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Mir-17-92 Cluster Dysregulation in Lymphoid Malignancies: Its Role in Limphomagenesis

Alejandro Roisman and Irma Slavutsky*

Laboratory of Genetics of Lymphoid Neoplasms, Institute of Experimental Medicine, Argentina

Abstract

MicroRNAs (miRNAs) are short, endogenous singled-stranded noncoding RNAs whose dysregulation has been implicated in important biologic processes, including cancer development. The principal mechanism of action of these master regulators is to control gene expression by suppressing mRNA translation and reducing mRNA stability. In particular, the miR-17-92 cluster is one of the most frequently miRNA expressed in different subtypes of non-Hodgkin lymphomas. Its widespread dysregulation in these pathologies suggests this cluster as a new biomarker that may supplement lymphoma diagnosis and prognosis, and also as an attractive target to design novel strategies for cancer therapy.

Editorial

microRNAs (miRNAs) are small non-coding single-stranded RNAs of 17-25 nucleotides in length that play central regulatory functions in gene expression and transcriptional control by targeting mRNAs and triggering its degradation and/or translational interference [1]. They are involved in important biologic processes, and its dysregulation has been associated with the pathogenesis of several diseases including tumor development and maintenance [2]. Some miRNAs are located in genomic regions involved in chromosomal alterations related to cancer and causally implicated in oncogenesis, acting as tumor suppressor genes or oncogenes [3].

In this context, experimental data have demonstrated the oncogenic properties of *miR17-92* polycistronic cluster in both hematological malignancies and solid tumors. This cluster is located in a region of 800 bp in the non-protein-coding gene C13 or f25 at 13q31.3 (4) that encodes for six distinct miRNAs (*miR-17, miR-18a, miR-19a, miR-20a, miR-19b-1,* and *miR-92a-1*). They constitute three families according to miRNA seed sequences: miR-17 (*miR-17, miR-20a* and *miR-18a*), miR-19 (*miR-19a* and *miR-19b-1*), and miR-92. *miR-17-92* cluster also presents two paralogs: *miR-106a-363* on chromosome X and *miR-106b-25* on chromosome 7. All these miRNAs show high sequence conservation across species suggesting evolutionary pressure to maintain such organization [5]. As a strong oncogene, *miR-17-92* regulates multiple cellular processes that favor malignant transformation [6], mainly due to gene amplification and *MYC*-mediated transcriptional upregulation [7,8]. Particularly, *miR-17-92* drives lymphomagenesis by suppressing the expression of multiple negative regulators of the *PI3K* (Phosphatidylinositide 3-kinase) and *NF-κB* (nuclear factor kappa B) pathways, and by inhibiting apoptosis [8].

Specific miRNAs characterize various subtypes of Non-Hodgkin Lymphomas (NHLs) and have essential roles in differentiation and lymphomagenesis. Among them, the *miR-17-92* cluster is the most frequently over-expressed in B-cell NHLs [9], including Diffuse Large B-cell Lymphoma (DLBCL), Mantle Cell Lymphoma (MCL), Chronic Lymphocytic Leukemia (CLL) and Burkitt Lymphoma (BL) [8].

In reference to MCL, different authors showed *miR-17-92* cluster up regulation in this entity [10,11]. Particularly, Navarro, et al. [10] found *miR-17* and *miR-20a* over expression with high MYC mRNA levels in tumors with a more aggressive clinical behavior, distinguishing two subgroups of MCL patients with different miR expression profiles associated to biological features. More recently, we have explored gene expression patterns of *SOXC* cluster and, *miR17, miR18a, miR19b* and *miR92a* members of the miR17-92 cluster and evaluated their correlation with biological and clinical characteristics of the disease [12]. Interestingly, unsupervised hierarchical clustering analysis revealed two distinctive subsets of tumors showing significant differences in important clinical variables: Cluster A associated with high expression of *SOX11, SOX12, miR19a* and *miR92a* signature linked to more aggressive disease and short survival, and Cluster B with *SOX4*, miR17 and

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Correspondence:
Irma Slavutsky, Laboratory of Genetics of Lymphoid Neoplasms, Institute of Experimental Medicine, Argentina, Tel: (5411) 4805-8803; Fax: (5411) 4803-9475;
E-mail: islavutsky@hematologia.anm.edu.ar

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miR18a over expression, exhibiting a reduced proliferating signature and a significantly better prognosis with longer overall survival. This combined analysis of coding and non coding genes in MCL represent a new approach that may contribute to improve the understanding of this pathology. In addition, experimental studies showed that over expression of *miR-17-92* mediates chemo- and radioresistance and enhances tumor growth in MCL cells, suggesting this cluster as a potential therapeutic target for patients with this lymphoma [13,14].

