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Short communication

miRNA signature associated with R–CHOP refractoriness in patients diagnosed with diffuse large B cell lymphoma

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ABSTRACT

Refractoriness remains as one of the challenges in patients with lymphoma under chemotherapy, and among biological regulators in cells driving this type of response are microRNAs (miRNAs). Different genes are constantly turned on or off according to the miRNAs expression profiles affecting the drug response in patients and their stability in serum and plasma makes them potential prognostic biomarkers in several diseases. Here we described a profile of miRNAs in plasma of diffuse large B cell lymphoma (DLBCL) patients. miRNA expression arrays were carried using pre-treatment plasma samples of sixteen patients, followed by a comparison between the responder and the non-responders. After six cycles of R–CHOP treatment, twelve out of sixteen patients were clinically diagnosed with complete response while in four patients no clinical response was observed. Between these groups, a signature of fifteen differential expressed miRNAs was found. The circulating miRNAs in plasma of patients with no response were related to the drug resistance in other types of cancer, by targeting genes involved in cell proliferation and apoptosis, among other cell processes.

1. Introduction

DLBCL is the most frequent non-Hodgkin lymphoma (NHL) in the United States, corresponding to 65% of the total cases of NHL [1,2], whereas in Mexico represent 48% [3]. A combination of chemotherapy (cyclophosphamide, doxorubicin, vincristine and prednisone) plus Rituximab (anti-CD20), reaches a response in up to 70% of the cases [4]. Nevertheless, a considerable percentage of patients remains refractory [5,6]. In this context, several research groups are studying molecular markers to predict response to treatment. miRNAs, small non-coding RNAs ranging from 17 to 25 bp and capable to regulate gene expression, started to be related to the drug resistance observed in cancer [7]. Because of its function as post-transcriptional regulators, an abnormal expression of miRNAs can affect important cellular pathways. Noteworthy, miRNAs are normally released into the bloodstream and travel around the vessels in lipid vesicles, exosomes, or bound to protein complexes [7–9]; and due to their stability, particular signatures of these circulating miRNAs can be detected and associated with prognosis or drug response in pathologies such as cancer [10]. Increased levels of miRNAs have been found in serum of patients diagnosed with prostate cancer, lung cancer, ovarian cancer, colorectal cancer, among others [11]. In this research, we analyzed the miRNA profile in pre-treatment plasma samples from a group of patients diagnosed with DLBCL.

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2. Materials and methods

2.1. Subjects and plasma samples

Patients diagnosed with DLBCL at the Hematology service from the Instituto Mexicano del Seguro Social (IMSS) were enrolled in the study. The diagnosed was based in a combination of clinical, laboratory and radiologic findings, followed by an excisional or incisional biopsy of a peripheral lymph node to confirm diagnosis [12]. After informed consent, along with medical history and physical exam, blood samples were obtained during the first visit. This repository was created the under the approval ID "Proteomica". All samples were collected before treatment in heparin tubes (Becton Dickinson) and centrifuged at 1000 rpm for 30 min at 4 °C, plasma was collected and stored at −80 °C for further analysis. Patients were staged according to the Ann Arbor criteria and the performance status to the Eastern Cooperative Oncology Group scale (ECOG) [13]. The clinical evolution was followed according to the therapy clinical outcomes as complete remission, partial remission, refractory therapy or mortality [14].

2.2. Plasma circulating miRNAs isolation

Total miRNAs were isolated from plasma samples using the miRNeasy Serum/Plasma kit (QIAGEN), following the manufacturer's instructions. Quantity and quality of total RNA were assessed using OD 260/280 measure in NanoDrop 8000 (NanoDrop Technologies) and the Experion Automated Electrophoresis System (Bio-Rad).

2.3. MicroRNAs expression microarray

miRNAs samples were processed using the miRNA complete labeling and hybridization kit (Agilent) and the miRNA spike-in kit (Agilent). The miRNA expression was measured employing microarrays 8 × 15K (Agilent) following manufacturer instructions and analyzed using a GenePix 4000B scanner (Molecular Devices).

