The MYC/miR-17-92 axis in lymphoproliferative disorders: A common pathway with therapeutic potential

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ABSTRACT

MicroRNAs (miRNAs) represent a class of small non-coding single-stranded RNA molecules acting as master regulators of gene expression post-transcriptionally by inhibiting the translation or inducing the degradation of target messenger RNAs (mRNAs). In particular, the miR-17-92 cluster is widely expressed in many different cell types and is essential for many developmental and pathogenic processes. As a strong oncogene, miR-17-92 can regulate multiple cellular processes that favor malignant transformation, promoting cell survival, rapid cell proliferation, and increased angiogenesis. The miR-17-92 cluster has been reported to be involved in hematopoietic malignancies including diffuse large B-cell lymphoma, mantle cell lymphoma, Burkitt’s lymphoma, and chronic lymphocytic leukemia. Given the multiple and potent effects on cellular proliferation and apoptosis exerted by the miR-17-92 cluster, miRNAs belonging to the cluster surely represent attractive targets for cancer therapy also in the context of lymphoproliferative disorders. In the present review, we focus on the role of the miR-17-92 cluster in lymphoproliferative disorders, including diagnostic/prognostic implications, and on the potential applications of anti-miRNAs based therapies targeting miRNAs belonging to the cluster.

INTRODUCTION

MicroRNAs (miRNAs) represent a class of small non-coding single-stranded RNA molecules of 17–27-nucleotides in length that act as master regulators of gene expression post-transcriptionally by inhibiting the translation or inducing the degradation of target messenger RNAs (mRNAs) with partially complementary sites in the 3′-untranslated regions [1, 2]. Given these multiple roles, miRNAs aberrant expression and dysregulation often results in human diseases and cancer [3–9]. The first miRNAs related with cancer were miR-15a/miR-16–1 whose cluster is located in the chromosome region 13q, commonly deleted in chronic lymphocytic leukemia (CLL) [10]. The deletion was proposed as one of the primary genetic event in CLL, due to a decreased expression of the miR-15a/miR-16–1 targeting the BCL2 gene [10]. Other evidence of the association between miRNA dysregulation and cancer came from studies revealing that many miRNAs are effectively located in genomic regions frequently involved in chromosomal alterations, including breakpoint deletions or amplifications related to cancer [11, 12]. Overall considered, these studies indicate that the contribute of miRNAs to cancer pathogenesis is dependent of two opposite functions: either they can act as tumor suppressors, as in the case of the miR-15a/miR-16–1 cluster in CLL, or they can act as oncogenes, as it has been proposed for the members of the miR-17-92 cluster that is the topic of the present review [13].

In this review we first describe the miR-17-92 cluster locus along with the main mechanism(s) of expression regulation and the major molecular interactions of the miR-17-92 cluster in normal and neoplastic B cells. Then, we review the main clinical and pathogenetic implications of miR-17-92 cluster expression in lymphoproliferative
disorders and the potential applications of anti-miRNAs based therapies targeting miRNAs belonging to the cluster.

**The miR-17-92 chromosomal locus**

The miR-17-92 polycistronic miRNA cluster is located in a region of 800 bp in the non-protein-coding gene C13orf25 at 13q31.3 (Figure 1A) [14]. The precursor transcript derived from the miR-17-92 gene (a.k.a. MIR17HG) contains six tandem-loop hairpin structures that ultimately yield the six mature miRNAs miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1 and miR-92a-1 [14]. Moreover, complementary miRNAs derived from the opposite strands of each miR-17-92 pre-miRNA have been identified. The biological importance of the miR-17-92 cluster is also underlined by the presence of paralogs on chromosome X and chromosome 7, the miR-106a-363 cluster and the miR-106b-25 cluster, respectively, that both contains homologous miRNAs to a subset of miR-17-92 components (Figure 1B). Three separate miRNA families according to miRNA seed sequences have been defined: the miR-17 (that includes miR-17, miR-20a and miR-18a), miR-19 (that includes miR-19a and miR-19b-1), and miR-92 families (Figure 1C). Both miR-17 and miR-19 families are composed also by miRNAs belonging to the paralogs (Figure 1C). All these miRNAs derive from an unique gene that, during the early evolution of vertebrates, underwent a series of different dysregulations, such as duplications, mutations and losses [15].