Studies on CLL patients found increased miR17 expression in unmutated and ZAP-70 positive cases [15]. Furthermore, a diminished miR-17 activity was seen in patients with *TP53* mutation/deletion [16], results that agree with those observed by Li et al. [17] that found low *miR-17* and *miR-20a* and high *miR-19a, miR-19b-1* and *miR-92a-1* mRNA levels in cases with *TP53* alterations in comparison with healthy donors. In addition, there are evidences of the induction of *miR-17-92* expression associated with *MYC* expression induced by the micro environmental, supporting the impact of these stimuli in miRNAs transcriptional regulation [18] as well as the interaction between MYC and *miR-17-92* cluster in CLL patients [15]. MYC is a transcription factor that has a key role in promoting tumorigenesis by activating and repressing target genes involved in many pathways associated to malignant development, being one of the most common abnormalities in cancer [19].

As known, DLBCL is the most common type of NHLs, showing three different molecular subtypes with distinct genetic aberrations and clinical outcome. Among them, the *miR-17-92* cluster is significantly upregulated in germinal center B-cell (GCB) subtype compared to activated B-cell [20, 21], whereas miR-17 is overexpressed in DLBCL originated within the central nervous system [22]. GCB-DLBCL frequently shows amplifications at 13q31.3 region that could be the cause of *miR-17-92* upregulation [7]. This mechanism is also observed in patients with Richter´s syndrome, in which 13q31.3 amplifications are observed at the time of transformation, associated to the gain of *MYC* and loss of *TP53*, supporting the involvement of the *miR-17-92* cluster in the acquisition of a more biologically aggressive disease [23]. *MYC* binds to the promoter of the *miR-17-92* cluster and to the *E2F1* promoter (a transcription factor that promotes G1-to-S phase progression) activating their transcription, while the *miR-17-92* repress the expression of *E2F1*, indicating the presence of a fine-tuned regulatory mechanism of proliferation [24]. In addition, *miR-17-92* cluster also impacts on B-Cell Receptor (*BCR*) signaling. Microarray studies showed *MYC* and *MIR17HG* loci amplifications, consistent with the high level of *MYC* and members of *miR-17-92* cluster required for *DLBCLs* to sustain *BCR* response, suggesting a lymphomagenic feed-forward regulatory loop in this pathology [25].

Consistent with those reported for other *NHL* subtypes, studies in *BL* pediatric patients, an aggressive disease characterized by reciprocal translocations of *MYC* with the immunoglobulin genes, found 13q31 amplification and higher levels of *miR17*, associated to a tendency for early relapse, confirming the importance of *MYC*/*miR17-92* axis in lymphoma development [26,27].

Although the number miRNAs analysis in primary cutaneous lymphomas is limited, some reports have evaluated the *miR-17-92* cluster expression. A recent study in primary cutaneous B-cell lymphomas [28] found *miR-106a* (paralog), *miR-20a* and *miR-20b* over expression as well as the down regulation of PTEN (Phosphatase and tensin homolog) tumor suppressor gene associated to disease progression. Interestingly, a new study of our group [29] in patients with Mycosis Fungoides (MF), the most frequent Cutaneous T-Cell Lymphoma (CTCL), found higher levels of *miR17, miR18a, miR19b* and *miR92a* in patients compared to controls. The analysis according to morphological subtypes showed *miR17* and *miR-18a* over expression in tumoral MF, meanwhile *miR19b* and *mir92a* exhibited increased levels in folliculotropic and transformed MFs. In addition, miRNA gene expression profiles showed that *miR17* and *miR19b* were upregulated in patients with deletion of 9p21.3 (*CDKN2A*) and/or 8q24.21 (*MYC*) gains, providing new insights in the comprehension of MF pathobiology. In line with our results, Ralfkiaer, et al. [30] also found enhanced expression of miR-17-92 paralogs, *miR-106a/363* and *miR-106b/25*, in advanced disease compared with early MF, suggesting a role for these *miRs* in disease progression. Previous reports [31,32] showed that *miR106b/25* is also upregulated in Sézary Syndrome, a rare and aggressive variant of *CTCL*, indicating a potential oncogenic function for this *miR17-92* paralog. In contrast Ballabio, et al. [33] found down regulation of *miR17, miR19a, miR92* and *miR106a* in this pathology, diminishing apoptosis rates and enhancing proliferation. More studies will clarify this discordant results.

Concluding, the present revision shows the important governing roles of *miR-17-92* cluster and its paralogs in lymphoid malignancies. Their widespread dysregulation in these pathologies suggests they may be considered as new biomarkers that may add new insights in lymphoma diagnosis and prognosis, and also as attractive targets to design novel strategies for cancer therapy.

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