2.4. Statistical analysis

Fisher's exact test was carried out using nominal variables, whereas the Mann-Whitney *U* test was used for numerical variables. A p-value ≤ 0,05 was considered statistically significant. Wilcoxon test was used for each miRNA expression signal. The results were generated using Rstudio Software with R version 3.6.2.

2.5. In silico predictions of genes from miRNAs

The impact of miRNAs on overall pathways was predicted using DIANA-microT web server [15] which allows miRNA target predictions and DIANA-mirPath for pathway discovery [16]. The predicted target genes for the up- and downregulated miRNAs were obtained from the microRNA Data Integration Portal [17]. The map presenting interaction between miRNAs and the predicted target genes was created using Cystoscope software [18].

3. Results

Blood samples were collected from 16 patients diagnosed with DLBCL, with an average age of 45.3 ± 18.8 years and being mostly women (n = 11, 68.8%). Regarding the clinical characteristics of the patients, 56% of them (n = 9) presented B symptoms at the initial diagnosis, whereas 68.7% (n = 11) were in a good status performance (ECOG 0 and 1) before chemotherapy, 43% (n = 7) had extranodal disease and bone marrow infiltration was found in 18.7% (n = 3) of the patients. Ann Arbor criteria were as following: two patients were stage 1, five patients were stage 2, six patients were stage 3, and three patients were stage 4.

Of a total of 16 patients recruited, 75% (n = 12) of them responded adequately to R–CHOP therapy (complete remission), since no disease was detected 6 months after treatment, whereas in the remaining 25% (n = 4) of the patients a partial or refractory response was observed after the R–CHOP scheme (Table 1).

After the bioinformatic processing of miRNA array data, up- and down-regulated genes were clustered according the clinical response. Overexpression of 9 miRNAs (miR-105-5p, miR-186-5p, miR-19a-3p, miR-572, miR-1267, miR-555, miR-205-5p, miR-490-5p, miR-520d-3p) was observed in pre-treatment DLBCL patients serum samples with no clinical response observed after treatment compared with patients with complete response, all 9 upregulated miRNAs were statistically significant ($p < 0.003$). On the other hand, 6 miRNAs (miR-100-5p, miR-1910-5p, miR-24-3p, miR-628-3p, miR-766-3p, miR-615-3p) were downregulated in the refractory response group (Fig. 1).

In order to find out an explanation for the achieved clinical outcome by identifying genes targeted by the dysregulated miRNAs, a target prediction was carried out using the mirDIP database, followed by the creation of an interaction map using Cytoscape (Fig. 2). To increase the probability of real affectation of genes by the mRNAs here reported, for the upregulated miRNAs, target genes regulated by three or less miRNAs where eliminated (Fig. 2A). Interestingly, one gene (ZNF652) was predicted to be targeted by 6 miRNAs, whereas 14 genes were targeted for 5 miRNAs and 75 genes were predicted to be recognized by 4 miRNAs. On the other hand, for the downregulated miRNAs, only target genes regulated by three miRNAs were included since genes sharing four or more miRNAs were not present and target genes regulated by two or less were eliminated (Fig. 2B). After this filtering, 12 genes were predicted to be affected by the downregulated miRNAs.

Next, the biological impact of the significant dysregulated miRNAs, was predicted carrying out a pathway enrichment analysis from the target genes using DIANA-miRPath. In this fashion, DIANA-miRPath first predicts the miRNA target genes and then estimates the pathways and ontologies that are statistically over-represented. For the 9 upregulated miRNAs, among the KEGG (Kyoto Encyclopedia of Genes and Genomes) annotated pathways affected by more than one miRNA are the TGF-beta signaling, proteoglycans in cancer, estrogen signaling and mTOR signaling (Fig. 3A). Other pathways were also significant but affected by less miRNAs such as ErbB signaling. In both cases, these pathways have been reported in cancer development, whereas the biological effect of these 9 miRNAs, in the Gene Ontology (GO) annotated categories (Fig. 3B), showed that the most significant process were: ion binding, organelle, cellular protein modification, biosynthetic, cellular nitrogen metabolic compounds, protein binding transcription factor activity, neurotrophin TKR receptor signaling pathway, epidermal growth factor receptor signaling pathway, cellular lipid metabolic process, molecular function and among others. Same approach was carried out for the 6 downregulated miRNAs and only three pathways were

Table 1
Clinical features between the grouped DLBCL patients.

