MicroRNAs: tiny players with a big role in the pathogenesis of leukemias and lymphomas

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Abstract

MicroRNAs (miRNAs) are small non-coding RNAs (ncRNAs) with important regulatory functions. After an initial phase, aimed at identifying whether a deregulation in miRNA expression occurred between hematologic malignancies and their normal counterparts, currently an increasing number of studies are focusing on the functional significance of these aberrations. The identification of miRNA targeted genes has cast a new light on the role of these tiny ncRNAs in human cancerogenesis, providing a new rationale to the accepted that miRNAs are aberrantly expressed in almost all human cancers (both solid and hematologic malignancies), with respect to the normal counterpart. This review will focus on the role of miRNAs in the pathogenesis of human leukemias and lymphomas, highlighting diagnostic, prognostic, and therapeutic implications of this class of ncRNAs. Table 1 summarizes the most frequently de-regulated miRNAs in hematologic malignancies.

miRNAs in chronic leukemias

Chronic lymphocytic leukemia

Chronic lymphocytic leukemia (CLL) is the most common type of leukemia, characterized by the slow accumulation in blood, bone marrow and lymphatic tissue of small, non-proliferating, mature B lymphocytes, which display typical surface markers such as CD19 and CD20 in addition to CD5. More than 50% of CLLs are characterized by hemizygous and/or homozygous deletion of the genomic region 13q14. Calin et al. showed that a cluster of miRNAs, namely miR-15a/16-1, is located at chromosome 13q14 and that these miRNAs, situated within a 30-kb region of loss in CLL, are both deleted or down-regulated in approximately 68% of CLL cases. Among the targets of miR-15a/16-1, was identified BCL2, an anti-apoptotic protein which is over-expressed in the majority of CLL B cells, and it is believed to mediate the anti-tumoral effect of these miRNAs. This finding is supported by the fact that restoration of miR15a/16-1 induces apoptosis in MEG-01 cell line, derived from acute megakaryocytic leukemia, pointing out a role for miR15a/16-1 as tumor-suppressor genes (TSGs) in CLL, and maybe in other malignancies in which this cluster is down-regulated or lost. Croce’s group first identified a unique microRNA signature associated with prognostic factors and disease progression in CLL, and described a germline mutation in pre-miR-16 sequence, which causes low levels of microRNA expression both in vitro and in vivo. This mutation was associated with deletion of the normal allele in leukemic cells of 2 CLL patients one of which with a family history of CLL and breast cancer. Interestingly, Ravetch et al. described a point mutation in the 3’-DNA adjacent to

miRNAs and leukemias

Leukemia is a malignant disorder of the blood or bone marrow characterized by an abnormal proliferation of blood cells. Based on the stage of differentiation of the malignant cells, leukemias can be divided into acute and chronic. Acute leukemias are characterized by the rapid increase of immature blood cells (blood cell progenitors or primitive stem cells with multilineage potential) and are the most common forms of leukemia in children, while chronic leukemias arise from more mature cells during differentiation and occur more often among adults. Additionally, the diseases are subdivided, according to the origin of the neoplastic cells, into lymphoid leukemias, concerning the lymphoid pathway (B and T cells) and myeloid leukemias, which involve the cells that normally go on to form red blood cells, granulocytes, monocytes and platelets. It was recently reported that the pattern of miRNA expression varies strongly during the differentiation of hematopoietic stem/progenitor cells, playing a critical role in events that result in hematologic disorders. Leukemia is a malignant disorder of the blood or bone marrow characterized by an abnormal proliferation of blood cells. Based on the stage of differentiation of the malignant cells, leukemias can be divided into acute and chronic. Acute leukemias are characterized by the rapid increase of immature blood cells (blood cell progenitors or primitive stem cells with multilineage potential) and are the most common forms of leukemia in children, while chronic leukemias arise from more mature cells during differentiation and occur more often among adults. Additionally, the diseases are subdivided, according to the origin of the neoplastic cells, into lymphoid leukemias, concerning the lymphoid pathway (B and T cells) and myeloid leukemias, which involve the cells that normally go on to form red blood cells, granulocytes, monocytes and platelets. It was recently reported that the pattern of miRNA expression varies strongly during the differentiation of hematopoietic stem/progenitor cells, playing a critical role in events that result in hematologic disorders.
miR-16-1 region, which lets down the expression of this miRNA in the CLL-prone New Zealand black mouse strain model, indicating that this miRNA functions as an oncosuppressor in CLL. By analyzing the results of miR15a/16-1 hyperexpression in MEG-01 cells and in CLL patients both at the transcriptome and at the proteome level, Calin et al. found that about 14% of all human genome is directly or indirectly affected by miR15a/16-1 cluster. Among the genes which are down-regulated by this cluster, there are both oncogenes (OGs) and TSGs, suggesting that even though the overall effect of miR15a/16-1 overexpression is anti-tumoral in CLL, it cannot be excluded that other pathways may be impacted and lead to an overall oncogenic outcome in other diseases. Further investigations are warranted to verify this hypothesis.

