

3rd International Conference on Chemo and BioInformatics

Kragujevac, September 25-26, 2025, Serbia



ICCBIKG 2025

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BOOK OF PROCEEDINGS

September 25-26, 2025
Kragujevac, Serbia

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3rd International Conference on Chemo and BioInformatics, Kragujevac, September 25-26, 2025, Serbia.

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Technical Editors:

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Proofreading:

Kristina Milisavljević

Press:

„Grafo Ink“, Kragujevac

Impression:

10 copies

Publisher:

Institute for Information Technologies, University of Kragujevac, Serbia, Jovana Cvijica bb, 2025

CIP - Каталогизacija у публикацији Народна библиотека Србије, Београд

54:004(048)(0.034.2)
57+61]:004(082)(0.034.2)

INTERNATIONAL Conference on Chemo and BioInformatics (3 ; 2025 ; Kragujevac)
Book of Proceedings [Elektronski izvor] / 3rd International Conference on Chemo and
BioInformatics, ICCBIKG 2025, September 25-26, 2025, Kragujevac, Serbia ; [editors Igor Saveljić,
Nenad Filipović]. - Kragujevac : University, Institute for Information Technologies, 2025
(Kragujevac : Grafo Ink). - 1 USB fleš memorija ; 1 x 2 x 3 cm

Sistemska zahtevi: Nisu navedeni. - Nasl. sa naslovne strane dokumenta. - Tiraž 10. - Bibliografija
uz svaki rad.

ISBN 978-86-82172-05-5

a) Хемија -- Информациона технологија -- Зборници b) Биомедицина -- Информациона
технологија -- Зборници

COBISS.SR-ID 176312073

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Bioinformatics analysis of microRNAs derived from HTR-8/SVneo potentially targeting *BCL2* in ovarian cancer cell line A2780

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DOI: 10.46793/ICCBIKG25.292D

Abstract: Our recent study demonstrated the ameliorative effect of extracellular vesicles (EVs) from trophoblast cells (TC-EVs) on ovarian cancer (OC) A2780 cells' sensitivity to cisplatin, likely via modulation of pro-apoptotic pathways. However, the mechanisms and the exact constituents of EVs which display pro-apoptotic effect in recipient cells remain unclear. The aim of this study is to investigate via *in silico* analysis whether microRNAs present in TC-EVs produced by HTR-8/SVneo cells could mediate the observed pro-apoptotic effect in OC and exert other cancer phenotype-related mechanisms. MicroRNA profiling results of TC-EVs were extracted from GEO dataset GSE182717 and microRNAs were ranked according to normalized read counts. Among 75 microRNAs presented with average rpm \geq 1000, 30 were identified as *BCL2* regulators. After the exclusion of microRNAs highly expressed in recipient A2780 cells, microRNA-mRNA network topology analysis identified 11 hub TC-EVs-abundant microRNAs. Gene ontology (GO) analyses indicated that potential targets of these hub microRNA genes were concentrated predominantly on "MAPKKK activity", "regulation of DNA-dependent transcription, elongation" and "ligase activity, forming carbon-oxygen" (molecular function category), while most hits belonged to "Pathways in cancer" and "MAPK signaling pathway". Prioritizing of potential candidates for future experimental validation relied on identifying hits for the most abundant TC-EVs *BCL2*-targeting microRNAs within a panel of downregulated microRNAs from cisplatin resistant OC cell lines (GSE1617848) and literature-supported effects on *BCL2* expression in OC. The most plausible candidate for TC-EVs-A2780 delivery analysis was found to be miR-16-5p. The presented results illustrate the potential relation between the delivery of TC-EVs microRNAs and apoptotic pathway activation in A2780. Additional findings on TC-EVs microRNA functions and candidate microRNA delivery are required for further interpretation of the contributing effect of microRNAs on experimentally observed changes in TC-EVs-treated A2780 cells.

Keywords: ovarian cancer, trophoblast, microRNA, extracellular vesicles.

1. Introduction

Ovarian cancer (OC), a highly lethal malignancy, frequently associates with chemoresistance, which is one of the major obstacles in cancer management and results in treatment failure [1]. Increasing evidence suggests a key role for extracellular vesicles (EVs)-mediated intercellular communication in various cellular processes involved in cancer progression. EVs contain placenta-specific miRNAs, which were shown to suppress cell proliferation and may help inhibit OC growth and metastasis, while promoting cancer cell death. In our recent study, we discovered an *in vitro* cisplatin-sensitizing effect in OC cells A2780 induced by treatment with trophoblast-derived EVs (TC-EVs), which likely stems from modulation of pro-apoptotic pathways. Since multitude of evidence supports the involvement of microRNA carried by EVs in the development of drug resistance in malignancy, we hypothesized that the activities of microRNAs within TC-EVs cargo may underlie the observed pro-apoptotic effect in A2780 cells. Therefore, our aim was to investigate through an *in silico* analysis whether microRNAs present in TC-EVs originating from HTR-8/SVneo trophoblast cells could mediate the observed cisplatin-sensitizing effect in OC and possibly exert other cancer phenotype-related mechanisms. Additionally, we searched for plausible microRNA candidates for future mechanistic studies on this issue.

2. Results and Discussion

HTR-8/SVneo TC-EVs non-coding RNA sequencing results were extracted from GEO dataset GSE182717 [2] and microRNAs were ranked according to average normalized read counts. A total of 75 microRNAs presented with $\text{rpm} \geq 1000$, which is considered as a threshold for highly expressed microRNAs. Among this subset, 30 microRNAs were experimentally proven and/or predicted regulators of *BCL2* expression, according to integrated data from miRTarBase, mirDIP, miRDB (**Fig. 1**). These results support the prominent effect of TC-EVs microRNA cargo on *BCL2* expression and, thereby, the reduction in anti-apoptotic activities in recipient cells.

