These miRNA were downregulated or upregulated in accordance with genomic deletion or amplification, which suggests that they contribute to tumorigenesis through altered regulation of target oncogenes or tumor suppressors. Consistent with that idea, miR-15a/16-1 is known to regulate Bcl2 in chronic lymphocytic leukemia, and miR-17-92 regulates the tumor suppressors p21, Pten and Bim in aggressive B-cell lymphomas. Dysregulation of other miRNA, including miR-21, miR-29, miR-150 and miR-155, have also been shown to play crucial roles in the pathogenesis of aggressive transformed, high-grade and refractory lymphomas. Addition of miRNA dysregulation to the original genetic events likely enhances tumorigenicity of malignant lymphoma through activation of one or more signaling pathways. (*Cancer Sci* 2013; 104: 801–809)

MicroRNA (miRNA) are non-coding regulatory RNA consisting of 20–24 nucleotides.[1–3] Regulatory RNA act by controlling the translation of proteins from mRNA, and by doing so play a crucial role in normal cell differentiation and proliferation.[1–3] Approximately 2500 miRNA have been identified in humans, and it is known that nearly all human protein-encoding genes can be controlled by miRNA in both healthy and malignant cells. Many miRNA alterations have also been reported in both hematological malignancies and solid tumors.[2,3] The role played by miRNA dysregulation in malignant lymphomas and other cancers is being actively studied worldwide. However, the available information remains incomplete and complex, so that the precise function of miRNA in carcinogenesis is unknown. In this review, we have summarized the actions of miRNA in distinct subtypes of malignant lymphomas, focusing in particular on their involvement in disease progression and transformation.

Discovery of MicroRNA Dysregulations in Hematological Malignancies

Abnormal expression of miRNA is now known to occur in many cancers, but it was first reported in chronic lymphocytic leukemia (CLL). In 2001, Dalla-Favera's group found reduced expression of the gene *DLEU2* through a detailed search of the minimal deleted region 13q14.[4] In 2002, Croce's group reported reduced expression of miR-15a and miR-16-1 from the common loss region of 13q14 in CLL.[5] They also showed that miR-15a and 16-1 were present in the non-coding region of *DLEU2*. Then, in 2003, overexpression of *BIC*, which encodes miR-155, was detected in children with Burkitt lymphoma (BL),[6] although miR-155 expression is usually absent in sporadic primary BL cases.[7] In 2004, Seto's group discovered the overexpression of a non-coding gene, *C13orf25*, in aggressive B-cell lymphomas.[8] *C13orf25* contained six mature miRNA sequences, suggesting that dysregulation mRNA plays a key role in lymphomagenesis.

On the basis of these reports, Croce's group hypothesized that miRNA instability plays a crucial role in carcinogenesis, and that aberrantly upregulated miRNA might suppress expression of tumor suppressors, while aberrantly downregulated miRNA might promote expression of oncoproteins.[9] In fact, it has now been demonstrated in various cancers that miRNA alter expression of tumor suppressors and oncoproteins by inhibiting translation of their respective mRNA (canonical function). Figure 1a provides a schematic illustration of the mechanisms governing the canonical miRNA functions in cancer. Eiring *et al.* (2010) demonstrate that a tumor-suppressive miRNA also exhibits a "decoy" function in chronic myelogenous leukemia (CML).[10] MiR-328 negatively regulate PIM1 oncoprotein by canonical function. In CML chronic phase, miR-328 combines to a transcription factor, hnRNP E2 (negative regulator of *CEBPA*/c-EBPα), as a "decoy," leading to differentiation from CML blast cells to granulocytes. In contrast, in CML blast crisis (BC) phase, downregulation of miR-328 leads to differentiation block of CML blast cells via activation of hnRNP E2. In CML BC, together with the enhanced expression of PIM1, the reduced expression of miR-328 leads to an increase in the production of undifferentiated blast cells. This finding is attracting attention as a new mechanism by which tumor-forming miRNA act; that is, regulation of target protein expression through a "decoy" (Fig. 1b). So far, the decoy function has only been demonstrated in CML, but the function may be associated with other cancers.

MiR-17-92 is the First MicroRNA Known to be Dysregulated in Malignant Lymphomas

13q31-32 amplification is a well-known genomic alteration in diffuse large B-cell lymphoma (DLBCL) that was recognized well before its response gene was identified. This is because there was no protein-coding gene in that region. In 2004, Seto's group carefully examined the expression of approximately 60

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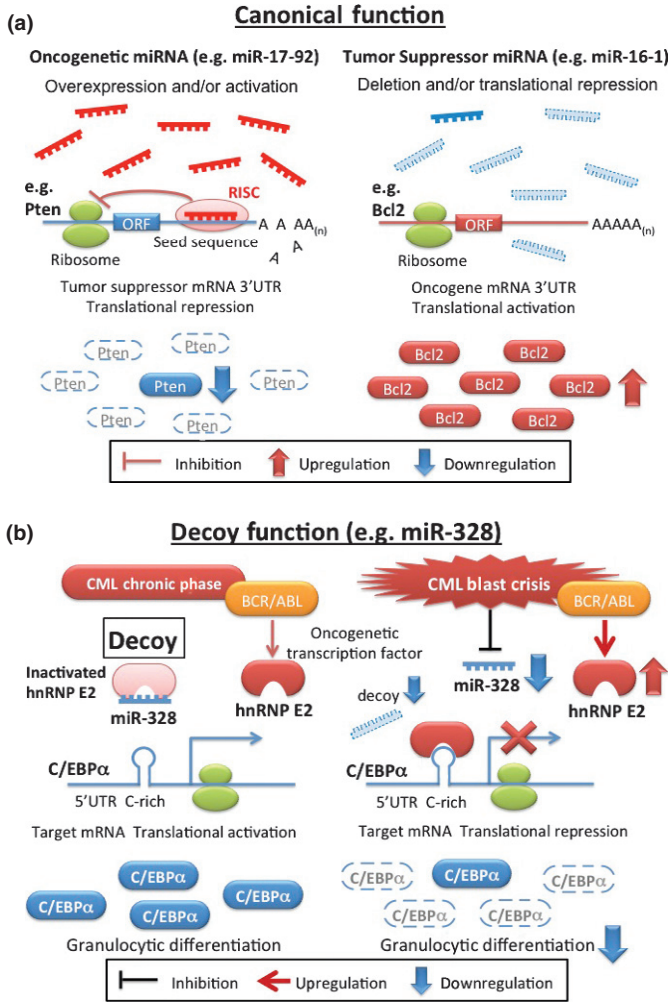

Fig. 1. Schematic diagram of cancer-related microRNA (miRNA) function. (a) Canonical function of oncogenic or tumor-suppressive miRNA are shown. Aberrantly upregulated miRNA (e.g. miR-17-92) might suppress expression of tumor suppressors (e.g. Pten), while aberrantly downregulated miRNA (e.g. miR-16-1) might promote expression of oncoproteins (e.g. Bcl2). (b) MiRNA (e.g. miR-328) as a decoy is shown.