		Responders	*Non-responders*	*p-value*
N		12	4	
Age		41,5 ± 19,14	57,0 ± 13,71	N.S.
Gender	Female	8	3	
	Male	4	1	N.S.
Clinical stage	I/II	4	2	
	III/IV	8	2	N.S.
LDH	Normal	4	1	
	High	8	3	N.S.
ECOG	0, 1	10	1	
	2, 3, 4	2	3	N.S.
Extranodal lesion	<2	11	4	
	≥2	1	0	N.S.
B symtoms	Yes	9	0	
	No	3	4	0,019[a]

[a] p-value ≤0,05 N.S.: not significant.

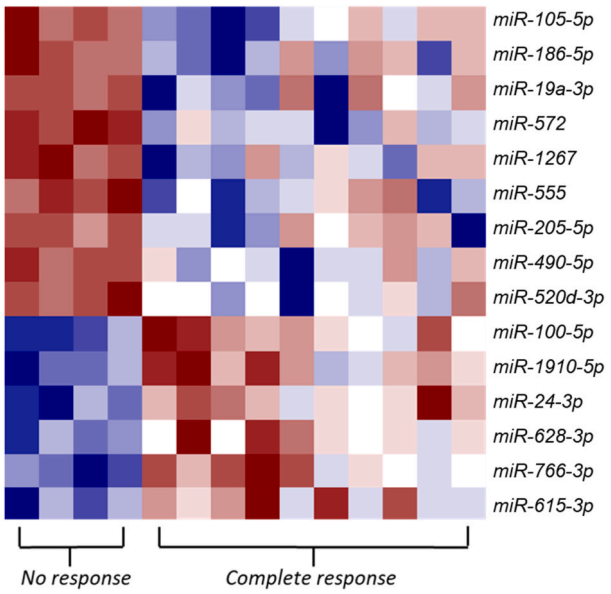

Fig. 1. Heat map. showing the miRNAs relative expression and the clustering based on the clinical outcome after treatment.

affected: the metabolism of xenobiotics by cytochrome P450, the Wnt signaling and the glycosaminoglycan biosynthesis-heparan sulfate, in the KEGG annotated pathways (Fig. 3C), whereas in the GO annotated categories, the pathways affected where very similar to the pathways affected for the up-regulated miRNAs, such as ion binding, organelle, cellular nitrogen compound metabolic process, as well as biosynthetic process (Fig. 3D).

4. Discussion

Refractoriness is still present in some DLBCL patients along with poor prognosis even after autologous stem cells transplantation (salvage therapy) [19]. Therefore, it is important to investigate new approaches to detected chemoresistance, accelerating the administration of more aggressive schemes that could be crucial for the patients.

In this research, 9 significant up-regulated miRNAs were found in the group of patients with clinical chemoresistance, whereas the same group of patients presented downregulation in 6 miRNAs in plasma before treatment.

The analysis of predicted target genes affected by the upregulated miRNAs showed some genes related to cancer development and other processes. Interestingly, the ZNRF3 gene, predicted to be targeted by four upregulated miRNAs (miR-1267, miR-186-5p, miR-19a-39 and miR-520d-3p) is a negative modulator of the oncogenic Wnt/β-catenin signaling, a well-known pathway involved in chemoresistance in several types of cancer [20,21], aligned with the clinical resistance observed in this study. In the other hand, the analysis of the predicted genes to be affected by the downregulated miRNAs, resulting in their over-expression, showed 12 genes affected by 3 miRNAs, among them was APOBEC3F (target by miR-24-3p, miR-766 and miR-1910-5p). This gene has been reported to be highly expressed in lymphoma cells and to promote an efficient repair of genomic DNA double-strand breaks (DNA) [22], leading to a protective phenotype against the DNA damage caused by chemotherapy [23,24]; which is aligned with the results found in this report, where the plasma circulating miRNAs targeting APOBEC3F were downregulated in the group with no response to R–CHOP, a therapeutic scheme known to cause DNA damage.