Another 2 miRNAs with a TGS function in CLL are miR-29b and miR-181b, which directly target TCL1 (T-cell leukemia/lymphoma 1A), an OG which co-activates the protein kinase AKT (v-akt murine thymoma viral oncogene homolog 1) and takes part in the regulation of many pathways involved in cell survival, proliferation and death. As evi-

### Table 1. Main aberrantly expressed miRNAs in hematologic malignancies.

| miRNA                   | Location         | Function | Targets                          | Malignancy                  |
|-------------------------|------------------|----------|----------------------------------|------------------------------|
| miR15a/16-1 cluster     | 13q14.3          | TSG/OG   | BCL2                             | CLL, HL                     |
| miR-29b                 | 7q32.3 (miR-29b-1) | TSG      | TCL1                             | CLL                         |
| miR-181b                | 1q31.3 (miR-181b-1) | TSG      | TCL1, TLR4, CARD8, CASP1, IL1B, SLCL1A1, MSR1, CD64 | CLL, AML                    |
| miR-181a                | 9q33.3 (miR-181a-1) | TSG      | BCL2, TLR4, CARD8, CASP1, IL1B, SLCL1A1, MSR1, CD64 | CLL, AML                    |
| miR-155                 | 21q21.3          | OG       | AGTR1, FGFR7, ZNF537, ZIC3, IKBKE | CLL, AML (FLT-IDT+), HL, NHL (BL, ABC-DLBCL) |
| miR-17-92 cluster       | 13q31.3          | OG/TSG   | E2F1, PTEN, BIM                 | CML, ALL, HL, NHL (B cell lymphomas) |
| miR-203                 | 14q32.33         | TSG      | ABL1                            | CML                         |
| miR-128a (miR-128-1)    | 2q21.3           | OG/TSG   | N/A                             | High in ALL vs. AML; low in HL EBV+ |
| miR-128b (miR-128-2)    | 3p22.3           | OG/TSG   | N/A                             | High in ALL vs. AML; low in HL EBV+ |
| let-7b                  | 22q13.31         | OG/TSG   | RAS                             | High in AML vs. ALL         |
| miR-223                 | Xq12             | OG       | N/A                             | High in AML vs. ALL         |
| miR-204                 | 9q21.11          | TSG      | HOXA10, MEIS1                   | AML (NPM1 mut)              |
| miR-34b                 | 11q23.1          | TSG      | CREB                            | AML                         |
| miR-9                   | 1q22 (miR-9-1)   | OG       | PRDM1/Blimp-1                   | HL                          |
|                        | 5q14.3 (miR-9-2) |          |                                  |                             |
|                        | 15q26.1 (miR-9-3) |         |                                  |                             |
| let-7a                  | 9q22.32 (let-7a-1) |        | RAS, PRDM1/Blimp-1              | HL                          |
|                        | 11q24.1 (let-7a-2) |        |                                  |                             |
|                        | 22q13.31 (let-7a-3) |       |                                  |                             |
| miR-96                  | 7q32.2           | TSG      | N/A                             | Low in HL EBV+              |
| miR-21                  | 17q23.1          | OG       | PTEN, PDCD4                     | HL, NHL (ABC-DLBCL)         |
| miR-24                  | 9q22.32 (miR-24-1) | TSG      | N/A                             | HL                          |
|                        | 19p12.8 (miR-24-2) |         |                                  |                             |
| miR-150                 | 19q13.33         | TSG      | N/A                             | HL                          |
| miR-221                 | Xp11.3           | OG       | N/A                             | NHL (ABC-DLBCL)             |
| miR-143                 | 5q33.1           | TSG      | ERK5                            | NHL (B-cell lymphomas)      |
| miR-145                 | 5q33.1           | TSG      | ERK5                            | NHL (B-cell lymphomas)      |

