

Identification of 11 Differentially Expressed Hub Genes and Their Upstream microRNAs in Nasal-type NK/T-cell Lymphoma Based on Clinical Sample Analysis

Daxia Cai^{1,*}, Ying Yang², Zewei Jiang³, Dongmei He^{1,*}

¹Institute of Hematology, Jinan University, Guangzhou, P.R. China

²Health Management Center, The First Affiliated Hospital of Jinan University, Guangzhou, China

³Department of Respiratory, The First Affiliated Hospital of Jinan University, Guangzhou, China

Email address:

thedm@jnu.edu.cn (Dongmei He), tfcdx620@stu2018.jnu.edu.cn (Daxia Cai), 305923790@qq.com (Ying Yang),

jiangzewei163@163.com (Zewei Jiang)

*Corresponding author

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Abstract: Nasal-type NK/T-cell lymphoma (nasal-type NKTL) is one of the most lethal cancers for. Our study aimed to identify hub differentially expressed genes (DE- genes) and their upstream microRNAs between nasal-type NK/T-cell lymphoma (NKTL) tumor samples and normal nasal tissues through integrated bioinformatics. The 503 DE-genes and 106 DE-miRNAs were identified between NKTL and human normal nasal samples. GO and KEGG analysis were significantly enriched in meiotic recombination, regulation of syncytium formation by plasma membrane fusion, deubiquitination, enriched in meiotic recombination, regulation of syncytium formation by plasma membrane fusion, and stem cell division. And 11 differential expression hub genes and their upstream microRNAs were identified between nasal-type NKTL and normal nasal samples. In summary, after a series of analyses, we found that 11 hub DE-genes and their upstream DE-miRNAs (CDC27-miR-548c-3p, FREM2-miR-373*, ARHGAP29-miR-548c-3p, QSER1-miR-548c-3p, CD3EAP-miR-149*, SF3A1-miR-548c-3p, AQP4-miR-29b, ZFP36L2-miR-142-3p, SRP72-miR-16, TSC22D2-miR-16, TSC22D2-let-7f, DOCK5-miR-16) between nasal-type NKTL and normal nasal samples. They are highly likely to be serve as promising biomarkers in nasal-type NKTL.

Keywords: Bioinformatics Analysis, Differentially Expressed Genes (DE-genes),

Differentially Expressed microRNAs (DE-miRNAs), Nasal-type NK/T-cell Lymphoma (nasal-type NKTL), microRNAs

1. Introduction

Non-Hodgkin lymphoma (NHL) is a highly heterogeneous proliferative disease that can further develop into B cell lymphoma (accounting for 80%-85% of NHL), and natural killer/T-cell lymphoma (accounting for 15%-20% of NHL). Nasal-type NKTL is a rare subtype of mature T- and NK-cell lymphoma leading to palatal deformity caused by cancer invasion through the hard palate, which accounts for approximately 10% of all peripheral NK/T-cell lymphomas in America [1]. Although the use of CCRT with platinum or

L-asparaginase-containing chemotherapy and the avoidance of anthracyclines can improve the prognosis of NKTL, patients still have a poor median survival time of less than 2 years according to global NKTL patient statistics [2]. More unfortunately, nearly half of the patients with newly diagnosed NKTL continue to experience disease progression, and the prognosis in patients with relapsed or refractory NKTL remains unsatisfactory [3]. Previous studies have reported that genetic aberrations, the cellular microenvironment, EBV infection, and epigenetic dysregulation are closely related to NKTL occurrence,

development, and metastasis [4]. A better understanding of the pathogenic mechanisms, especially those of nasal-type NKTL, will provide important insights into the biology of this disease. Therefore, it is urgently necessary to explore the molecular mechanisms underlying nasal-type NKTL occurrence, development, and metastasis to develop targeted therapies and improve prognosis.

MicroRNAs (miRNAs) are a class of noncoding single-stranded RNA molecules with hairpin structures of approximately 22 nucleotides that are involved in regulating the expression of protein-coding genes [5]. At the same time, miRNA regulates gene expression at the posttranscriptional level by pairing with the 3'-untranslated region (3'UTR) of the target gene mRNA. Each miRNA can have multiple target genes and several miRNAs can regulate the same gene. In recent decades, miRNAs have been considered to be involved in the regulation of all aspects of cancers, including proliferation, differentiation and metabolism [6]. However, few studies based on large-scale human tissue studies of differentially expressed miRNAs focused on nasal-type NKTL have been reported.