The six members of the miR-17-92 cluster can act independently and/or coordinately to target various mRNA, according to the degree of binding affinity and the seed sequences of the various members of the cluster (Figure 1C). As a strong oncogene, miR-17-92 regulates multiple cellular processes that favor malignant transformation promoting cell survival, rapid cell proliferation, and increased angiogenesis [16–19]. Given the oncogenic role of the miR-17-92 cluster, the primary transcript for these miRNAs was named ‘OncomiR-1’ [17].

The 13q31.3 human genomic locus undergoes amplification in several types of lymphoproliferative disorders and solid tumors [20, 21], and, consistently, aberrant overexpression of the miR-17-92 cluster in the absence of amplification is also frequently observed in some tumors. The miR-17-92 cluster has been reported to be involved in hematopoietic malignancies including diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), Burkitt’s lymphoma (BL), and CLL (Table 1) [14, 21–26]. In general, a significant over expression of pri- miR-17-92 has been observed in 65% of B-cell lymphoma patients [17].

**Expression regulation of the miR-17-92 cluster**

A number of oncogenic transcription factors (TFs) regulate the expression of miR-17-92 cluster thus influencing its oncogenic activity (Figure 2) [27, 28]. In particular, MYC, the first identified transcription regulator of miR-17-92, activates miR-17-92 expression by directly binding to its genomic locus [17, 18, 29]. Similarly, miR-17-92 can be also upregulated by MYCN, as demonstrated in neuroblastoma cells [30, 31]. In addition to MYC, TFs belonging to the E2F family, e.g. E2F1, E2F2, E2F3, are other potent inducers of the miR-17-92 cluster [32]. The E2F TFs are essential for cell cycle progression; in fact, they activate a large number of S phase genes, including thymidine kinase, DNA polymerase, Cyclin A and Cyclin E. Thus, cycling cells are likely to have elevated levels of miR-17-92 due to periodic burst of E2F activity during S phase, while quiescent cells may have reduced miR-17-92 levels. Other TFs that directly activate the transcription of miR-17-92 are two TFs belonging to the ETS family, SPI-1 and FLI-1, as demonstrated in the murine Friend’s leukemia model [33]. Finally, STAT3 can also regulate the expression of the miR-17-92 cluster at transcriptional level [34]. Notably, miR-17-92 can be also transcriptionally repressed by tumor suppressors, e.g. TP53 in hypoxia-treated cells, or via histone modification [35–37].

**Major molecular interactions of the miR-17-92 cluster**

The major functional evidence of the oncogenic activity of miR-17-92 comes from several studies employing B-cell lymphoma in-vivo mouse models. In a first model, in which MYC is driven by the immunoglobulin heavy chain enhancer (Eμ) as a transgene, the enforced expression of a truncated miR-17-92 lacking the miR-92a-1, e.g. miR-17–19b, collaborated with the MYC to accelerate lymphomagenesis. Of note, the overexpression of miR-17–19b not only promotes the oncogenesis of MYC expressing B cells, but also alters the cell fate of transformed B cells. In fact, while the majority of B cell lymphomas derived from the Eμ-MYC transgene have a mature B-cell phenotype, B-cell lymphomas resulting from the collaboration between miR-17–19b and MYC are mostly derived from precursor cells [17]. In this context, a key oncogenic role is conducted by miR-19a and miR-19b-1 as indicated by the fact that mutations of both miR-19 miRNAs nearly abolish the oncogenic cooperation between MYC and miR-17-92 [38–40]. On the other hand, in Eμ-MYC chimeric mice, it was demonstrated that this oncogenic cooperation is significant stronger when miR-92a-1 is deleted within the oncomir, as well as when the seed sequence of the miR-92a-1 is mutated [41]. Moreover, mutations of miR-20a or of miR-17 did not affect oncogenesis in the Eμ-MYC model [41].