OG: oncogene; TSG: tumor suppressor gene; BCL2: B-cell CLL/lymphoma 2; TCL1: T-cell leukemia/lymphoma 1b; TLR4: toll-like receptor 4; CARD8: caspase recruitment domain family, member 8; ZNF537: zinc finger homeobox 3; ZIC3: zinc family member 3 (odd-paired homolog, Drosophila); HOXA10: inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase epsilon; E2F1: E2F transcription factor 1; PTEN: phosphatase and tensin homolog; BCL2-like 11 (apoptosis facilitator); ABL1: c-abl oncogene 1, receptor tyrosine kinase; RAS: rat sarcoma virus; HOXA10: homeobox A10; MEIS1: myeloid ecotropic viral integration site 1 homolog; CREB: cAM P responsive element binding protein 1; PRDM1/Blimp-1: PR domain containing 1, with ZNF domain; PDCD4: programmed cell death 4 (neoplastic transformation inhibitor); ERK5: mitogen-activated protein kinase 7; N/A: not available; CLL: chronic lymphocytic leukemia; ALL: acute lymphocytic leukemia; CML: chronic myeloid leukemia; AML: acute myeloid leukemia; HL: Hodgkin’s lymphoma; NHL: Non-Hodgkin’s lymphoma; BL: Burkitt’s lymphoma; DLBCL: diffuse large B-cell lymphoma; ABC: activated B-cell phenotype; EBV+: Epstein-Barr virus positive; FLT-IDT+: Ims-related tyrosine kinase 3 gene internal tandem duplication; NPM1 mut: nucleophosmin-1 mutation.
denced by transgenic mouse models, TCL1 is a marker of aggressive CLL and its high levels are associated with high levels of ZAP-70 (70 kD zeta chain-associated protein kinase) and unmutated IgV status which are both markers of poor prognosis in CLL. In a recent study, a correlation between low levels of miR-29c and poor prognosis was observed in CLL patients. In a 110 patient cohort with a median follow-up of 72 months, the authors showed for the first time that a specific threshold of expression for miR-29c and miR-223 can predict treatment-free survival (TFS) and overall survival (OS). While miR-181b targets TCL1, miR-181a directly targets BCL2, together with miR-15a/16-1 cluster, suggesting a central role of the miR-181 family members in the pathogenesis of CLL. A study aimed at investigating a possible correlation between the two groups of miRNAs was warranted.

Finally, miR-155 was shown to be up-regulated in CLL versus normal CD19+ B cells, and the role of this miRNA will be analyzed more extensively in the paragraph of lymphomas.

**Chronic myeloid leukemia**

Using microarray analysis (miCHIP) and miRNA-specific quantitative real-time reverse transcriptase-polymerase chain reaction (miR-qRT-PCR), Venturini et al. reported BCR-ABL1- and c-MYC-dependent transactivation of miR-17-92 cluster, a polycistronic gene located in human chromosome 13 ORF 25 (C13orf25) at 13q31-q32 and composed of 7 mature miRNAs namely miR-17-5p, miR-17-3p, miR-18a, miR-19a, miR-20a, miR-19b and miR-92-1, in chronic myeloid leukemia cell lines. BCR-ABL1-MYC pathway can induce this transactivation in early chronic phase but not in blast crisis CML CD34+ cells, suggesting a role for miR-17-92 cluster in the pathogenesis of chronic myeloid leukemia (CML).