As gene-chip and RNA sequencing technology are widely used to identify genomic changes during tumour progression, the Gene Expression Omnibus (GEO) has played an important role in bioinformatics analysis. This provides an efficient tool to discover differentially expressed genes (DE-genes) and differentially expressed miRNAs (DE-miRNAs). Based on the GEO database and comprehensive bioinformatics analysis, this study focused on exploring the DE-genes in nasal-type NKTL and their upstream miRNAs, as well as the possible molecular mechanisms in the development of nasal type NKTL compared with normal human nasal tissues. Therefore, we mined and analysed the data from multiple datasets in the GEO database to highlight the characteristics of gene expression and their upstream miRNAs and provide a basis for further research in human nasal-type NKTL.

2. Materials and Methods

2.1. Microarrays and Screening for Differentially Expressed Genes and Differentially Expressed miRNAs

We logged in to the National Center for Biotechnology Information (NCBI) GEO database (<https://www.ncbi.nlm.nih.gov/geo>) to search for the microarrays we needed. Then, to ensure the rigor and accuracy of our research, only datasets comparing mRNA/miRNA expression in human nasal-type NKTL samples with that in human normal nasal samples were included. Carefully read the complete information of the searched datasets and then selected the most suitable datasets for further analysis. Then, the GSE80631 [7] and GSE31377 [8] datasets were selected in our study. The dataset GSE80631 is a GPL6883 platform (Illumina HumanRef-8 v3.0 expression beadchip)-based dataset. We selected 13 human normal nasal samples and 19 human nasal-type

NKTL samples from dataset GSE80631. GSE31377 is based on the platform of GPL8227 (Agilent-019118 Human miRNA Microarray 2.0 G4470B (miRNA ID version)). We selected 2 human normal nasal samples and 17 human nasal-type NKTL samples from dataset the GSE31377.

We used the “LIMMA” from the R package of the bioconductor project to normalize the data. To conduct the differential expression analysis of the miRNAs and genes in nasal-type NKTL samples compared to normal nasal tissues, the related codes were entered into R, and the DE-genes and DE-miRNAs were analysed through the “limma” package in the bioconductor package (<http://www.bioconductor.org/>). p -value<0.05 and $|\log_{2}FC| > 1$ were set as the cut-off criteria for identifying DE-genes and DE-miRNAs. At the same time, volcano plots of the DE-genes and DE-miRNAs were generated by R.

2.2. Prediction of Target Genes for DE-miRNAs

The potential target genes of the top 10 most upregulated and downregulated DE-miRNAs were obtained from the overlapping part of the predictive results derived from TargetScanHuman [9] Release 7.2 (<http://www.targetscan.org/>), miRTarBase [10] Release 7.0 (<http://mirtarbase.mbc.nctu.edu.tw/>), and miRDB [11] Version 5.0 (<http://mirdb.org/>) through calculating and drawing custom Venn diagrams in the web tool Bioinformatics & Systems Biology (<http://bioinformatics.psb.ugent.be/webtools/Venn/>). The TargetScanHuman Release 7.2, which was updated on March 2018, is a web server that predicts the biological targets of miRNAs by searching for the presence of conserved sites that match human 3'UTRs and the orthologues of each miRNA. The miRTarBase Release 7.0 is an experimentally validated microRNA-target interactions database, which is updated on September 15, 2017. miRDB Version 5.0 was released in August 2014, and is an online database for miRNA target prediction and functional annotations.

2.3. Enrichment Analysis

Metascape3.0 (<http://metascape.org/>) [12] was introduced to perform functional and pathway enrichment analysis of the DE-genes and the predicted target genes of the selected top 10 upregulated DE-miRNAs and top 10 downregulated DE-miRNAs, including determination of the Gene Ontology (GO) terms for the biological process (BP), cellular component (CC) and molecular function (MF) categories, Reactome Gene Sets, Canonical Pathways, CORUM, and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways.

2.4. Conjoint Analysis of DE-genes and DE-miRNAs

Due to inhibition by miRNAs of posttranscriptional gene expression via their specific binding to target messenger RNA (mRNA), 10 upregulated DE-genes were crossed with the predicted target genes of the top 10 downregulated DE-miRNAs, and 10 downregulated DE-genes were crossed with the predicted target genes of the top 10 upregulated

DE-miRNAs by calculating and drawing custom Venn diagrams in the web tool Bioinformatics & Systems Biology to obtain more convincing DE-miRNAs, DE-genes, and the one-to-one relationships.