Regarding the oncogenic cooperation between MYC and miR-17-92 [42], it has been demonstrated that MYC directly suppresses through miR-17-92 the expression of the chromatin regulatory genes SIN3B, HBP1, SUI420 and BTG1 and the proapoptotic gene BCL2L11 (a.k.a. BIM), this suppression contributing to maintain survival, autonomous proliferation, and self-renewal.
Figure 1: The miR-17-92 cluster. A. Genomic localization of the miR-17-92 cluster (MIR17HG). The two transcripts of the gene are reported in blue. The miRNAs belonging to the cluster are reported in red. The panel of the figure was created modifying the output of the UCSC genome browser. B. Structure of the miR-17-92 cluster (MIR17HG, located on chromosome 13) and of the two paralogs (located on chromosomes X and 7). Both paralogs contains homologous miRNAs to a subset of miR-17-92 components. C. miRNA families of the miR-17-92 cluster. Four separate miRNA families according to miRNA seed sequences have been defined: the miR-17, miR-18, miR-19 and miR-92 families. miR-17, miR-18 and miR-19 families are composed also by miRNAs belonging to the paralogs. Seed sequences are reported in bold.
Moreover, according to another study [43], mice with exogenously induced miR-17-92 overexpression in lymphocytes developed an aggressive lymphoproliferative disorder associated with autoimmunity followed by a premature death. This study also reported that, in the transgenic lymphocytes, the miR-17-92 cluster down-regulated PTEN and BCL2L11, thus enhancing proliferation and survival [43]. This observation was confirmed by other studies employing B cell specific transgenic mouse models, in which miR-17-92 overexpression induced B cell malignancies such as splenic B cell lymphomas or B cell leukemia/lymphomas [44, 45]. Seventeen genes, predicted to be targets of the miR-17-92 cluster, have been found consistently downregulated in Eμ miR-17-92 cells [45]. In transgenic mice specifically overexpressing miR-17-92 in B cells [29], the miR-17-92 cluster drives lymphomagenesis by suppressing the expression of multiple inhibitors of the PI3K and NFκB pathways and by inhibiting the mitochondrial apoptosis pathway [29]. In the same study, miR-17-92-driven lymphoma cells showed constitutive activation of the PI3K and NFκB pathways, and chemical inhibition of these pathways was useful to treat these lymphomas [29]. Moreover, as described in mice overexpressing miR-17-92 in hematopoietic lineages [46], the expression of the miR-17-92 cluster in a limited number of hematopoietic cells is sufficient to develop B cell malignancies, further highlighting the ability of miR-17-92 to act as driver of tumorigenesis. On the other hand, the role of the miR-17-92 cluster in the B cell development is also defined by the fact that a deficiency of miR-17-92 impairs this process, particularly at the pre-B to pre-B transition stage, due to enhanced apoptosis occurring in the pre-B cells during both fetal and adult B cell development [19].

Among the miRNAs belonging to the miR-17-92 cluster, miR-17 and miR-20a are those that target the largest number of genes. In particular, these miRNAs are able to control the expression of genes with antagonizing functions, e.g. promoting or suppressing cell cycle progression [47], thus reflecting the complex and partially conflicting effects of miRNAs in tumor growth. In this context, the E2F TFs, direct targets of MYC [48], are among the genes down-regulated by miR-17 and miR-20a. Thus, a tightly controlled proliferative loop is represented by MYC that simultaneously activates the E2F TFs and limits their translation by a miRNA-based mechanism [18]. In this process, a role can be exerted by RB1 and the other hypophosphorylated retinoblastoma proteins that inhibit E2F TFs and, in turn, are repressed by miR-17 and miR-20a [49, 50]. CCND1 (a.k.a. Cyclin D1) is also regulated by miR-17 and miR-20a. On the other hand, both E2Fs and CCND1 are able to bind the miR-17-92 promoter establishing a negative feedback loop [32, 51, 52].

The miR-17 can also act as regulator of cell cycle by directly targeting more than 20 genes involved in the G1/S phase cell cycle transition. In this context, miR-17, by inhibiting the mitogen-activated kinase JNK2, a cell cycle promoting protein [47], may have also a tumor suppressive role that has been demonstrated by evidence showing that loss of heterozygosity at 13q31.3 is associated with tumor progression and poor prognosis in several cancers [12, 53].

### Interaction of the miR-17-92 cluster with the B cell receptor (BCR)

The role of the miR-17-92 cluster has also been investigated in the regulation of the BCR pathway. In this context, information has been obtained by taking advantage of the P493–6 cell line, an Epstein-Barr virus-immortalized lymphoblastoid cell line with a tet-repressible MYC gene and a significant enrichment of MYC repressed genes, all with the predicted binding sites for miRNAs of the miR-17-92 cluster [54]. In particular, genes for the ITIM-containing proteins CD22 and CD32b were identified as direct targets of the miR-17-92 cluster. Moreover, either MYC or miR-17-92 expression have been found necessary to sustain phosphorylation of the BCR pathway proteins SYK and BLNK upon BCR ligation. Furthermore, stimulation of the BCR response in miR-17-92 overexpressing cells results

