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FUNCTIONAL ANALYSIS OF CHEMORESISTANCE-RELATED miRNAs IN OVARIAN AND TESTICULAR TUMORS

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Introduction

MicroRNAs (miRNAs) are post-transcriptional regulators of gene expression and are deregulated in ovarian (OC) and testicular (TC) cancers. Studies suggest that they play an important role in chemoresistance to platinum, the basis for chemotherapeutic drugs (cisplatin or carboplatin) frequently used in the treatment of gonadal tumors. However, the functional role of these small molecules in chemoresistance in these types of tumors is not fully understood.

Methods

Therefore, chemoresistance-related miRNAs were selected from experimentally validated studies (EVS; **Table 1**) for search, gene enrichment, and functional analysis of their target genes to identify the biological pathways that they can regulate via mRNA-miRNA-target interaction network and, then understand the role of these molecules in OC and TC chemoresistance. The miRNAs were selected from EVS deposited in BioMedCentral, PubMed, and Google Scholar databases. Only EVS (cell assay and/or luciferase reporter) regarding the association of miRNA to chemoresistance in OC and TC were included **(Table 1)**. The search for target genes was conducted in the miRTargetLink 2.0 tool, which uses information from the miRTarBase 7.0 database, the main repository of EVS about miRNA-mRNA-target interactions. Target genes enrichment in *Kyoto Encyclopedia of Genes and Genomes* (KEGG) and/or Reactome pathways was developed using the STRING: *functional protein association networks* v.11.0. The KEGG and Reactome databases are repositories of experimentally validated biological pathways and processes and associated genes **(Figure 1)**. Functional analyses were performed separately by tumor type and were conducted and represented in graphs by use of the software R v.4.4.1.

Results

In OC, 13 studies identified that 14 miRNAs were deregulated (7 down and 7 upregulated), which can regulate 411 genes **(Figure 1; Table 1)**. In TC, 4 studies reported 6 downregulated miRNAs, which can regulate 108 genes **(Figure 1; Table 1)**. The functional analysis of these target genes by tumor type revealed that some of them are involved in the platinum resistance pathway (KEGG: hsa01524) in OC (18 genes) and TC (5 genes) **(Figure 1)**. The AKT2, BCL2, CASP8, and CNDK1A genes were enriched within this pathway in both analyses, suggesting that although regulated by different miRNAs in OC and TC, the possibility of chemoresistance is maintained **(Figure 1)**. Only miR-383-5p and miR-497 were deregulated (downregulated) in both tumors and can regulate 40 genes related to many important pathways for chemoresistance such as apoptosis, cell cycle, and growth **(Figure 1-2)**. Interestingly, the P-glycoprotein gene (P-pg or ABCB1), responsible for the efflux of chemotherapeutic agents in tumor cells, can be regulated by miR-21-5p in OC and miR-302a-3p in TC.

Conclusions

Thus, we identified miRNAs that regulate genes (18 in OC; 5 in TC) associated with platinum resistance, four of these genes are common to both tumors. miR-383-5p and miR-497 are common to both tumors and can affect apoptosis, growth, and cell cycle. miR-21-5p and miR-302a-3p can regulate P-gp, responsible for the efflux of chemotherapeutic agents in tumor cells. Therefore, the studied miRNAs are related to genes associated with chemoresistance and may be potential therapeutic targets.

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Table1: Analyzed studies synthesis. (↑) Upregulated. (↓) Downregulated.