3. Results

3.1. Identification of Differentially Expressed Genes and miRNAs

To identify DE-miRNAs and DE-genes between nasal-type NKTL patient samples and normal nasal tissues, the GSE80631 and GSE31377 data were normalized and differential expression analysis was conducted using the “limma” software package. Then, visualization of normalized data is shown in Figure 1. Based on this differential expression analysis and our screening criteria (p -value<0.05, $|\logFC| >1$), a total of 503 genes were found to be significantly differentially expressed in nasal-type NKTL samples when compared to normal nasal tissues, including 281 upregulated and 222 downregulated genes. At the same time, 106 significantly DE-miRNAs were discovered, of which 57 were upregulated and 49 were downregulated. Furthermore, the top 20 upregulated DE-genes and

downregulated DE-genes (Appendix Table 3), downregulated DE-miRNAs and upregulated DE-miRNAs (Appendix Table 4) were ranked by $|\logFC|$ in Appendix Tables 3-4.

Table 1. More convinced upregulated DE- genes and their upstream miRNAs.

upregulated DE-genes	downregulated DE-miRNAs	logFC
CDC27	hsa-miR-548c-3p	2.41476
FREM2	hsa-miR-373*	2.235638
ARHGAP29	hsa-miR-548c-3p	2.001139
QSER1	hsa-miR-548c-3p	1.802661
CD3EAP	hsa-miR-149*	1.77193
SF3A1	hsa-miR-548c-3p	1.6008

DE=differentially expressed. *represents immature miRNAs.

Table 2. More convinced downregulated DE- genes and their upstream miRNAs.

downregulated DE-genes	upregulated DE-miRNAs	logFC
AQP4	hsa-miR-29b	-2.10407
ZFP36L2	hsa-miR-142-3p	-1.93154
SRP72	hsa-miR-16	-1.54929
TSC22D2	hsa-let-7f	-1.48424
TSC22D2	hsa-miR-16	-1.48424
DOCK5	hsa-miR-16	-1.09845

DE=differentially expressed.