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### Table 1: miR-17–92 cluster overexpression in lymphoproliferative disorders

| Disease         | miR-17-92 dysregulation                      | Genomic aberrations | References |
|-----------------|---------------------------------------------|---------------------|------------|
| DLBCL           | overexpression                              | 13q31.3 amplification; MYC aberration in complex karyotypes | [17]; [26]; [57]; [58]; [59]; [61]; [62]; [64]; [65]; [56] |
| MCL             | overexpression                              | 13q31.3 amplification | [24]       |
| BL              | overexpression                              | 13q31.3 amplification; MYC translocation | [77]; [78]; [79]; [80]; [81]; [82] |
| CLL             | overexpression upon microenvironmental stimuli compared to the unstimulated counterpart | absence of associated genomic aberrations | [22]; [94] |

Abbreviations: DLBCL, diffuse large B cell lymphoma; MCL, mantle cell lymphoma; BL, Burkitt’s lymphoma; CLL, chronic lymphocytic leukemia.
in enhanced calcium influx and elevated levels of MYC. Consistently, inhibition of the miR-17-92 cluster was demonstrated to diminish the BCR response as measured by SYK and BLNK phosphorylation [54].

**Dysregulation of the miR-17-92 cluster in DLBCL**

DLBCL is a heterogeneous lymphoproliferative disease in which different molecular subtypes have been identified involving the deregulation of distinct signalling pathways [55]. Among the three molecular DLBCL subtypes recognized by gene-expression profiling, those classified as germinal centre B cell-like (GCB) DLBCL harbour frequent 13q31.3 amplification. Overexpression of the miR-17-92 cluster members was a consequence of such an amplification, as found in leukemia/lymphoma cell lines bearing 13q amplification [56], or due to an overexpression of MYC [17, 26, 57–59]. In DLBCL, MYC gene aberrations were found in less than 10% of the cases at diagnosis [60] and in almost 20% at first relapse [61, 62]. MYC aberration in DLBCL usually associates with complex karyotypes and BCL2 and BCL6 rearrangements [63]. MYC protein overexpression...
Dysregulation of the miR-17-92 cluster in BL

In a recent study [76], high miR-17-92 overexpression has been found in BL, thus confirming that the activation of the MYC/miR-17-92 axis is a general feature of this disease. In addition, gain of 13q31.3 has been found to occur in about 10–20% of BLs and to associate with miR-17-92 overexpression [77, 78]. Of note, the MYC gene is translocated to one of the immunoglobulin loci in virtually all BLs. In particular, the typical translocation of MYC into the immunoglobulin heavy chain locus is observed in about 80% of BLs whereas the variant translocation into either the κ or λ light chain loci occurs at a frequency of about 10% [79]. The juxtaposition of the immunoglobulin heavy chain or of the κ/λ light chain loci with MYC are required for the induction of translocated MYC transcription [80–82]. The transcription of the translocated MYC is greater than that seen in resting B-cells and similar to that of actively dividing non-malignant B cells such those infected by EBV [79]. This overexpression can induce higher miR-17-92 levels. Moreover, the deletion of miR-17-92 in established MYC-driven lymphoma cell lines decreased the capability to growth in tissue culture and immunodeficient hosts, in keeping with the concept that miR-17-92 levels influences proliferation of these cells [39].

Dysregulation of the miR-17-92 cluster in CLL

In a study in which miRNA expression was compared in CLL with or without TP53 abnormalities [83], a significant down regulation of miR-17 in cases harbouring TP53 deletion/mutation was shown. These data were subsequently confirmed in an another study in which CLL patients lacking TP53 expression and displaying aggressive disease exhibit reduced miR-17 and miR-20a level of expression and increased miR-19a,
miR-19b-1 and miR-92a-1, whereas miR-18a levels were unchanged, compared to healthy normal controls [44]. In contrast, patients expressing wild type TP53, exhibit increased levels of miR-17 and miR-20a, unchanged levels of miR-18a, miR-19a, miR-19b-1 and lower levels of miR-92a-1 [44]. The loss of TP53 may selectively effect the processing of miR-17-92 miRNA, resulting in the imbalanced expression of its encoded units [84].

Concerning the ability of miRNA belonging to the miR-17-92 cluster to predict disease outcome, the debate is still open. In this context, miR-20a expression has been found to correlate with time to treatment in CLL [85].