expressed sequence tags (EST) and found that 1 EST, BCO40320, was strongly expressed in accordance with 13q31 amplification in DLBCL. They then identified a novel gene, *C13orf25*, from the EST using the 5′ or 3′ rapid amplification of cDNA end (RACE) method.[8] *C13orf25* contains the miR-17-92 polycistron, encoding six miRNA (miR-17-5p, miR-18, miR-19a, miR-19b, miR-20a and miR-92-1), which can be divided into the miR-19 and miR-17 families. Subsequent investigation revealed that the miR-17-92 is overexpressed in aggressive B-cell lymphomas (DLBCL, mantle cell lymphoma [MCL] and BL) with genomic amplification of 13q31 (Fig. 2a).[8,11–13] Based on those reports[8], Hannon & Hammond's group investigated the polycistron's potential to act as an oncogene. They first transduced miR-17-19b into stem cells from the fetal liver of Eu-Myc mice, and then inoculated the transduced cells into irradiated Eu-Myc mice. They found that the death rate among mice inoculated with miR-17-19b was higher than among control mice due to the induction of B-cell leukemia. They also showed that miR-17-92 could induce tumor formation by acting in concert with Myc.[14] At the same time, Mendell's group demonstrated that Myc could upregulate miR-17-92 and that E2F is a direct target of the miR-17 family,[15] although it remains unknown whether reduction of E2F expression is associated with lymphomagenesis. Dews *et al.* (2006) reveal that miR-18, another member of the miR-17-92 polycistron, regulates thrombospondin1 and connective tissue growth factor, whose downregulation activates angiogenesis in colon cancer.[16] In 2008, two groups, respectively, demonstrated miR-17-92 target gene(s) involved in normal B-cell development. Using miR-17-92 knockout mice, Jacks' lab showed that deletion of miR-17-92 could induce upregulation of the pro-apoptotic protein Bim with inhibition of differentiation from pro-B cell to pre-B cell transition.[17] In addition, Rajewsky's lab established miR-17-92 transgenic mice,[18] which developed lymphoproliferative disease because the miR-17-92 reduced expression of Bim protein; however, they did not develop lymphomas. Nonetheless, these reports suggest the pro-apoptotic protein Bim is a likely target of miR-17-92 during B-cell lymphomagenesis.

The findings summarized above strongly suggest that by enhancing anti-apoptotic capability in B-cell lymphomas, downregulation of Bim by miR-17-92 contributes to lymphomagenesis. However, in MCL, there have been several cases in which both miR-17-92 overexpression via 13q31 amplification and loss of *BCL2L11*/Bim via 2q13 homozygous deletion were observed.[11,12] This fact led us to the idea that miR-17-92 has an additional target, at least in some cases. Using the Jeko-1 MCL cell line, which shows both 13q31 amplification and homozygous deletion of Bim, our group discovered that miR-17-92 can also regulate *CDKN1A*/p21. When we knocked down miR-17 and miR-20, cell cycling was arrested at G1/S via upregulation of *CDKN1A*/p21. Conversely, when we transduced miR-17-19b into the SUDHL4 B-cell lymphoma cell line, which otherwise does not show upregulation of miR-17-92, *CDKN1A*/p21 was downregulated and G1/S progression was enhanced. These results demonstrate that in addition to Bim, the miR-17-92 also regulates p21.[19]

In 2009, two groups (He *et al.* and Ventura *et al.*) demonstrated that miR-19 could regulate the tumor suppressor Pten, thereby enhancing anti-apoptotic potential via upregulation of the AKT/mTOR pathway (Fig. 2b).[20,21] Collectively, these reports suggest that miR-17-92 regulates several targets in different B-cell lymphoma subtypes (miR-17 family: Bim and p21; miR-19 family: Pten), and that the upregulation of miR-17-92 is an additional genetic event that enhances the tumorigenicity of the original cancer.

Differences in MicroRNA Expression Can Define The Lymphoma Subtype

Since the discovery of the upregulated expression of miR-17-92 in malignant lymphomas, the genomes of various subtypes of malignant lymphomas have been screened for miRNA expression. Details of the dysregulation of miRNA in malignant lymphoma are summarized in Table 1.

MicroRNA may even be differentially expressed within a single tumor entity, such as DLBCL (activated B-cell [ABC] *vs* germinal center B-cell [GCB]) or anaplastic large cell lymphoma (ALCL) (anaplastic lymphoma receptor tyrosine kinase [ALK] positive [+] *vs* ALK negative [−]), and the difference may be crucial to the pathogenesis of the lymphoma subtype.

Diffuse large B-cell lymphoma (DLBCL) can be divided into two distinct subtypes: ABC and GCB types.[22] Lenz *et al.* (2008) report that 13q31 amplification (*C13orf25*) frequently occurs in GCB but not in ABC-type DLBCL.[23] They further show that DLBCL overexpressing miR-17-92 also express *MYC* and their target genes at significantly higher levels than those without this abnormality. Interestingly, 10q23 (*PTEN*) deletion is frequently seen in GCB DLBCL without 13q amplification. Both 13q31 amplification and 10q23 deletion could downregulate Pten, suggesting that altered AKT-mTOR signal-

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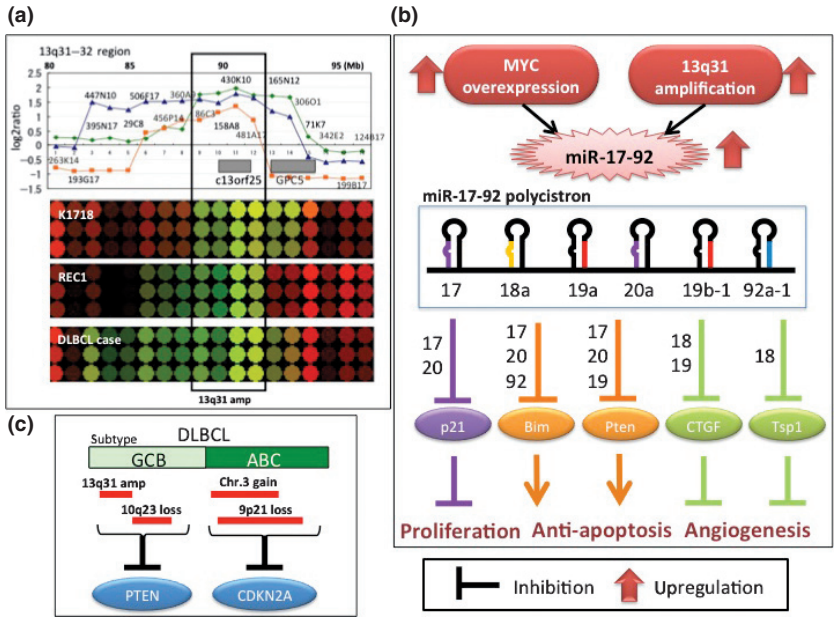

Fig. 2. C13orf25/miR-17-92 is the first oncogenic microRNA (miRNA). (a) Array based CGH for B-cell lymphoma cell lines (Karpass1718, REC1) and a primary diffuse large B-cell lymphoma (DLBCL) sample. Green spots show genomic amplification and red spots show genomic deletion. *C13orf25* is located in a common amplification region at 13q31-q32. 13q32 (C13orf25 region) amplification commonly occurred among examined cell lines and a primary case. (b) Schematic illustration of miR-17-92 function in B-cell lymphomas. Genomic amplification of 13q32 and/or Myc overexpression can induce upregulation of miR-17-92, which include six mature miRNA. Each miRNA family (miR-17 family and miR-19 family) has distinct target(s) in lymphoma genesis. (c) Genomic amplification and deletion of DLBCL subtypes. Activated B-cell (ABC) DLBCL is showing 9p21 (*CDKN2A*).[23] In contrast, germinal center B-cell (GCB) DLBCL is showing either 13q31 amplification or 10q23 loss, yielding Pten loss.[23]

ing may be important in GCB DLBCL (Fig. 2c). Significantly higher levels of miR-155 are present in the ABC type than the GCB type.[24] Because AID, which is an essential regulator of class switch recombination and somatic hypermutation in germinal B-cells,[25] is expressed in the germinal center and miR-155 can regulate this expression, it seems likely that miR-155 is downregulated in GCB DLBCL. In ABC DLBCL, miR-155 may act to regulate tumor suppressors, but the precise target(s) has not yet been identified. In addition, Malumbres *et al.* (2009) provide evidence that germinal center-enriched miR-125b downregulates expression of *IRF4* and *PRDM1*, and memory B-cell-enriched miR-223 downregulates expression of LMO2.[26] These reports also suggest that miRNA play crucial roles in different DLBCL subtypes. Furthermore, miR-181a and miR-222 have been shown to predict overall survival and progression-free survival in rituximab cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP)-treated DLBCL patients.[26–28] In addition, miR-155 is shown to be upregulated in primary mediastinal large B-cell lymphoma.[29]

It was also recently reported that miRNA dysregulation in ALCL differs between the ALK (+) and ALK (−) subtypes. Merkel *et al.* (2010) show that ALK (+) and ALK (−) could be distinguished based on their distinct miR-17-92 profiles: miR-17-92 was more strongly expressed in the ALK (+) subtype. Moreover, miR-29a and miR-101 were downregulated in ALCL and its forced expression reduced proliferation of only the ALK (+) subtype *in vitro*.[30,31] These miRNA can be hallmarks for distinguishing ALK (+) or ALK (−) subtypes.