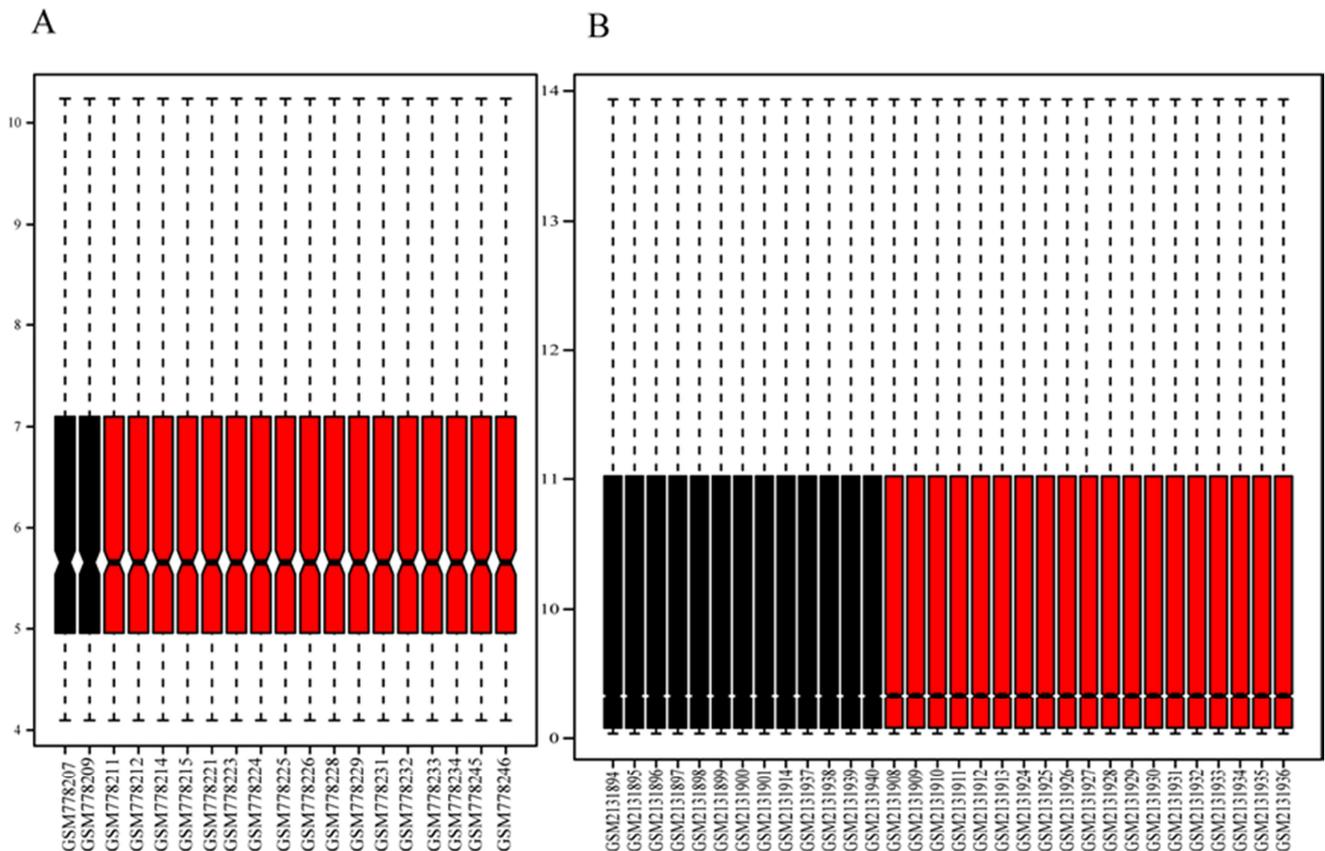


Figure 1. Normalization of datasets GSE31377 (A) and GSE80631 (B).

3.2. Prediction of Target Genes of DE-miRNAs

Based on the screening of DE-miRNAs in the previous step, the top 10 DE-miRNAs were selected for target gene

prediction. The top 10 upregulated DE-miRNAs were hsa-miR-21, hsa-miR-142-3p, hsa-let-7f, hsa-miR-16, hsa-miR-29a, hsa-let-7g, hsa-miR-142-5p, hsa-miR-20a, hsa-miR-29b, and hsa-miR-451. The top 10 downregulated

DE-miRNAs were hsa-miR-1225-5p, hsa-miR-373*, hsa-miR-647, hsa-miR-483-3p, hsa-miR-485-3p, hsa-miR-498, hsa-miR-1224-3p, hsa-miR-149*, hsa-miR-548c-3p, and hsa-miR-1224-5p. We searched for the above target genes of miRNAs in the databases miRTarBase, TargetScanHuman and miRDB. The genes predicted by the three databases were identified as target genes for DE-miRNAs. Finally, 1207 miRNA targets were predicted by three databases as the targets of top the 10 upregulated DE-miRNAs (Appendix Table 5). In the same way, 564 miRNA targets were identified as the targets of the top 10 downregulated DE-miRNAs (Appendix Table 6).

3.3. Pathway and Process Enrichment Analysis

Through Metascape3.0, enrichment analysis was carried out for DE-genes and the predicted target genes of DE-miRNAs. The networks of enriched terms were visualized using Cytoscape (Figures 2 and 3), where each node represents an enriched term and is coloured first by its cluster ID (Figures 2A1, B1, 3A1 and B1) and then by its *p*-value (Figures 2A2, B2, 3A2 and B2). More details on the pathway and process enrichment analyses are shown in Appendix Tables 7-8. The top 5 results for the pathway and process enrichment analyses for the upregulated DE-genes included meiotic recombination, regulation of syncytium formation by plasma membranes, cytokine-cytokine receptor interaction, and deubiquitination. Only the regulation of syncytium formation by plasma membranes belongs to GO biological processes, while the others belong to the KEGG pathway category. The top 20 clusters of significantly

enriched terms for the upregulated DE-genes are shown in Figure 2A1 and A2. The top 5 pathway and process enrichment analyses for predicted target genes of the top 10 downregulated DE-miRNAs included covalent chromatin modification, pathways in cancer, intracellular signalling by second messengers, regulation of cellular amide metabolic process, and protein deacetylation. Except for pathways in cancer (KEGG pathway category) and intracellular signalling by second messengers (Reactome Gene Sets category), all above results belong to the GO biological processes category. The top 20 clusters of significantly enriched terms for predicted target genes of the top 10 downregulated DE-miRNAs are shown in Figure 2B1 and B2. The top 5 pathway and process enrichment analyses for the downregulated DE-genes included divalent metal ion transport, intracellular mRNA localization, hair follicle maturation, stem cell division, and the ERK1 and ERK1 cascades. They all belong to the GO biological processes category. There were only 17 clusters of significantly enriched terms for downregulated DE-genes; therefore, only 17 clusters are shown in Figure 3A1 and A2. The top 5 pathway and process enrichment analyses for 10 predicted target genes of upregulated DE-miRNAs included heart development, blood vessel development, muscle structure development, pathways in cancer, and response to growth factor. Only pathways in cancer belong to the KEGG pathway category, while others belong to GO biological processes. The top 20 clusters of significantly enriched terms for predicted target genes of the 10 upregulated DE-miRNAs are shown in Figure 3B1 and B2.