Regarding the capacity of microenvironmental stimuli to induce miRNA expression, in a study of some of us [22], expression of miRNAs from the miR-17-92 cluster were up-regulated upon TLR9 triggering by CpG, compared to unstimulated cells, in CLL cells bearing an unmutated BCR, whereas no difference was detected in the context of a mutated configuration. In this study, the miR-17-92 overexpression due to TLR9 stimulation was correlated with the concomitant gene expression signature. In particular, it has been shown that the enforced expression of miR-17 in primary unmutated IGHV CLL cells reduces the expression of the tumor suppressor genes E2F5, TP53INP1, TRIM8 and ZBTB4. Among these genes, ZBTB4 and TP53INP1 are involved in apoptosis regulation through CDKN1A and TP53 [86, 87], E2F5 is involved in the G1 arrest [88], and TRIM8, is involved in the degradation of SOCS1, a well-known regulator of the response to CpG [89]. All these genes were identified as direct targets of miR-17, as evidenced by their significant downregulation upon ectopic miR-17 overexpression. In the same study [22], we also demonstrated that the stable and sustained up-regulation of miRNAs belonging to the miR-17-92 cluster in unmutated IGHV CLL by CpG is preceded by induction of MYC, thus providing evidence of an associative interaction between MYC and miR-17-92 cluster also in CLL cells. In agreement with these results, miR-17 transfection was also demonstrated to be sufficient to reduce apoptosis induced by serum deprivation in a series of primary unmutated IGHV CLL cells. Consistently, as indicated by experiments in primary CLL cells, transfection with miR-17-92 cluster antagonmiRs reduces bromo-deoxy-uridine incorporation in CpG-stimulated unmutated IGHV CLL cells [22]. Moreover, the expression of miR-17 was demonstrated to be significant higher in unmutated IGHV CLL cells expressing high ZAP70 compared with the IGHV-mutated/ZAP70-low counterpart [22]. This evidence could suggest that IGHV-unmutated/ZAP70-high CLL cells are more frequently subjected to signals capable of activating the TLR9 pathway, or, alternatively, that the former cells have a greater capacity to respond to microenvironmental signals, including those delivered through TLR9 stimulation [90–93].

Further evidence regarding the induction of miR-17-92 expression by microenvironmental stimuli has been provided in another study in which miRNAs belonging to the miR-17-92 cluster have been found to be differentially expressed and up regulated by the co-culture with stromal cells with or without the co-stimulation with the CD154 molecule [94]. Specifically, four out of the six members of the miR-17-92 cluster, i.e. miR-17, miR-20a, miR-18a and miR-19b-1, resulted significantly regulated by CD154. Other members of the family were also induced but with lower, not significant extent, i.e. miR-19a and miR-92a-1. In the same study, it has been also shown that, for all the members of the miR-17-92 cluster except miR-92a-1, stromal cell culture produced an increase in miRNA expression, which was further increased by CD154. In this context, the most highly expressed members of the cluster following CD154 culture were miR-17 and miR-19b-1 [94]. Of note, also in this case, miR-17-92 up-regulation was associated with MYC, in particular, MYC expression was induced by stromal cell culture with a further increase due to CD154 culture [94].

These data indicate that miR-17-92 cluster over expression may be not only due to genomic abnormalities but also to microenvironmental stimuli capable to influence miRNA expression [22, 94].

**Future perspectives**

The discovery of miRNAs acting as oncogenes or oncosuppressors have introduced novel treatment approaches. The more frequently proposed modality of therapy targeting miRNAs is to silence oncomiRs through anti-miRNAs oligonucleotides or to overexpress oncosuppressors miRNAs using miRNA mimics [95–97]. In general, artificial miRNAs or anti-miRNAs are small, stable, and, theoretically, easy to deliver to cells, possibly by packaging them into lipid based and/or antibody-conjugated nanoparticles [95–97]. However, these oligonucleotides still remain to be fully tested for efficacy and safety for a therapeutic use, although very recently a few phase II clinical trials have been performed [98, 99].

Given the multiple and potent effects on cellular proliferation and apoptosis exerted by the miR-17-92 cluster, miRNAs belonging to the cluster surely represent attractive targets for cancer therapy. In this context, in a study by us [100], it has been recently demonstrated that in-vitro administration of a specific oligonucleotide targeting endogenous miR-17 effectively reduces miR-17 expression and the proliferation of CLL-like MEC-1 cells. Consistently, it has been also demonstrated that, when injected in-vivo in tumor generated by subcutaneously injected MEC-1 cells in SCID mice, this specific oligonucleotide dramatically reduces tumor growth and significantly increase mouse survival. This evidence could represent a proof of principle for the use of specific anti-miRNAs oligonucleotides targeting miRNAs.
of the miR-17-92 cluster as a therapeutic tool in CLL and in lymphoproliferative disorders where miR-17-92 amplification and/or overexpression have a proved pathogenetic role, as discussed in the present review.

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CONFLICTS OF INTEREST

There are no conflict of interest to disclose.

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