To not only investigate affected genes, but also processes regulated by the miRNAs, an enrichment analysis with their predicted target genes was carried out and several pathways associated to cancer development observed. For instance, proteoglycans and glycosaminoglycans biosynthesis related pathways have been reported to be involved in cancer

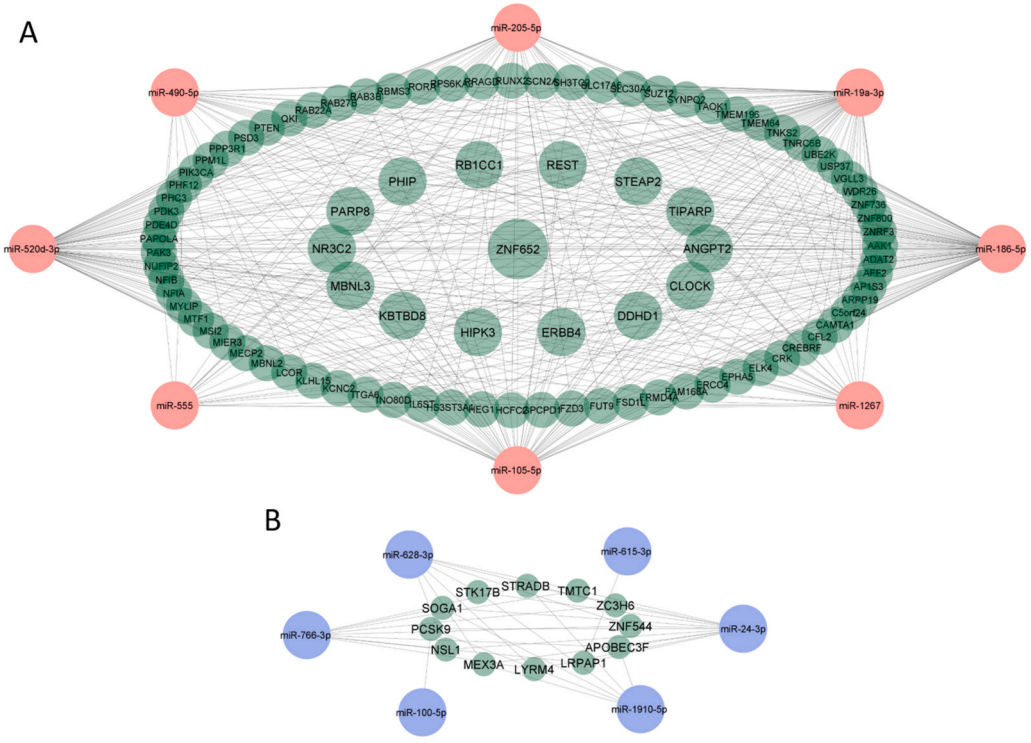

Fig. 2. miRNA-target networks. (A) An interaction map between the upregulated miRNAs (red circles) and their target genes (green circles) was created after eliminating genes targeted by three or less miRNAs. Size of the green circles is related to the number of miRNAs targeting the genes (4, 5 or 6 miRNAs). (B) Same map was created for downregulated miRNAs (blue circles), but only genes targeted by three miRNAs were used since no target genes were share for 4 or more RNAs.