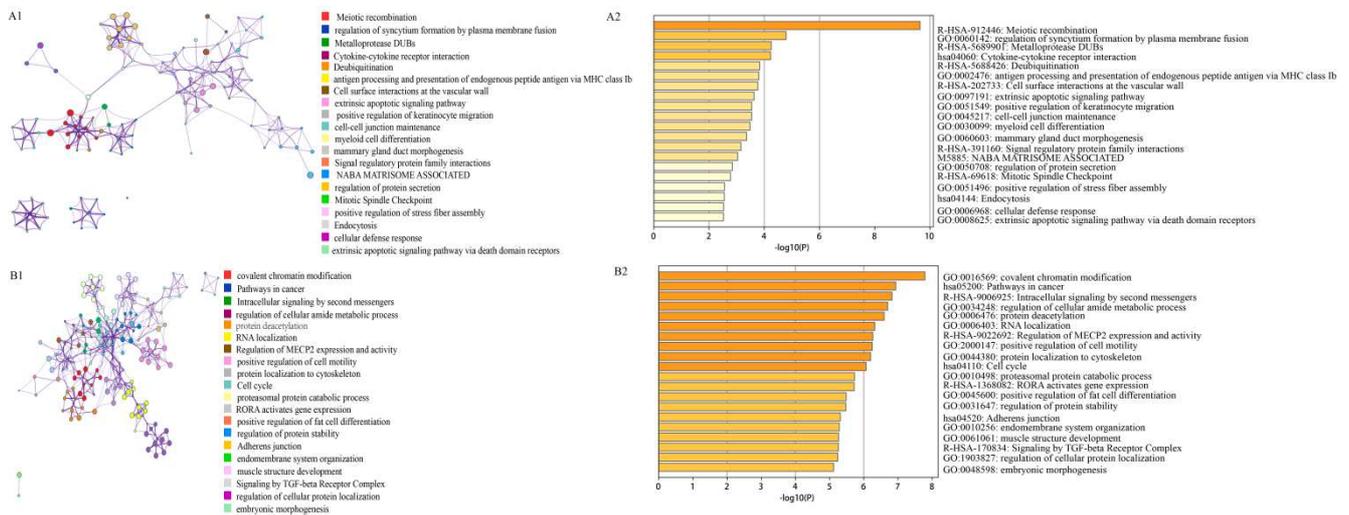


Figure 2. Functional enrichment of upregulated DE-genes and predicted target genes of the top 10 downregulated DE-miRNAs: (A) The visualized networks of enriched upregulated DE-genes, where each node represents an enriched term and is colored first by its cluster ID (A1) and then by its P-value (A2). (B) The visualized networks of enriched predicted target genes of top 10 downregulated DE-miRNAs, where each node represents an enriched term and is colored first by its cluster ID (B1) and then by its P-value (B2). DE=differentially expressed.