Altogether, differences in miRNA expression likely contribute to the distinct behaviors of different lymphoma subtypes through regulation of specific genes and their transcripts.

MicroRNA Dysregulation Strongly Contributes the Pathogenesis of Aggressive Lymphomas

Functional analyses of miRNA have been conducted with aggressive lymphomas, including BL, MCL and NK/T-cell lymphoma. BL is characterized by the dysregulated expression of *MYC* as a consequence of translocations involving the *MYC* (8q24) and immunoglobulin genes. It has also been shown that AID is required for the *MYC* translocation and development of BL.[32] MiR-155 expression is reduced in BL,[7] and recent work by Dorsett *et al.* demonstrates that miR-155 suppresses AID-mediated MYC-IGH translocation.[33] This suggests that downregulation of 25miR-155 in germinal center lymphoid tissue is a deeply associated first hit event in BL. Furthermore, several epidemiologic subtypes of BL (endemic, sporadic and HIV-associated) share a homogeneous microRNA profile, distinct from that of DLBCL,[34] which confirms the potential relevance of this signature in the diagnosis of BL.

Mantle cell lymphoma is characterized by t(11,14)(q13;q32), which results in overexpression of *CCND1*/CyclinD1, and is presumed to derive from naïve pre-germinal center $CD5^+$ B-cells (subset [30%] of MCL derive from antigen experienced cells with identity of immunoglobulin heavy chain variable region gene of 92–98% with the germline).[35,36] Underlying MCL is a larger number of genetic alterations than is seen in other lymphoma subtypes.[12,37] Many miRNA aberrations and miRNA dysregulation have also been identified in MCL.[38–41] Essential is dysregulation of miR-29, miR-15a/16-1, miR-26 and miR-17-92. miR-17-92 is frequently upregulated in MCL, and because miR-17-92 appears to negatively regulate *CDKN1A*/p21,[19] increases in its expression could enhance cell cycle progression. miR-16-1 is expressed normally in MCL, as compared to its expression in normal $CD5^+$ B-cells,[42,43] but Chen *et al.* demonstrate that the 3′UTR of *CCND1* is frequently truncated or mutated in MCL, which inhibits the interaction of miR-16-1 with the "seed" sequence of the 3′UTR of *CCND1*, thereby contributing to continuous upregulation of CyclinD1.[43] In addition, some miRNA have been shown to act as regulators of polycomb-group repressive complex proteins. MiR-16-1 can regulate BMI1 translation, which would enhance anti-apoptotic potential by negatively regulating pro-apoptotic genes, such as *PMAIP1*/Nox*a* and *BCL2L11*/Bim.[42]

In aggressive B-cell lymphomas, such as BL, DLBCL and MCL, overexpression of *MYC* is strongly associated with their aggressiveness. Zhang *et al.* (2012) show that MYC, HDAC3 and EZH2 form a repressive complex tethered to miR-29 promoter elements to epigenetically repress miR-29 transcription in MYC-expressing lymphoma cells. Downregulation of miR-29 induces upregulation of CDK6 (cell cycle progression) and IGF-1R (anti-apoptosis). Furthermore, MYC can regulate transcription of miR-26a, whose downregulation leads to upregula-

Table 1. MicroRNA dysregulation in malignant lymphoma

MicroRNA	Subtype	Expression	Target proteins	References	Notes
let-7f	NMZL	Up		Craig *et al.*[60]	Versus FL
let-7a	cHL	Up	BLIMP1	Nie *et al.*[67]	In Hodgin's cells
miR-9	BL	Down		Lenze *et al.*[34]	Versus DLBCL
	cHL	Up	BLIMP1	Nie *et al.*[67]	In Hodgkin's cells
miR-15a	MCL	Down		Beà *et al.*[37], Zhang *et al.*[68]	Downregulated by MYC-HDAC3
	CTCL (SzS)	Down		Ballabio *et al.*[69]	Versus CD4+ cells
miR-16-1	FL	Down		Karube *et al.*[57]	t(14;18)–negative specific
	cHL	Up		Gibcus *et al.*[70]	Versus NHL
	CTCL(SzS)	Down		Ballabio *et al.*[69]	Versus CD4+ cells
	MCL	Down	BCL2, BMI1	Beà *et al.*[37], Zhang *et al.*[68], DiLisio *et al.*[41]	Down-regulated by MYC, downregulated in MCL SP DiLisio *et al.*[41]
miR-18a	DLBCL	Up		Alencar *et al.*[28]	Versus B-cells, poor OS (R-CHOP)
miR-20a/b	FL	Up	p21	Oshiro *et al.*[55]	Versus CD19+ B-cells
miR-17-92	MCL	Up	p21,PTEN	Zhang *et al.*[39], Rao *et al.*[71]	Versus CD19+ B or IgD B-cells, poor OS
	cHL	Up		Gibcus *et al.*[70]	Versus NHL
	BL	Up		Tagawa *et al.*[13]	Versus 13q31 amp(−) BL
	DLBCL(GCB)	Up	PTEN	Lenz *et al.*[23], Fassina *et al.*[72]	Versus ABC type (Lenz *et al.*[23]) GC-DLBCL from high-grade FL
	ALCL-ALK (+)	Up		Merkel *et al.*[30]	Versus ALK (−) ALCL
miR-21	SMZL	Up		Ruiz-Ballesteros[62], Bouteloup *et al.*[63]	Versus normal spleen (aggressive SMZL) (Ruiz-Ballesteros[62]), poor OS (Bouteloup *et al.*[63])
	NK/T	Up	PDCD4, PTEN	Karube *et al.*[46], Yamanaka *et al.*[47]	Versus CD56 cells
	cHL	Up		Navarro *et al.*[73], Gibcus *et al.*[70]	Versus reactive lymph nodes, versus NHL
	DLBCL	Up		Malumbres *et al.*[26], Lawrie *et al.*[74,75]	Versus GCB DLBCL (cell line) (Malumbres *et al.*[26] and Montes-Moreno *et al.*[27]
miR-23a	BL	Down		Lenze *et al.*[34]	Versus DLBCL
	cHL	Up		Navarro *et al.*[73]	Versus reactive lymph nodes
miR-23b	BL	Down		Lenze *et al.*[34]	Versus DLBCL
miR-26a	BL	Down		Lenze *et al.*[34]	Versus DLBCL
	MCL	Down		Zhao *et al.*[38], Navarro *et al.*[40]	Versus CD5+ B-cells
	FL	Down		Karube *et al.*[57]	t(14;18)–negative cases
miR-26b	BL	Down		Lenze *et al.*[34]	Versus DLBCL
	cHL	Down		Navarro *et al.*[73]	Versus reactive lymph nodes
	SMZL	Down		Bouteloup *et al.*[63]	In HCV-positive patient
miR-29a	SMZL	Down		Arribas *et al.*[61], Ruiz-Ballesteros[62]	Versus FL, MCL, and CLL with splenic involvement (Arribas *et al.*[61]), Versus normal spleen (Ruiz-Ballesteros[62])
	ALCL-ALK(+)	Down	MCL-6	Desjobert *et al.*[31]	Versus ALK (−) ALCL
	MCL	Down	CDK6, IGF-1R	Beà *et al.*[37], Zhao *et al.*[38]	Epigenetically down-regulated by MYC-HDAC-EZH2 (Zhao *et al.*[38])
miR-29b	BL	Down		Lenze *et al.*[34]	Versus DLBCL
	SMZL	Down		Arribas *et al.*[61]	Versus FL, MCL, and CLL with splenic involvement
miR-29c	NMZL	Up		Craig *et al.*[60]	Versus lymph node with reactive lymphoid hyperplasia
	FL	Down		Karube *et al.*[57]	t(14;18)–negative cases
miR-30a	BL	Down		Lenze *et al.*[34]	Versus DLBCL
miR-30b	cHL	Down		Navarro *et al.*[73]	Versus reactive lymph nodes
miR-30d	BL	Down		Lenze *et al.*[34]	Versus DLBCL
miR-31	ATL	Down	NIK/NF-kB	Bellon *et al.*[53]	Versus CD4+ cells
	cHL	Down		Navarro *et al.*[73]	Versus reactive lymph nodes
miR-34a	DLBCL	Up	FOXP1	Liu[59]	Associated with transformation from gastric MALT to DLBCL
miR-96	cHL EBV+	Down		Navarro *et al.*[73]	Versus EBV-negative cHL
miR-101	FL	Down		Karube *et al.*[57]	t(14;18)–negative cases
	ALCL	Down		Merkel *et al.*[30]	Inhibition of prolifelation in ALK(+) type (cell lines)
miR-125b	DLBCL	Up	IRF4, BLIMP1	Malumbres *et al.*[26]	in GC-enriched cells
miR-128a/b	cHL EBV+	Down		Navarro *et al.*[73]	Versus EBV-negative cHL
miR-135a	cHL	Down	JAK2	Navarro *et al.*[73,76]	Versus reactive pymph nodes, poor outcome
miR-142-3p	NK/T EBV+	Down	IL1A	Motsch *et al.*[77]	Versus NK/T EBV(−) cells
	ATL	Up		Yin *et al.*[52]	Versus HTLV1 infected cells, versus CD4+ cells