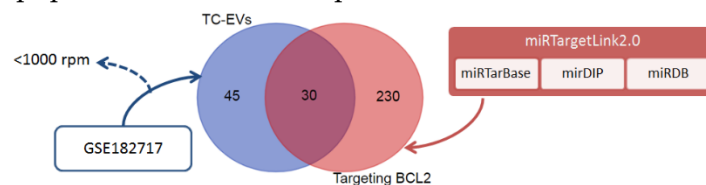


Figure 1. Abundant microRNAs contained in TC-EVs predicted and/or experimentally confirmed to target *BCL2* ($n=30$).

We presumed that the most effective microRNAs delivered by TC-EVs would be the ones deficient in the recipient OC cells. Therefore, in order to explore the biological significance of the abundant TC-EVs microRNAs, we excluded from selection microRNAs which are highly expressed in recipient A2780 cells [3]. MicroRNA-mRNA network topology analysis identified 11 hub microRNAs among most abundant TC-EVs

microRNAs (**Fig. 2A**). Gene ontology (GO) and KEGG pathway analyses indicated that potential targets of hub microRNA genes were concentrated predominantly on the molecular function terms “MAPKKK activity”, “regulation of DNA-dependent transcription, elongation”, “ligase activity, forming carbon-oxygen bonds”, “single-stranded RNA binding” and “ATP binding” (**Fig. 2B**), while pathway annotation resulted in most hits belonging to “Pathways in cancer” (298 hits) and “MAPK signaling pathway” (239 hits), which is consistent with our hypothesis about the biological relevance of TC-EVs-derived microRNAs in malignancies. Literature data also supported the dysregulation of most of the identified hub microRNAs in OC cells [4-8].

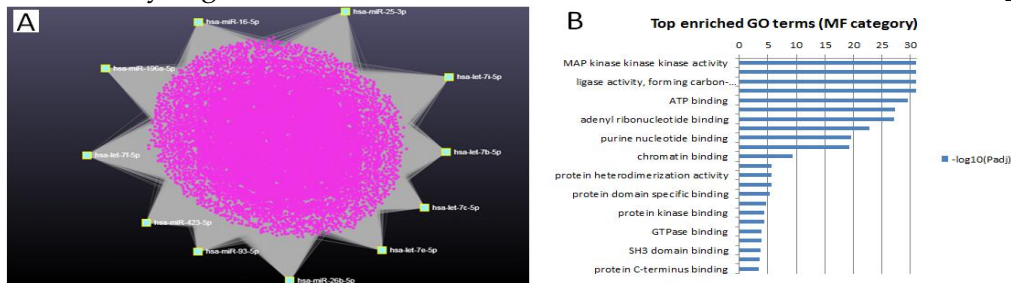


Figure 2. (A) microRNA–mRNA interaction network of the selected microRNAs abundant in TC-EVs. (B) Gene ontology (GO) analysis of genes targeted by 11 hub microRNAs from TC-EVs: molecular function category.

Prioritizing of potential candidates for future experimental validation relied on making cross-sections of hits for the most abundant *BCL2*-targeting microRNAs from TC-EVs with the panel of downregulated microRNAs in two cisplatin resistant OC cell lines and previous literaturally supported effects on *BCL2* expression in OC. The search resulted in two candidates, one of which was functionally characterized as a direct regulator of *BCL2* expression in OC, including A2780 cells [5]. According to the obtained results, the most plausible candidate for TC-EVs-A2780 delivery analysis was miR-16-5p, which is also one of the identified hub microRNAs.

3. Methodology

3.1. Identification of abundant HC-EVs microRNAs

Non-coding RNA profiling results of HTR-8/SVneo TC-EVs were extracted from GEO dataset GSE182717 (GPL16791 platform, Illumina HiSeq 2500) [2] and microRNAs were ranked according to averaged normalized read counts.

3.2. Identification of microRNAs targeting *BCL2*

MicroRNAs targeting *BCL2* were identified as predicted or experimentally validated hits by searching the miRTargetLink2.0 database which integrates data from three online databases used (miRTarBase, miRDB and mirDIP). The resulting pool of microRNAs was compared with the list of abundant microRNAs from TC-EVs (cross-section).

3.3. microRNA–mRNA interaction network construction

Highly expressed microRNAs from the recipient A2780 cells were excluded from the selection of abundant TC-EVs microRNAs (top 20) for microRNA–mRNA interaction

network construction. Identification of these A2780 microRNAs was based on the results extracted from GSE209922 (GPL24676 platform, Illumina NovaSeq 6000) dataset [3] and ranking according to average normalized read counts. The microRNA–mRNA interaction network was constructed using miRNet2.0. Degree ≥ 6000 and betweenness ≥ 5.8 million were used to identify hub microRNAs, which were subjected to GO analysis and KEGG pathway in order to characterize their biological function.

3.4. Identification of candidate microRNA for experimental validation

A panel of downregulated DEGs in two cisplatin resistant OC cell lines (A2780CIS and A2780CP20) from GSE161784 was extracted and a cross-section was made with the hits for the abundant *BCL2*-targeting TC-EVs microRNAs. The resulting microRNA pool was used for literature database search on the involvement in *BCL2* regulation in OC.

4. Conclusion

A significant portion of microRNAs highly expressed in TC-EVs are potential regulators of *BCL2*. Additionally, this microRNA pool associates with other biological functions relevant for OC onset/progression or chemoresistance. Among them, the most plausible candidate for further functional analysis seems to be miR-16-5p.

Acknowledgment

This research is funded by the Ministry of Science, Technological Development and Innovation, Republic of Serbia, Contract No: 451-03-136/2025-03/200019.

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