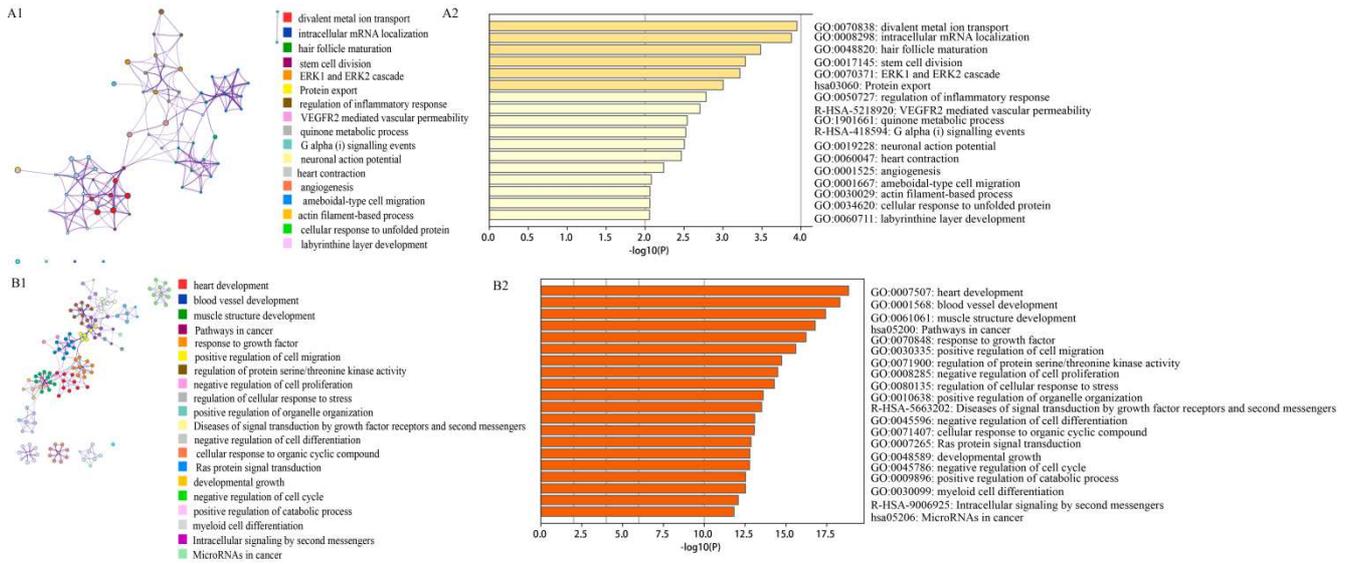


Figure 3. Functional enrichment of downregulated DE-genes and predicted target genes of upregulated DE-miRNAs: (A) The visualized networks of enriched downregulated DE-genes, where each node represents an enriched term and is colored first by its cluster ID (A1) and then by its P-value (A2). (B) The visualized networks of enriched target genes of the 10 predicted target genes of upregulated DE-miRNAs, where each node represents an enriched term and is colored first by its cluster ID (B1) and then by its P-value (B2). DE=differentially expressed.