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Table 1. (continued)

MicroRNA	Subtype	Expression	Target proteins	References	Notes
miR-142-5p	BL	Down		Lenze *et al.*[34]	Versus DLBCL
	MALT(gastric)	Up	TP53INP1	Saito *et al.*[78]	Poor reactivity to *H. pylori* eradication therapy
miR-146a	BL	Down		Lenze *et al.*[34]	Versus DLBCL
	NK/T	—	TRAF6	Paik *et al.*[79]	Low miR-146a patients have poor prognosis
	DLBCL(ABC)	Up		Malumbres *et al.*[26]	Versus GCB DLBCL (cell line)
miR-146b	BL	Down		Lenze *et al.*[34]	Versus DLBCL
	DLBCL(ABC)	Up		Malumbres *et al.*[26]	Versus GCB DLBCL (cell line)
miR-150	MCL	Down		Beà *et al.*[37]	Versus CD19+ or IgD B-cells
	NK/T	Down	DKC1, AKT2	Yamanaka *et al.*[47]	Versus CD56 cells
	cHL	Down		Gibcus *et al.*[70]	Versus NHL
	PCMZL	Down		Monsálvez *et al.*[80]	Inferior PFS
miR-155	MCL	Up		Beà *et al.*[37]	Versus CD19+ or IgD B-cells
	BL	Down	AID	Kluiver *et al.*[81], Kluiver *et al.*[7], Dorsett *et al.*[33], Lenze *et al.*[34]	Versus DLBCL (Lenze *et al.*[34])
	SMZL	Up		Ruiz-Ballesteros[62]	Versus normal spleen
	NK/T	Up	SHIP1	Karube *et al.*[46], Yamanaka *et al.*[47]	Versus CD56 cells
	DLBCL(ABC)	Up		Eis *et al.*[24], Malumbres *et al.*[26], Lawrie *et al.*[75]	Versus GCB DLBCL
	PMBCL	Up		Kluiver *et al.*[29]	Versus GCB DLBCL
	cHL	Up		Gibcus *et al.*[70]	Versus NHL
	ALCL-ALK(-)	Up		Merkel *et al.*[30]	Versus ALK(+) ALCL
	MALT(gastric)	Up	TP53INP1	Saito *et al.*[78]	In cases with poor reactivity to *H. pylori* eradication therapy
	ATL	Up		Yin *et al.*[52]	Versus HTLV1 infected cells, versus CD4+ cells
	PCMZL	—		Monsálvez *et al.*[80]	Poor PFS
miR-181a	DLBCL	Up		Alencar *et al.*[28]	R-CHOP-treated DLBCL patients have better PFS
	DLBCL(GCB)	Up		Lawrie *et al.*[75]	GCB specific (cell lines)
	ATL	Down		Yin *et al.*[52]	Versus HTLV1 infected cells, versus CD4+ cells
miR-194	FL	Up	SOCS2	Oshiro *et al.*[55]	Versus CD10+ B-cells
miR-205	NK/T EBV(+)	Up	BCL6	Motsch *et al.*[77]	Versus EBV-negative NK/T
	CTCL	Down		Ralfkiaer *et al.*[82]	Versus benign skin disease or normal skin
miR-221	BL	Down		Lenze *et al.*[34]	Versus DLBCL
	NMZL	Up	LMO2	Craig *et al.*[60]	Versus FL and lymph node with reactive lymphoid hyperplasia
	DLBCL(ABC)	Up		Lawrie *et al.*[74]	Versus GCB DLBCL (cell line)
miR-222	BL	Down		Lenze *et al.*[34]	Versus DLBCL
	DLBCL	Up		Malumbres *et al.*[26], Montes-Moreno *et al.*[27], Alencar *et al.*[28]	R-CHOP-treated DLBCL patients have inferior PFS and/or OS
	DLBCL(ABC)	Up		Malumbres *et al.*[26], Lawire (2008)	Versus GCB DLBCL (cell line)
miR-223	NMZL	Up	LMO2	Craig *et al.*[60]	Versus FL
		Up	LMO2	Malumbres *et al.*[26]	Memory B-cell-enriched, but not in centroblasts
	CTCL(SzS)	Down		Ballabio *et al.*[69]	Versus MF, Versus CD4+
	MALT(gastric)	Up		Leich *et al.*[58]	In high stage and cases with poor reactivity to *H. pylori* eradication therapy
miR-574-3p	DLBCL(ABC)	Up		Malumbres *et al.*[26]	Versus GCB DLBCL (cell line)
miR-574-5p	DLBCL(ABC)	Up		Malumbres *et al.*[26]	Versus GCB DLBCL (cell line)
	CTCL(SzS)	Up		Ballabio *et al.*[69]	Versus CD4+ cells
miR-768-3p	AITL/PTCLnos	—		Valleron *et al.*[83]	pre-miR-768 overlaps snoRNA HBII-239 (favourable outcome)

ABC, activated B-cell-like; AITL, angioImmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; ATL, adult T cell leukemia; BL, Burkitt lymphoma; cHL, classical hodgkin lymphoma; CTCL, cutaneous T cell lymphoma; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein–Barr virus; FL, follicular lymphoma; GCB, germinal center B-cell-like; HCV, hepatitis C virus; MALT, mucosa-associated lymphoid tissue lymphoma; MCL, mantle cell lymphoma; MF, mycosis fungoides; NHL, non-Hodgkin lymphoma; NK/T, natural killer/T-cell lymphoma; NMZL, nodal marginal zone lymphoma; OS, overall survival; PCMZL, primary cutaneous marginal zone B-cell lymphoma; PFS, progression free survival; PMBCL, Primary mediastinal large B-cell lymphoma; PTCLnos, peripheral T-cell lymphomas not otherwise specified; R-CHOP, Rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone chemotherapy; SMZL, splenic marginal zone lymphoma; SP, side population; SzS, Sézary syndrome.