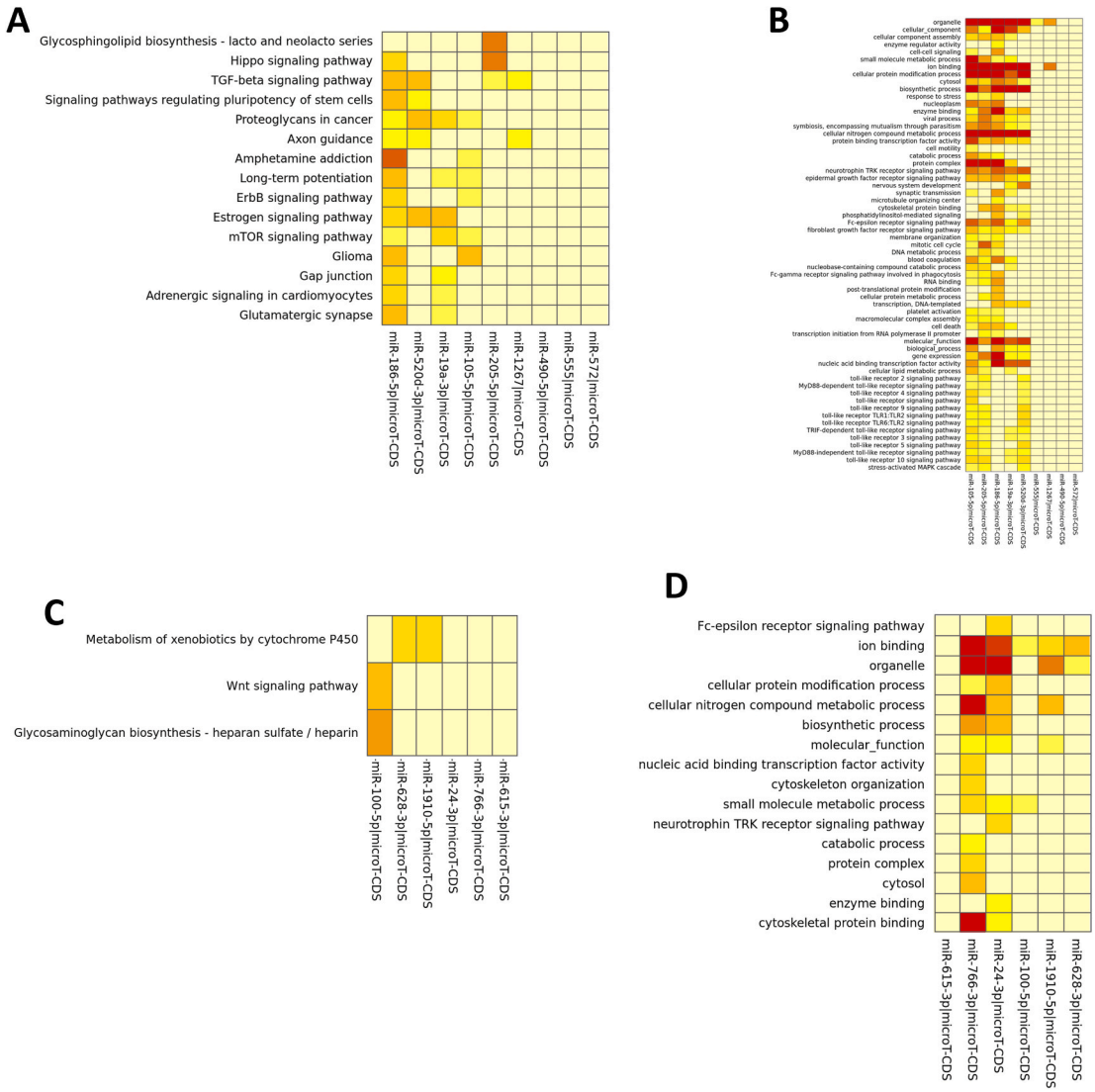

Fig. 3. Predicted biological functions to be the most impacted by the dysregulated miRNAs included in the signature. (A, B) The impact of the 9 upregulated miRNAs on the KEGG and Gene Ontology (GO) biological pathways, respectively, predicted with DIANA microT-CDS tool. (C, D) The impact of the 6 downregulated miRNAs on the KEGG and Gene Ontology (GO) biological pathways, respectively, predicted with DIANA microT-CDS tool. Heatmap representation of the pathways and the significance (determined from log (p-values)) with each miRNA with red indicating the highest level of significance and yellow the lowest level of significance.

