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

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# 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].

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**Copyright** © 2017 Irma Slavutsky. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 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  $NF-\kappa B$  (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

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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