Recently, Bueno et al. identified a fragile chromosomal region lost in specific hematopoietic malignancies, which encodes about 12% of all genomic miRNAs, including miR-203 which directly targets ABL1. In a T-cell lymphoma model, both genetic and epigenetic mechanisms inactivated this miRNA. Specifically the miR-203 promoter resulted hypermethylated in chromosome Philadelphia positive (Ph+) tumors, including B-cell ALLs, primary CMLs and cultured CML cell lines while no methylation was observed in hematopoietic tumors that do not carry ABL1 alterations. Re-expression of miR-203 reduces ABL1 and BCR-ABL1 fusion protein levels and inhibits tumor cell proliferation in an ABL1-dependent manner, putting forward the role of miR-203 as a TSG whose re-expression might have therapeutic benefits in specific hematopoietic malignancies. It would be intriguing to investigate whether the silencing effect of miR-203 on ABL1 can have any indirect or modulatory consequence on the miR-17-92 cluster.

**miRNAs in acute leukemias**

**Acute lymphocytic leukemia**

Acute lymphocytic leukemia (ALL) is one of the most common malignancies observed in the pediatric age and it represents about the 80% of cases of acute leukemia in children. It arises from the clonal proliferation of lymphoid progenitors in the bone marrow whose consequence is the occurrence of several different cytoptensin in the peripheral blood associated with the appearance of peripheral blast cells. In 2007, Zanette et al. analyzed miRNA expression profiles in 7 ALL samples and 6 normal CD19+ samples in order to compare them. They first reported the involvement of miR-128b, miR-204, miR-218, miR-331 and miR-181b-1 in hematologic malignancies, with miR-128b as the most represented miRNA in ALL. In their analysis also the miR-17-92 cluster resulted up-regulated in all 7 samples. The nucleotide sequences and organization of this cluster is highly conserved in vertebrates, and its expression is tightly regulated during B-cell development. A role of miR-17-92 cluster to promote survival of early B-cell progenitors in a cell-autonomous manner, and control cell survival during the pro-B to pre-B transition was recently suggested by Ventura et al. They proposed that in human B-cell lymphomas miR-17-92 overexpression is induced at the pro-B to pre-B transition where it acts to silence the expression of the pro-apoptotic protein Bim, leading to an abnormal survival of pro-B lymphocytes. In another study, Mi et al. tried to understand the distinct mechanisms in leukaemogenesis between ALL and AML and to identify markers for diagnosis and treatment, performing a large-scale genomewide microRNA expression profiling assay. They identified 27 miRNAs that are differentially expressed between ALL and AML. Among them, miR-128a and miR-128b which are up-regulated in ALL vs. AML, and let-7b, miR-223 which are down-regulated in ALL vs. AML, can lead to a differential diagnosis between the acute leukemias, with an accuracy of 98%. Furthermore, they found that overexpression of miR-128 in ALL was at least partly associated with its promoter hypomethylation and not with an amplification of its genomic locus, suggesting an important role of epigenetics in the regulation of the expression of miRNAs in acute leukemias. The leukemic mechanism of miR-128b remains still poorly understood.

**Acute myeloid leukemia**

Recently, several works have analyzed which aberrancies in the miRNome (defined as the full spectrum of miRNAs expressed in a particular cell type) occur in acute myeloid leukemia (AML) patients. Garzon et al. investigated 240 AML patient samples to determine whether miRNAs are associated with cytogenetic abnormalities and clinical features in acute myeloid leukemia. For this purpose, they evaluated miRNA expression of CD34+ cells and 122 untreated adult AML cases using a microarray platform. They identified some miRNAs differentially expressed between CD34+ normal cells and the AML samples whose expression was also closely associated to selected cytogenetic and molecular abnormalities, such as t(11q23), isolated trisomy 8, and FLT3-ITD (fms like tyrosine kinase 3 in tandem duplication) mutations. Furthermore, they found that patients with high expression of miR-191 and miR-199a were associated with worse overall and event-free survival than AML patients with low expression, suggesting a possible prognostic role for these 2 miRNAs.