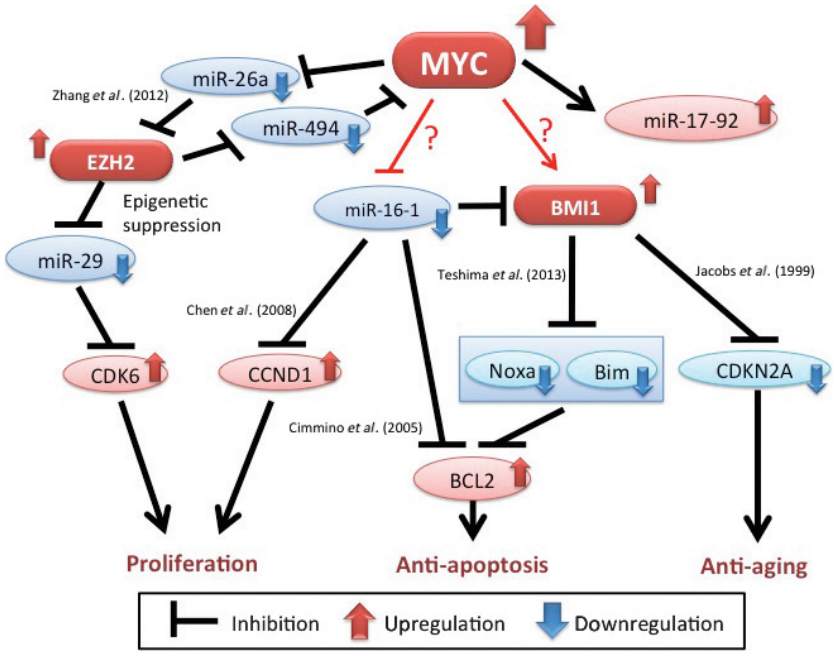

Fig. 3. Schematic illustration of microRNA (miRNA) dysregulation in mantle cell lymphoma (MCL) or aggressive B-cell lymphoma with MYC overexpression.

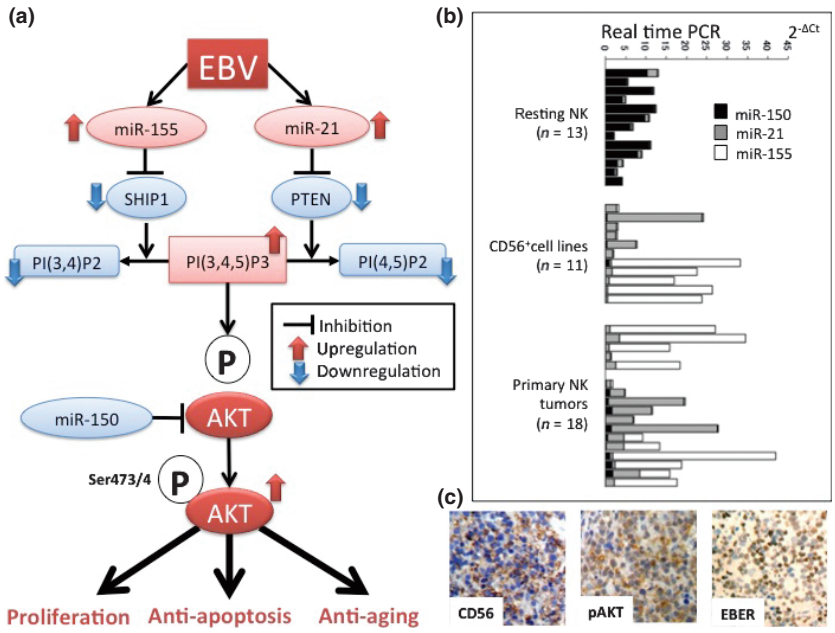

Fig. 4. microRNA (miRNA) dysregulation in NK/T-cell lymphoma. (a) Schematic illustration of the role of miR-21, miR-155 and miR-150 in NK-cell tumor. (b). Expressions of miR-21, miR-155 and miR-150 in normal NK-cell, NK-cell lymphoma/leukemia cell lines and primary samples. (c). Immunostaining of CD56, pAKT$^{ser473/4}$ and EBER against an example of NK/T-cell lymphoma case (extra nodal type). EBV, *Epstein–Barr* virus.

tion of EZH2. This, in turn, reduces miR-494 expression, leading to upregulation of MYC. This MYC-miR-26a-EZH2-miR-494 positive feedback loop is observed in aggressive MCL, especially in the cases with MYC upregulation.[39] A schematic illustration of these complicated signals is shown in Figure 3.

NK-cell leukemia and NK/T-cell lymphoma are tumors derived from natural killer cells (sCD3$^-$CD56$^+$TCR$^-$) whose onset and development are governed to a great extent by *Epstein–Barr* virus (EBV). Because the pathogenesis of NK/T-cell lymphoma remained largely unknown, comparative genomic hybridization and/or gene expression profiling were conducted to detect the genes responsible.[44,45] Approximately 10 to 20% of NK/T-cell lymphoma cases show a 6q deletion, which affects expression of the AIM1, PRDM1 and FOXO3 transcription factors.[45,46] We hypothesized that the remaining 80% of cases might show miRNA aberrations. By screening for miRNA expression, our group found that miR-21 and miR-155 were upregulated and miR-150 was downregulated in primary NK-cell tumors and cell lines.[47,48] We also found that expression of miR-21 and miR-155 was mutually exclusive, suggesting that these two miRNA target different downstream genes in the same signal cascade. Indeed, miR-21 negatively regulates the tumor suppressors Pten and PDCD4 in NK-cell leukemia, while miR-155 regulates an inositol phospholipid phosphatase, Ship1, in NK/T-cell lymphoma.[47–51] Pten and Ship1, respectively, regulate dephosphorylation of phosphatidylinositol (3–5)-trisphosphate (PIP3) to phosphatidylinositol 4,5-bisphosphate (PIP2) and PIP5 to PIP3, and their downregulation likely leads to activation of AKT signaling.[50] We also found that miR-150 is downregulated in NK and T-cell lymphomas, which could directly affect AKT2 and dyekerin,

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which induce cellular senescence. Consequently, downregulation of miR-150 has an anti-aging effect, leading to immortalization within NK-cell tumors (Fig. 4).[48] These findings suggest that EBV infection may cause the upregulation of several miRNA, including miR-21 and miR-155, as infection with EBV is associated with immortalization of lymphoid cells.[52]

Bellon *et al.* (2009) found that several miRNA were dysregulated in adult T-cell leukemia, which is an aggressive tumor entity.[53] Furthermore, Yamagishi *et al.* (2012) discovered that miR-31 regulates an NF-κB-inducing kinase that plays a central role in non-canonical signaling and constitutive activation of the NF-κB pathway.[54] However, there is also evidence that the gene expression and genomic profiles distinctly differ between leukemia and lymphoma,[55] suggesting that miR-31 contributes to tumorigenesis in the former but not the latter. Further study will be required to determine whether miR-31 plays an important role as a tumor-suppressive miRNA in lymphomas.