development [25,26]. Another pathway regulated by miRNAs here described is the mTOR signaling, an intracellular member of the activator cascade within the BCR pathway, a well-known cascade responsible for cellular proliferation, survival, differentiation and migration of normal and malignant B cells [27,28]. In addition, pathways and processes associated to drug resistance were regulated as well by the miRNAs here found, such as the fatty acid biosynthesis and metabolism. Fatty acid receptor GPCR120, has been described as responsible to up-regulate ABC transporters and trigger chemoresistance in breast cancer [29], and the fatty acid synthase was reported to be involved in DLBCL progression [30]. In addition, the neurotrophin TRK receptor signaling has also found to be regulated by these miRNAs, being associated to a more aggressive DLBCL phenotype, rituximab-resistance and pro-survival response to chemotherapeutic agents [31–35]. Wnt signaling, as previously mentioned involved in the response to drug therapy in DLBCL, was regulated by the miRNAs here found [36,37].

Overall, the predicted target genes to be regulated by plasma circulating miRNAs here described, are involved in pathways related to drug resistance, and some of them specifically in DLBCL and the rituximab treatment.

Additionally, some of the miRNAs found in this study have been previously reported as biological markers for cancer development, cell survival, prognosis and response therapy. With respect to the up-regulated miRNAs here reported, mir-105 was found to be elevated in plasma of triple negative breast cancer patients and reported as predictive marker for stemness, drug resistance and metastasis [38,39]; miR-19a-3p was associated to chemoresistance by modulation of the PTEN expression in hepatocellular carcinoma [40]; mir-572 was reported to be responsible for cell proliferation in ovarian cancer by targeting genes such as SOCS, p2 and PPP2R2C [41,42]; miRNA-205-5p is capable to induce chemoresistance in hepatocellular carcinoma cells by targeting PTEN/JNK/ANXA3 pathway, as well as to induce the resistance to paclitaxel in endometrial cancer by downregulating FOXO1 [43,44], a pro-apoptotic transcription factor in DLBCL cells, associated to a doxorubicin-resistant phenotype [45].

Of note, mir-520d-3p, also up-regulated in patients with no response, is one of five miRNAs described as signature for a non-invasive biomarker to predict the clinical outcome in DLBCL patients under the R–CHOP scheme [46], in a similar research carried out for different group; suggesting an consistent role in the chemoresistance to R–CHOP therapy.

Regarding the downregulated miRNAs, a low expression of miR-24-

3p have been observed in the paclitaxel-resistant prostate cancer cell (PCa) [47], and associated to etoposide (VP16) and cisplatin (DDP) resistance in small cell lung cancer [48–50]. In the case of miRNA-628 and mir-766-3p, they have been implied with tumor suppressor functions in leukemia [51,52] and hepatocellular carcinoma [53,54], respectively.

5. Conclusion

In this study, a miRNA signature (9 up-regulated and 6 down-regulated) was found to be related to the chemoresistance in the R–CHOP scheme, and although further experiments are needed to validate its capacity to function as a predictive tool for the clinical outcome, previous reports are aligned to the findings here described.

CRediT authorship contribution statement

Oscar Raul Fajardo-Ramirez: Conceptualization, Writing - original draft. **Luis Villela:** Conceptualization. **Jocelyn Nikita Campa-Carranza:** Software, Formal analysis. **Antonio Ali Perez-Maya:** Writing - review & editing. **Gissela Borrego-Soto:** Writing - review & editing, Writing - original draft. **Martin Ivan Wah-Suarez:** Investigation, Data curation. **Iram Pablo Rodríguez-Sánchez:** Software, Formal analysis. **Patricio A. Zapata-Morin:** Software, Formal analysis. **Rocio Ortiz-Lopez:** Writing - review & editing. **Victor Manuel Treviño:** Software, Formal analysis. **Mariano Garcia-Magariño:** Investigation, Data curation. **Ivan Alberto Marino-Martinez:** Conceptualization, Writing - original draft, Writing - original draft.

Declaration of competing interest

The authors do not have any current potential personal, political or financial interest in the material, information, or techniques described in this paper.

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