In normal karyotype, AML nucleophosmin-1 (NPM1) and FLT3-ITD mutations are frequently found. In NPM1 mutated cases up-regulation of miR-10a, -10b, several let-7 and miR-29 family members, as well as down-regulation of miR-204 were observed. Intriguingly, miR-204 targets the HOX genes HOXA10 and MEIS1, suggesting that the HOX up-regulation observed in NPMc+ AML (cytoplasmic nucleophosmin) may be due at least in part to loss of HOX regulator-miRNAs. FLT3-ITD+ samples showed up-regulation of miR-155 which was demonstrated to be strongly but independently associated with FLT3-ITD mutations. In a retrospective study conducted on samples of leukemia cells from patients who had cytogenetically normal AML and high-risk molecular features such as FLT3-ITD+, a wild-type NPM1 or both, Marcucci et al. found that expression levels of microRNA-181 family were inversely correlated with those of predicted target genes encoding proteins which take part in pathways controlled by toll-like receptors and interleukin-1β (Table 1). In another study, Fazi et al. analyzed patient’s primary leukemia blasts, and demonstrated that those carrying the t(8;21), which generates the most common acute myeloid leukemia-associated fusion protein AML1/ETO, exhibited low levels of miRNA-223, a regulator of myelopoiesis. They showed that miR-223 is a direct transcriptional target of AML1/ETO which causes heterochromatin silencing of this miRNA by recruiting chromatin remodeling enzymes at an AML1-binding site on the pre-miR-223 gene. Ectopic miR-223 expression, RNA interference against AML1/ETO, or demethylation enhance miR-223 levels and restore cell differentiation. These findings confirm a central role of miR-223 in
miRNAs and lymphomas

MiRNAs are involved in the pathogenesis of both Hodgkin and non-Hodgkin lymphomas. There are many studies that describe the role of miRNAs in these two groups of lymphomas.

Hodgkin lymphoma
Nie et al. showed that miR-9 and let-7a target PRDM1/Blimp-1 in Hodgkin lymphoma cell lines. In fact, the levels of miR-9 and let-7a inversely correlated with PRDM1/Blimp-1 expression in Hodgkin lymphoma (HL) cells. Similar to their in vitro counterparts, the majority of cells in primary HL cases showed weak to no PRDM1/Blimp-1 expression. Navarro et al. analyzed the expression of miRNAs in 49 HL patients and 10 reactive lymph node cases. They identified 25 miRNAs discriminating HL from reactive lymph nodes and 36 miRNAs differentially expressed in nodular sclerosis and mixed cellularity subtype.

The obtained results, validated in a set of different cell lines, showed that miR-9, miR-128a, and miR-128b were selectively down-regulated in HL with EBV. Moreover, only one of the miRNAs differentially expressed in EBV cases was enclosed in the 25 miRNA that distinguishes HL from reactive lymph nodes, leading to the intriguing conclusion that EBV might not be a relevant event in HL pathogenesis.

Gibcus et al. described a specific miRNA expression profile in HL cell lines. By comparing HL with a panel of B-cell non-Hodgkin lymphomas, they identified a signature of HL-specific miRNAs, which included miR-17-92 cluster members, miR-16, miR-21, miR-24, and miR-155. A significant down-regulation in HL was observed for miR-150 whereas an important up-regulation in HL was shown for miR-155. Moreover, the authors identified AGTR1, FGFR7, ZNF537, ZIC3, and IKKBE as true miR-155 target genes in HL. Interestingly, high levels of miR-155 have also been observed in the germinal center during normal lymphopoesis. Since HL has its origin in the lymph-nodal germinal center, the hypothesis that overexpression of miR-155 is a result of an aberrant lymphopietic block of differentiation in the germinal center is compelling.

Non-Hodgkin lymphomas
Up-regulation of miR-155 has also been described in Non Hodgkin lymphomas (NHLs), as well as in several other solid and hematologic malignancies. The first hint of miR-155 involvement in lymphomagenesis derived from the observation that the final part of the B-cell integration cluster (BIC) non-coding RNA (ncRNA), where miR-155 is positioned, increases MYC-mediated lymphomagenesis in a chicken experimental model. Klüver et al. showed that the expression of both miR-155 and its host gene is induced by protein kinase C and NF-kB in several cell lines, except Ramos, a Burkitt's lymphoma cell line, in which, for yet unclear reasons, the overexpression of BIC is not accompanied by up-regulation of miR-155. Transgenic and knockout (KO) miR-155 mice models have significantly contributed to clarify the function of this ncRNA. In Costinean's transgenic mouse model, miR-155 overexpression caused a polyclonal pre-leukemic pre-B-cell proliferation followed by full blown B-cell malignancy, providing in vivo evidence of this miRNA involvement in the pathogenesis of hematologic malignancies.