MiRNA May Contribute to Disease Progression and Transformation of Low Grade Lymphomas

MicroRNA do not appear to be as important for the pathogenesis of low grade B-cell lymphomas (e.g. follicular lymphoma [FL] and marginal zone lymphoma [MZL]) as for high-grade and transformed lymphomas (e.g. FL/MZL to DLBCL).

Follicular lymphoma is characterized as a indolent B-cell lymphoma, with approximately 80% of cases possessing t (14;18)(q32;q21). In FL with the translocation, the miRNA profile showed upregulation of miR-20a/b and miR-194, which target *CDKN1A* and *SOCS2*, respectively, potentially contributing to tumor-cell proliferation and survival.[56] Karube *et al.* (2007) demonstrate that CD10-negative FL cases are usually t (14;18)-negative and/or morphologically high-grade (Grade 3a or b), and, therefore, high-dose intensive chemotherapy (R-CHOP) is required. Leich *et al.* (2011) report that these t (14;18)-negative cases, whose subtype was initially described by Karube *et al.*,[57] have a distinct miRNA profile frequently characterized by downregulation of miR-16-1, miR-26a, miR-101, miR-29 and miR-138.[58] Because these miRNA are known to function as tumor-suppressive miRNA, their downregulation may be associated with the pathogenesis of some FL subtypes and high-grade FL.

Expression of miRNA in marginal zone lymphomas (MZL) has also been analyzed. The results suggest they are likely important in advanced stage or transformed cases of MZL and DLBCL. MiRNA expression has been analyzed in MALT type, nodal type and splenic type MZL. A study of gastric MALT type MZL revealed that high levels of miR-223 expression are a marker of MALT stratification and correlate with increased $E2A^+$ expression, higher clinical stage and diminished response to *Helicobacter pylori* eradication therapy.[59] Large B-cell lymphomas that originate in the stomach, and which are presumably derived from the MALT, exhibit a MYC-miRNA signature, and transformation of MALT to DLBCL is associated with MYC, which negatively regulates miR-34a, leading to downregulation of FOXP1.[60] Studies of nodal MZL confirm that these tumors have distinctive features that distinguish them from FL cases. As compared to FL, nodal MZL shows greater expression of miR-221, miR-223 and let-7f, which is a signature very similar to that exhibited by memory B-cells and cells isolated from the normal marginal zone. Expression of these miRNA is enhanced in nodal MZL, whereas FL strongly expresses miR-494. Upregulation of miR-223 and miR-221, which target the germinal center-related genes LMO2 and CD10, could be partially responsible for expression of a marginal zone signature.[61] In splenic MZL, the miR-29 cluster is commonly lost and its expression silenced.[62-64] In addition, increased expression of miR-21 is associated with an adverse outcome in splenic MZL.[63]

Conclusion

MicroRNA have now been shown to play both oncogenic (e.g. miR-17-92) and tumor-suppressive (e.g. miR-15/16) roles in aggressive lymphoma subtypes (e.g. MCL and NK/T-cell lymphoma) and relapsed cases (e.g. MCL). Some miRNA (e.g. miR-34a) have also been shown to contribute to phenotypic transformation of malignant lymphoma (e.g. FL to DLBCL). However, only two miRNA (miR-16-1 and miR-21) are known to be cancer-inducible based on their activity: miR-16-1 knockout mice and transgenic mice overexpressing miR-21, respectively, develop CLL and B-cell leukemia with no original genetic event.[65,66] More often, however, miRNA dysregulation likely adds to original genetic events, and the resultant aberrations enhance tumorigenicity through activation of additional signaling pathways. Consequently, analysis of miRNA expression may be more useful for evaluation of disease progression and transformation than for classification of various lymphoma entities. For novel treatments against lymphoma, miRNA itself or the appropriate antisense could be useful therapeutic agents, but future functional studies with distinct lymphoma subtypes will be required to determine whether that is the case.

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Disclosure Statement

The authors have no conflict of interest.

References

1 Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell* 2004; **116**: 281–97.
2 Calin GA, Croce CM. MicroRNA signatures in human cancers. *Nat Rev Cancer* 2006; **6**: 857–66.
3 Baer C, Claus R, Plass C. Genome-wide epigenetic regulation of miRNAs in Cancer. *Cancer Res* 2013; **73**: 473–7.
4 Migliazza A, Bosch F, Komatsu H *et al.* Nucleotide sequence, transcription map, and mutation analysis of the 13q14 chromosomal region deleted in B-cell chronic lymphocytic leukemia. *Blood* 2001; **97**: 2098–104.
5 Calin GA, Dumitru CD, Shimizu M *et al.* Frequent deletions and down-regulation of micro- RNA genes miR15 and miR16 at 13q14 in chronic lymphocytic leukemia. *Proc Natl Acad Sci USA* 2002; **99**: 15524–9.
6 Metzler M, Wilda M, Busch K *et al.* High expression of precursor microRNA-155/BIC RNA in children with Burkitt lymphoma. *Genes Chromosom Cancer* 2004; **39**: 167–9.
7 Kluiver J, van den Berg A, de Jong D *et al.* Regulation of pri-microRNA BIC transcription and processing in Burkitt lymphoma. *Oncogene* 2007; **26**: 3769–76.
8 Ota A, Tagawa H, Karnan S *et al.* Identification and characterization of a novel gene, C13orf25, as a target for 13q31-q32 amplification in malignant lymphoma. *Cancer Res* 2004; **64**: 3087–95.
9 Calin GA, Sevignani C, Dumitru CD *et al.* Human microRNA genes are frequently located at fragile sites and genomic regions involved in cancers. *Proc Natl Acad Sci USA* 2004; **101**: 2999–3004.
10 Eiring AM, Harb JG, Neviani P *et al.* miR-328 functions as an RNA decoy to modulate hnRNP E2 regulation of mRNA translation in leukemic blasts. *Cell* 2010; **140**: 652–65.