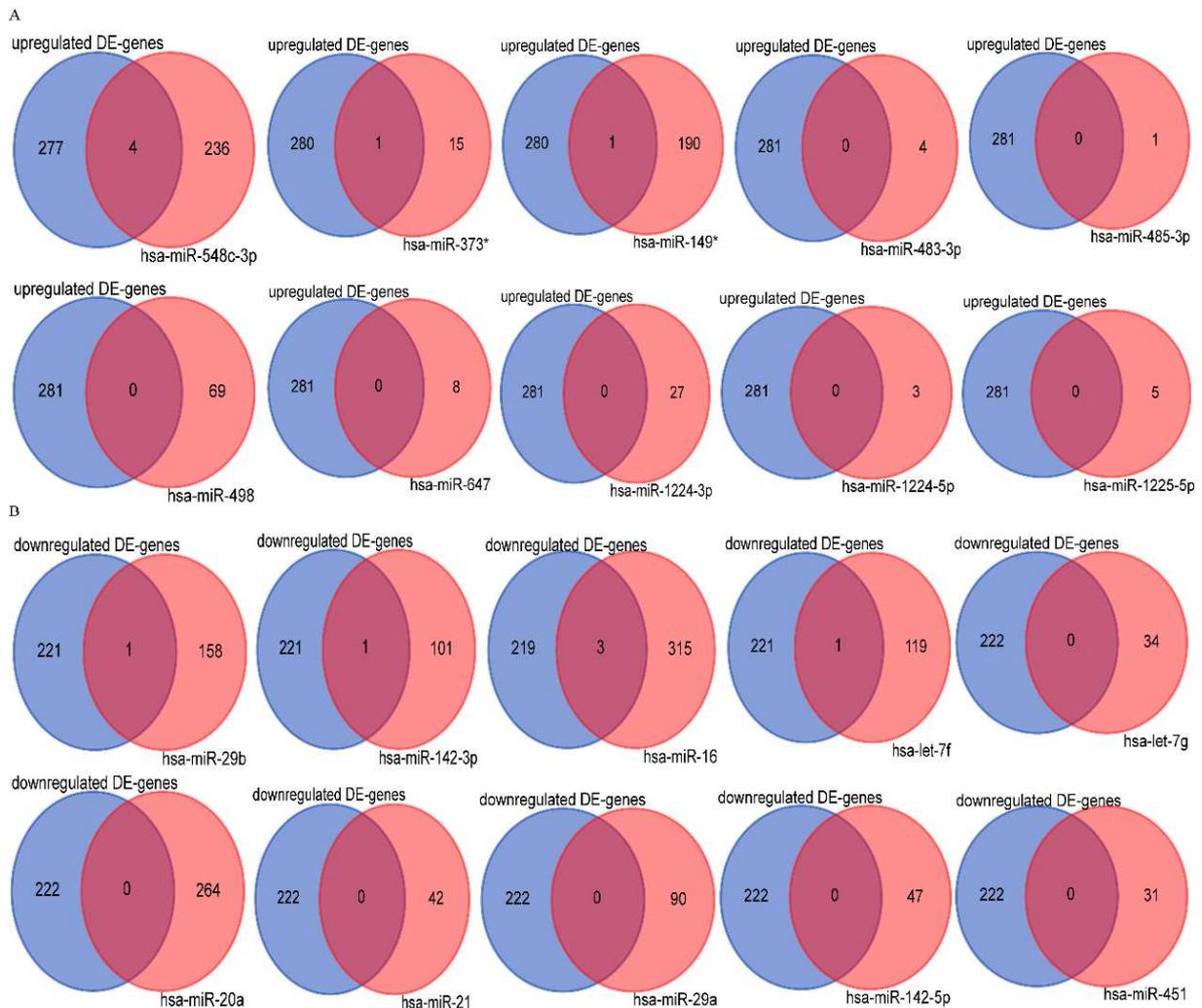


Figure 4. The intersection of upregulated DE-genes and the target genes of downregulated DE-miRNAs (A) and upregulated DE-miRNAs (B). DE=differentially expressed.

3.4. Conjoint Analysis of DE-miRNAs and DE-genes

To connect DE-miRNAs with DE-genes, the predicted target genes of DE-miRNAs were intersected with the DE-genes (Figure 4). In the end, we obtained six upregulated and five downregulated DE-genes and their upstream miRNAs. The upregulated DE-genes and their upstream miRNAs are shown below (Table 1). They were CDC27 (Cell Division Cycle 27)-miR-548c-3p, FREM2 (FRAS1 Related Extracellular Matrix 2)-miR-373*, ARHGAP29 (Rho GTPase Activating Protein 29)-miR-548c-3p, QSER1 (Glutamine and Serine Rich 1)-miR-548c-3p, CD3EAP (CD3e Molecule Associated Protein)-miR-149*, and SF3A1 (Splicing Factor 3a Subunit 1)-miR-548c-3p. At the same time, we found downregulated DE-genes and their upstream miRNAs (Table 2). They were AQP4 (Aquaporin 4)-miR-29b, ZFP36L2 (ZFP36 Ring Finger Protein Like 2)-miR-142-3p, SRP72 (Signal Recognition Particle 72)-miR-16, TSC22D2 (TSC22 Domain Family Member 2)-miR-16, TSC22D2-let-7f, and DOCK5 (Dedicator of Cytokinesis 5)-miR-16.

4. Discussion

The treatment of patients with NKTL has improved over the past decades. Gene therapy is increasingly becoming an effective way to treat cancer based on the identification of DE-genes in human disease. Abnormal expression of miRNAs is involved in regulating all aspects of the occurrence, invasion and metastasis of cancers, which play an important role in cancer diagnosis and treatment [6]. However, until now, DE-genes and DE-miRNAs focused on nasal-type NKTL compared with normal nasal NKTL have rarely been reported. Fortunately, the integration of bioinformatics and microarray technology has enabled more effective ways to identify DE-genes and DE-miRNAs, which can help to discover potential effective targets for the diagnosis and treatment of nasal-type NKTL patients. It is necessary to further study the functions of miRNAs, predict their target genes and understand the interaction between miRNAs and target genes in nasal-type NKTL at present.

In the present study, we screened an eligible gene dataset and miRNA dataset in the GEO database and obtained DE-genes and DE-miRNAs after standardized processing. A total of 503 significantly DE-genes were discovered, of which 281 were upregulated and 222 were downregulated. Furthermore, 106 miRNAs were screened out to be significantly differentially expressed in human nasal-type NKTL samples when compared to human normal nasal samples, including 57 upregulated and 49 downregulated miRNAs. A total of 1207 miRNA targets were predicted for the top 10 upregulated DE-miRNAs, and 564 miRNA targets were identified for the top 10 downregulated DE-miRNAs. At last, the one-to-one relationship between DE-genes and DE-miRNAs were obtained. Through enrichment analysis, we found that meiotic recombination, regulation of syncytium formation by plasma membrane fusion,

deubiquitination, cytokine-cytokine receptor interaction, divalent metal ion transport, intracellular mRNA localization, hair follicle maturation, ERK1 and ERK2 cascade, and stem cell division were more likely to be involved in the development of nasal-type NKTL. Meiotic recombination events have been implicated in cancer development, including ovarian carcinomas, lung adenocarcinoma, head and neck squamous cell carcinoma, liver cancer, bladder urothelial carcinoma, and breast cancer, but meiotic recombination events in nasal-type NKTL have not yet been reported [13]. For nasal-type NKTL, regulation of syncytium formation by plasma membrane fusion is thought to be related to the Epstein-Barr virus (EBV) entry mechanism, which is useful for the development of infection inhibitors and developing EBV vaccine approaches [14]. Metalloprotease deubiquitinases can regulate the ubiquitin signalling cascade, which are thought to be new regulators in cancer progression, such as non-small cell lung cancer [15], but their involvement in nasal-type NKTL has not been previously reported.