Cancer	miRNAs	Chemoresistance	Gene/pathway affected	Reference
Ovarian	miR-146a ↓	Platina	SOD2	Cui et al., 2016
	miR-93↑	Platina	PTEN	Fu et al., 2012
	miR-152↓	Platina	DNMT1	Xiang et al., 2013
	miR-185↑	Platina	DNMT1	Xiang et al., 2014
	miR-106a↑	Paclitaxel	BCL10; caspase-7	Huh et al., 2013
	miR-591↓	Paclitaxel	ZEB1	Huh et al., 2013
	miR-21-5p↑	Platina	RBPMS	Báez-Vega et al., 2016
	miR-141↑	Platina	KEAP1	Jaarveld et al., 2013
	miR-376c-3p ↑	Platina	ACVR1C; ALK-7	Ye et al., 2010
	miR-130a-3p ↓	Platina	XIAP	Zhang et al., 2013
	miR-130a-5p ↑	Platina	PTEN	Yang et al., 2012
	miR-29 ↓	Platina	COL1A1	Yu et al., 2013
Testicular	miRNA-106b-5p↓	Platina	TDRG1	Wei et al., 2018
	miR-302a-3p ↓			
	miR-302b-3p ↓	Platina	SPRY4/MAPK/ERK/PI3K/Akt	Das et al., 2019
	miR-302c-3p ↓			
Ovarian/Testicular	miR-383-5p ↓	Paclitaxel	TRIM27	Jiang et al., 2019
	miR-497 ↓	Platina	p70S6K1; mTOR	Xu et al., 2015

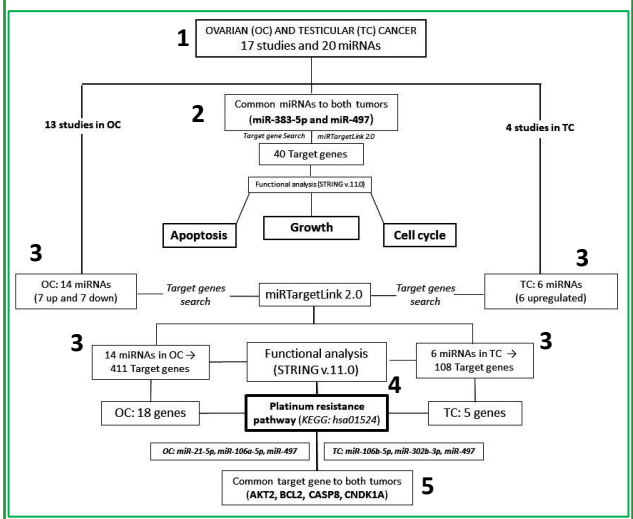

Figure 1: Study Flowchart. **(1)** Eighteen studies reported that circHIPK3 is upregulated and acts as a sponge for 15 miRNAs in GIT; **(2)** Two miRNAs are common to both tumors and can regulate 40 target genes that regulate apoptosis, growth and cell cycle; **(3)** The miRNAs deregulated in both tumors can regulate 411 in OC and 108 in TC target genes; **(4)** The analysis functional of OC and TC target genes converge to regulation to platinum resistance pathway; **(5)** Were highlight 4 important genes associated with this pathway that are common to both tumors.

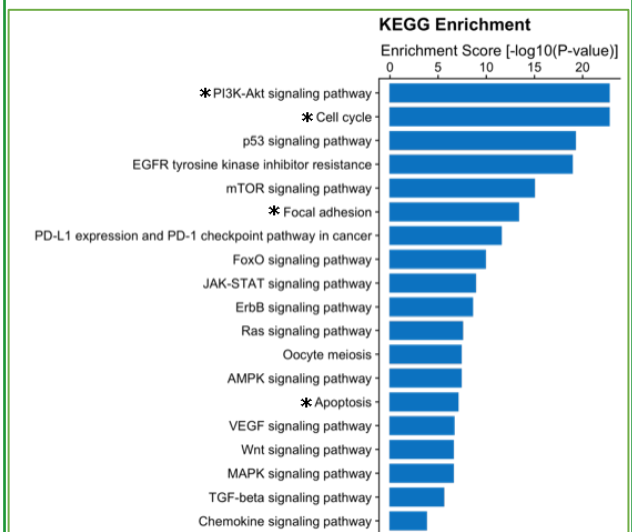

Figure 2: Gene enrichment of miR-383-5p and miR-497 target genes in important pathways for tumorigenesis. (*) Important pathways for the chemoresistance..