11 Tagawa H, Seto M. A microRNA cluster as a target of genomic amplification in malignant lymphoma. *Leukemia* 2005; **19**: 2013–6.
12 Tagawa H, Karnan S, Suzuki R *et al.* Genome-wide array-based CGH for mantle cell lymphoma: identification of homozygous deletions of the proapoptotic gene BIM. *Oncogene* 2005; **24**: 1348–58.
13 Tagawa H, Karube K, Tsuzuki S, Ohshima K, Seto M. Synergistic action of microRNA-17 polycistron and MYC in aggressive cancer development. *Cancer Sci* 2007; **98**: 1482–90.
14 He L, Thomson JM, Hemann MT *et al.* A microRNA polycistron as a potential human oncogene. *Nature* 2005; **435**: 828–33.
15 O'Donnell KA, Wentzel EA, Zelller KI, Dang CV, Mendell JT. C-Myc-regulated microRNas modulate E2F1 expression. *Nature* 2005; **435**: 839–43.
16 Dews M, Homayouni A, Yu D *et al.* Augmentation of tumor angiogenesis by a Myc-activated microRNA cluster. *Nat Genet* 2006; **38**: 1060–65.
17 Ventura A, Young AG, Winslow MM *et al.* Targeted deletion reveals essential and overlapping functions of the miR-17~92 family of miRNA clusters. *Cell* 2008; **132**: 875–86.
18 Xiao C, Srinivasan L, Calado DP *et al.* Lymphoproliferative disease and autoimmunity in mice with elevated miR-17-92 expression in lymphocytes. *Nat Immunol* 2008; **9**: 405–14.
19 Inomata M, Tagawa H, Guo Y-M *et al.* MicroRNA-17-92 downregulates expression of distinct targets in different B-cell lymphoma subtypes. *Blood* 2009; **113**: 396–402.
20 Olive V, Bennett MJ, Walker JC *et al.* miR-19 is a key oncogenic component of mir-17-92. *Genes Dev* 2009; **23**: 2839–49.
21 Mu P, Han YC, Betel D *et al.* Genetic dissection of the miR-17~92 cluster of microRNAs in Myc-induced B-cell lymphomas. *Genes Dev* 2009; **23**: 2806–11.
22 Alizadeh AA, Eisen MB, Davis RE *et al.* Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. *Nature* 2000; **403**: 503–11.
23 Lenz G, Wright GW, Emre NC *et al.* Molecular subtypes of diffuse large B-cell lymphoma arise by distinct genetic pathways. *Proc Natl Acad Sci U S A* 2008; **105**: 13520–25.
24 Eis PS, Tam W, Sun L *et al.* Accumulation of miR-155 and BIC RNA in human B cell lymphomas. *Proc Natl Acad Sci USA* 2005; **102**: 3627–32.
25 Muramatsu M, Kinoshita K, Fagarasan S *et al.* Class switch recombination and hypermutation require activation-induced cytidine deaminase (AID), a potential RNA editing enzyme. *Cell* 2000; **102**: 553–63.
26 Malumbres R, Sarosiek KA, Cubedo E *et al.* Differentiation stage-specific expression of microRNAs in B lymphocytes and diffuse large B-cell lymphomas. *Blood* 2009; **113**: 3754–64.
27 Montes-Moreno S, Martinez N, Sanchez-Espiridión B *et al.* miRNA expression in diffuse large B-cell lymphoma treated with chemoimmunotherapy. *Blood* 2011; **118**: 1034–40.
28 Alencar AJ, Malumbres R, Kozloski GA *et al.* MicroRNAs are independent predictors of outcome in diffuse large B-cell lymphoma patients treated with R-CHOP. *Clin Cancer Res* 2011; **17**: 4125–35.
29 Kluiver J, Poppema S, de Jong D *et al.* BIC and miR-155 are highly expressed in Hodgkin, primary mediastinal and diffuse large B cell lymphomas. *J Pathol* 2005; **207**: 243–9.
30 Merkel O, Hamacher F, Laimer D *et al.* Identification of differential and functionally active miRNAs in both anaplastic lymphoma kinase $(ALK)^+$ and ALK^- anaplastic large-cell lymphoma. *Proc Natl Acad Sci USA* 2010; **107**: 16228–33.
31 Desjobert C, Renalier MH, Bergalet J *et al.* MiR-29a down-regulation in ALK-positive anaplastic large cell lymphomas contributes to apoptosis blockade through MCL-1 overexpression. *Blood* 2011; **117**: 6627–37.
32 Robbiani DF, Bothmer A, Callen E *et al.* AID is required for the chromosomal breaks in c-myc that lead to c-myc/IgH translocations. *Cell* 2008; **135**: 1028–38.
33 Dorsett Y, McBride KM, Jankovic M *et al.* MicroRNA-155 suppresses activation-induced cytidine deaminase-mediated Myc-Igh translocation. *Immunity* 2008; **8**: 630–38.
34 Lenze D, Leoncini L, Hummel M *et al.* The different epidemiologic subtypes of Burkitt lymphoma share a homogenous micro RNA profile distinct from diffuse large B-cell lymphoma. *Leukemia* 2011; **25**: 1869–76.
35 Jaffe ES, Harris NL, Stein H, Campo E, Pileri SA, Swerdlow SH. Introduction and over review of the classification of the lymphoid neoplasms. In: Swerdloe AH, Campo E, Harris NL, Jaffe ES, Stein H, Thiele J, Vardiman JW, eds. *World health classification of tumors. Pathology & Genetics of tumors of haematopoietic and lymphoid tissues*. Washington, Lyon: IARC press, 2008; 158−78.
36 Hadzidimitriou A, Agathangelidis A, Darzentas N *et al.* Is there a role for antigen selection in mantle cell lymphoma? Imunogenetic support from a series of 807 cases. *Blood* 2011; **118**: 3088–95.
37 Beà S, Salaverria I, Armengol L *et al.* Uniparental disomies, homozygous deletions, amplifications, and target genes in mantle cell lymphoma revealed by integrative high-resolution whole-genome profiling. *Blood* 2009; **113**: 3059–69.
38 Zhao JJ, Lin J, Lwin T *et al.* microRNA expression profile and identification of miR-29 as a prognostic marker and pathogenetic factor by targeting CDK6 in mantle cell lymphoma. *Blood* 2010; **115**: 2630–9.
39 Zhang X, Zhao X, Fiskus W *et al.* Coordinated silencing of MYC-mediated miR-29 by HDAC3 and EZH2 as a therapeutic target of histone modification in aggressive B-cell lymphomas. *Cancer Cell* 2012; **22**: 506–23.
40 Navarro A, Beà S, Fernández V *et al.* MicroRNA expression, chromosomal alterations, and immunoglobulin variable heavy chain hypermutations in mantle cell lymphomas. *Cancer Res* 2009; **69**: 7071–8.
41 Di Lisio L, Gómez-López G, Sánchez-Beato M *et al.* Mantle cell lymphoma: transcriptional regulation by microRNAs. *Leukemia* 2010; **24**: 1335–42.
42 Teshima K, Nara M, Watanabe A *et al.* Dysregulation of *BMI1* and microRNA-16 collaborate to enhance an anti-apoptotic potential in the side population of refractory mantle cell lymphoma. *Oncogene* 2013; in press.
43 Chen RW, Bemis LT, Amato CM *et al.* Truncation in CCND1 mRNA alters miR-16-1 regulation in mantle cell lymphoma. *Blood* 2008; **112**: 822–9.
44 Nakashima Y, Tagawa H, Suzuki R *et al.* Genome-wide array-based comparative genomic hybridization of natural killer cell lymphoma/leukemia: different genomic alteration patterns of aggressive NK-cell leukemia and extranodal NK/T lymphoma, nasal type. *Genes Chromosom Cancer* 2005; **19**: 247–55.
45 Iqbal J, Kucuk C, Deleeuw RJ *et al.* Genomic analyses reveal global functional alterations that promote tumor growth and novel tumor suppressor genes in natural killer-cell malignancies. *Leukemia* 2009; **23**: 1139–51.
46 Karube K, Nakagawa M, Tsuzuki S *et al.* Identification of FOXO3 and PRDM1 as tumor-suppressor gene candidates in NK-cell neoplasms by genomic and functional analyses. *Blood* 2011; **118**: 3195–204.
47 Yamanaka Y, Tagawa H, Takahashi N *et al.* Aberrant overexpression of microRNAs activate AKT signaling via down-regulation of tumor suppressors in natural killer-cell lymphoma/leukemia. *Blood* 2009; **114**: 3265–75.
48 Watanabe A, Tagawa H, Yamashita J *et al.* The role of microRNA-150 as a tumor suppressor in malignant lymphoma. *Leukemia* 2011; **25**: 1324–34.
49 Horn S, Endl E, Fehse B *et al.* Restoration of SHIP activity in a human leukemia cell line downregulates constitutively activated phosphatidylinositol 3-kinase/Akt/GSK-3b signaling and leads to an increased transit time through the G1 phase of the cell cycle. *Leukemia* 2004; **18**: 1839–49.
50 Freeburn RW, Wright K, Burgess SJ *et al.* Evidence that SHIP-1 contributes to phosphatidilinositol 3,4,5-trisphosphate metabolism in T lymphocytes and can regulate novel phosphoinositide 3-kinase effectors. *J Immunol* 2002; **169**: 5441–50.
51 O'Connell RM, Chaudhuri AA, Rao DS, Baltimore D. Inositol phosphatase SHIP1 is a primary target of miR-155. *Proc Natl Acad Sci USA* 2009; **106**: 7113–18.
52 Yin Q, McBride J, Fewell C *et al.* MicroRNA-155 is an Epsein-Barr virus-induced gene that modulates Epstein−Barr virus-regulated gene expression pathways. *J Virol* 2008; **82**: 5295–306.
53 Bellon M, Lepelletier Y, Hermine O, Nicot C. Deregulation of microRNA involved in hematopoiesis and the immune response in HTLV-I adult T-cell leukemia. *Blood* 2009; **113**: 4914–417.
54 Yamagishi M, Nakano K, Miyake A *et al.* Polycomb-mediated loss of miR-31 activates NIK-dependent NF-κB pathway in adult T cell leukemia and other cancers. *Cancer Cell* 2012; **21**: 121–35.
55 Oshiro A, Tagawa H, Ohshima K *et al.* Identification of subtype-specific genomic alteration of aggressive type of adult T cell lymphoma/leukemia. *Blood* 2006; **107**: 4500–507.
56 Wang W, Corrigan-Cummins M, Hudson J *et al.* MicroRNA profiling of follicular lymphoma identifies microRNAs related to cell proliferation and tumor response. *Haematologica* 2012; **97**: 586–94.
57 Karube K, Guo Y, Suzumiya J *et al.* CD10-MUM1+ follicular lymphoma lacks BCL2 gene translocation and shows characteristic biologic and clinical features. *Blood* 2007; **109**: 3076–9.
58 Leich E, Zamo A, Horn H *et al.* MicroRNA profiles of t(14;18)-negative follicular lymphoma support a late germinal center B-cell phenotype. *Blood* 2011; **118**: 5550–58.
59 Liu TY, Chen SU, Kuo SH, Cheng AL, Lin CW. E2A-positive gastric MALT lymphoma has weaker plasmacytoid infiltrates and stronger expression of the memory B-cell-associated miR-223: possible correlation with stage and treatment response. *Mod Pathol* 2010; **23**: 1507–517.
60 Craig VJ, Cogliatti SB, Imig J *et al.* Myc-mediated repression of microRNA-34a promotes high-grade transformation of B-cell lymphoma by dysregulation of FoxP1. *Blood* 2011; **117**: 6227–36.
61 Arribas AJ, Campos-Martín Y, Gómez-Abad C *et al.* Nodal marginal zone lymphoma: gene expression and miRNA profiling identify diagnostic markers and potential therapeutic targets. *Blood* 2012; **119**: e9–e21.
62 Ruiz-Ballesteros E, Mollejo M, Mateo M, Algara P, Martinez P, Piris MA. MicroRNA losses in the frequently deleted region of 7q in SMZL. *Leukemia* 2007; **21**: 2547–9.