Conversely, KO mice models showed impairment of cytokine production towards T2 lymphocyte differentiation, and compromised function of dendritic cells, confirming the data of Tili et al., who showed a central role of miR-155 in regulating the immune response.

In a subgroup of NHLs, the diffuse large B-cell lymphomas (DLBCL), miR155 up-regulation occurs in the activated B-cell phenotype (ABC-DLBCL) with respect to the germinal center B-cell-like phenotype (GCB-DLBCL). Since ABC-DLBCL and GCB-DLBCL have 5-year survival rates of 30% and 39%, respectively, miR-155 expression harbors prognostic implications. In ABC-DLBCL also high levels of miR-21 and miR-221 were described, suggesting a 3 miRNA-signature specific of the histotype of DLBCL with severe prognosis. Roehle et al. compared the miRNAome of DLBCL, follicular lymphomas and reactive lymph nodes. In particular, they found that 4 miRNAs (namely miR-330, -17-5p, -106a and -210) can discriminate DLBCL, follicular lymphomas and reactive lymph nodes with an accuracy of 98%. It is compelling that among the de-regulated miRNAs of Roehle's work, there are miR-17-5p and miR-106a, members of two paralogous clusters with a documented role as oncogenes in several human malignancies.

Located at 13q31-32, miR-17-92 cluster is frequently amplified in malignant B-cell lymphomas, and is over-expressed in 65% of B-cell lymphoma patients. Overexpression of miR-17-92 in murine multipotent progenitor cells (MPPs) of MYC-transgenic mice caused an increased lymphomagenesis. Xiao et al. generated mice with high miR-17-92 lymphoctic expression and described a higher rate of lymphoproliferative disorders, autoimmunity and premature death. These pathological characteristics were induced by down-regulation of the oncosuppressor genes PTEN and BIM. O'Donnell et al. showed that c-MYC activates 2 members of the cluster (namely miR-17-5p and miR-20a), which directly target E2F1, a c-MYC transactivated transcription factor promoting cell-cycle progression. In summary, by directly transactivating E2F1 and indirectly (through miR-17-92 cluster) repressing its translation, c-MYC functions as a key-regulator of cell-cycle progression. Recently, Li et al. investigated genome-wide miRNA expression and copy number in 86 DLBCLs (59 primary tumors and 27 cell lines), and identified a collection of miRNAs that robustly segregated DLBCLs into three subgroups not related to the cell-of-origin classification, extent of T-cell infiltrate and tumor site. In particular, the three newly identified subsets of DLBCLs had different prognosis and showed a markedly different MYC transcriptional activity, which was correlated with the dominance of MYC-regulated miRNAs in their expression signatures. Finally, also miR-143 and miR-145 expression is reduced in B-cell malignancies.

In Burkitt's lymphoma Raji cell line, restoration of these two miRNAs caused a dose-dependent growth inhibitory effect linked to a down-regulation of Erk5, a MAP kinase directly targeted by miR-143 and miR145.

Conclusions
There is increasing evidence in literature to support a central role for miRNAs in the pathogenesis of hematologic malignancies. Aberrancies in miRNA expression lead to abnormal gene regulation and, ultimately, to a severe alteration in proteic effectors with oncogenetic and/or oncosuppressor function. From the initial contribution of high-throughput techniques, which allowed the identification of the de-regulated miRNAs, currently many efforts are being made to understand the
functional implications of miRNA aberrant expression. For several hematologic malignancies, a clear diagnostic and prognostic role of miRNA de-regulation has been demonstrated. The identification of miRNA targeted mRNAs is clarifying which oncogenic pathways are affected by the leukemic/lymphomatous miRNome. This knowledge represents the essential background to the development of new miRNA-based therapeutic approaches, which combine the advantage of a physiologic molecule (such as an miRNA-derived drug), to the possibility of targeting with a single molecule several members of the same and/or of several aberrantly activated pathways in the malignancy. More studies are warranted to determine how big is the impact of these tiny RNA molecules in human cancerogenesis. However, there is no doubt that these ncRNAs play a role in hematologic malignancies. Decoding this role has diagnostic, prognostic and therapeutic implications of the utmost importance.

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