doi: 10.1111/cas.12160

63 Bouteloup M, Verney A, Rachinel N *et al.* MicroRNA expression profile in splenic marginal zone lymphoma. *Br J Haematol* 2012; **156**: 279–81.
64 Peveling-Oberhag J, Crisman G, Schmidt A *et al.* Dysregulation of global microRNA expression in splenic marginal zone lymphoma and influence of chronic hepatitis C virus infection. *Leukemia* 2012; **26**: 1654–62.
65 Medina PP, Nolde M, Slack FJ. OncomiR addiction in an in vivo model of microRNA-21-induced pre-B-cell lymphoma. *Nature* 2010; **467**: 86–90.
66 Klein U, Lia M, Crespo M *et al.* The DLEU2/miR-15a/16-1 cluster controls B cell proliferation and its deletion leads to chronic lymphocytic leukemia. *Cancer Cell* 2010; **17**: 28–40.
67 Nie K, Gomez M, Landgraf P *et al.* microRNA-mediated downregulation of PRDM1/Blimp-1 in Hodgkin/Reed–Sternberg cells: a potential pathogenetic lesion in Hodgkin lymphomas. *Am J Pathol* 2008; **173**: 242–52
68 Zhang X, Chen X, Lin J *et al.* Myc represses miR-15a/miR-16-1 expression through recruitment of HDAC3 in mantle cell and other non-Hodgkin B-cell lymphomas. *Oncogene* 2012; **3**: 300–308.
69 Ballabio E, Mitchell T, van Kester MS *et al.* MicroRNA expression in Sezary syndrome: identification, function, and diagnostic potential. *Blood* 2010; **116**: 1105–13.
70 Gibcus JH, Tan LP, Harms G *et al.* Hodgkin lymphoma cell lines are characterized by a specific miRNA expression profile. *Neoplasia* 2009; **11**: 167–76.
71 Rao E, Jiang C, Ji M *et al.* The miRNA-17∼92 cluster mediates chemoresistance and enhances tumor growth in mantle cell lymphoma via PI3K/AKT pathway activation. *Leukemia* 2012; **26**: 1064–72.
72 Fassina A, Marino F, Siri M *et al.* The miR-17-92 microRNA cluster: a novel diagnostic tool in large B-cell malignancies. *Lab Invest* 2012; **92**: 1574–82.
73 Navarro A, Gaya A, Martinez A *et al.* MicroRNA expression profiling in classic Hodgkin lymphoma. *Blood* 2008; **111**: 2825–32.
74 Lawrie CH, Soneji S, Marafioti T *et al.* MicroRNA expression distinguishes between germinal center B-cell-like and activated B cell-like subtypes of diffuse large B cell lymphoma. *Int J Cancer* 2007; **121**: 1156–61.
75 Lawrie CH, Saunders NJ, Soneji S *et al.* MicroRNA expression in lymphocyte development and malignancy. *Leukemia* 2008; **22**: 1440–46.
76 Navarro A, Diaz T, Martinez A *et al.* Regulation of JAK2 by miR-135a: prognostic impact in classic Hodgkin lymphoma. *Blood* 2009; **114**: 2945–51.
77 Motsch N, Alles J, Imig J *et al.* MicroRNA profiling of Epstein–Barr virus-associated NK/T-cell lymphomas by deep sequencing. *PLoS ONE* 2012; **7**: e42193.
78 Saito Y, Suzuki H, Tsugawa H *et al.* Overexpression of miR-142-5p and miR-155 in gastric mucosa-associated lymphoid tissue (MALT) lymphoma resistant to Helicobacter pylori eradication. *PLoS ONE* 2012; **7**: e47396.
79 Paik JH, Jang JY, Jeon YK *et al.* MicroRNA-146a downregulates NFκB activity via targeting TRAF6 and functions as a tumor suppressor having strong prognostic implications in NK/T cell lymphoma. *Clin Cancer Res* 2011; **17**: 4761–71.
80 Monsálvez V, Montes-Moreno S, Artiga MJ *et al.* MicroRNAs as prognostic markers in indolent primary cutaneous B-cell lymphoma. *Mod Pathol* 2013; **26**: 171–81.
81 Kluiver J, Haralambieva E, de Jong D *et al.* Lack of BIC and microRNA miR-155 expression in primary cases of Burkitt lymphoma. *Genes Chromosom Cancer* 2006; **45**: 147–53.
82 Ralfkiaer U, Hagedorn PH, Bangsgaard N *et al.* Diagnostic microRNA profiling in cutaneous T-cell lymphoma (CTCL). *Blood* 2011; **118**: 5891–900.
83 Valleron W, Ysebaert L, Berquet L *et al.* Small nucleolar RNA expression profiling identifies potential prognostic markers in peripheral T-cell lymphoma. *Blood* 2012; **120**: 3997–4005.