In our study, six upregulated and five downregulated DE-genes and their upstream miRNAs were identified by analysing the one-to-one relationship between DE-genes and DE-miRNAs. CDC27-miR-548c-3p, FREM2-miR-373* and ARHGAP29-miR-548c-3p were the top 3 upregulated genes and their upstream miRNAs in the nasal-type NKTL samples compared with normal nasal tissues. CDC27 (also known as ANAPC3) was recently reported to be related to tumour progression and poor survival in T-cell lymphoblastic lymphoma [16]. Additionally, FREM2 has been found to play an important role in the malignant progression of prostate adenocarcinoma [17], and it is also thought to be a biomarker of glioblastoma stem cells [18]. It has been demonstrated that miR-373* can inhibit cell proliferation in colon cancer [19], and downregulation of miR-373* was confirmed in childhood B-cell precursor acute lymphoblastic leukaemia [20]. ARHGAP29 is involved in the development and migration of tumors. Moreover, Margit Schraders et al. demonstrated that ARHGAP29 may be involved in mantle cell lymphoma development and maintenance through signal transduction [21]. There are few reports focused on CDC27, FREM2, ARHGAP29, QSER1, CD3EAP, SF3A1, miR-548c-3p, miR-373*, miR-548c-3p, miR-548c-3p, miR-149* and miR-548c-3p in nasal-type NKTL, and we believe these are worthy of further research.

In the present study, five downregulated DE-genes and their upstream miRNAs were identified (Table 2). AQP4 (miR-29b), ZFP36L2 (miR-142-3p) and SRP72 (miR-16) were the top 3 downregulated genes (upstream miRNAs) in nasal-type NKTL samples compared with normal nasal tissues. MicroRNA-29b is downregulated in cerebral ischaemia and participates in the occurrence and development of cerebral ischaemia by targeting AQP4 regulation [22]. Furthermore, AQP4 induces paraneoplastic syndrome by antibody production, which may be the mechanism of acute myelogenous leukaemia coexisting with

optic neuritis after transplantation [23]. At the same time, AQP4 has been demonstrated to be involved in cell proliferation, invasiveness, migration, and apoptotic potential in glioma cells [24]. miR-29b has been reported to promote the occurrence and development of acute myeloid leukaemia [25] by participating in the regulation of tumour cell proliferation and apoptosis. Repression of miR-29b participates in regulation in cutaneous T-cell lymphoma through the miR-29b-BRD4 axis [26]. Moreover, it was demonstrated that miR-29s could alter the expression of targets involved in critical cancer pathways in Burkitt's lymphoma, such as cell cycle control, apoptosis inhibition and DNA methylation [27]. Moreover, T lymphoma invasion and metastasis 1 (Tiam1) was identified as a direct target of miR-29b [28]. However, so far, we have not found reports on miR-29b focused on nasal-type NKTL, which may become the innovation point and hot spot of future research. ZFP36L2 (also known as TIS11D, one of the NOTCH RNA repressors), dysfunction is associated with the pathogenesis of certain types of leukaemia, such as acute myeloid leukaemia and Burkitt's lymphoma [29]. In addition, ZFP36L2 plays a role in the development of acute lymphoblastic leukaemia [30]. However, there is little literature focused on the relationship between these genes and microRNAs (AQP4, ZFP36L2, SRP72, TSC22D2, DOCK5, miR-29b, miR-142-3p, miR-16, and let-7f) in nasal-type NKTL patients, which may deserve more in-depth research.

In our study, CDC27, ARHGAP29, QSER1, SF3A1 (miR-548c-3p), FREM2- miR-373*, CD3EAP-miR-149*, AQP4-miR-29b, ZFP36L2-miR-142-3p, SRP72, TSC22D2, DOCK5 (miR-16), and TSC22D2-let-7f were identified between nasal-type NKTL and normal nasal samples. Among them, eleven differentially expressed genes (CDC27, FREM2, ARHGAP29, QSER1, CD3EAP, SF3A1, AQP4, ZFP36L2, SRP72, TSC22D2, DOCK5) and six differentially expressed miRNAs (miR-548c-3p, miR-373*, miR-149*, miR-29b, miR-142-3p, let-7f) have been confirmed to be associated with other types of lymphoma, other cancers, or other non-neoplastic diseases. However, few DE-genes and DE-miRNAs focused on nasal-type NKTL have been explored, which may be an innovation of future research. The DE-genes and DE-miRNAs can serve as biomarkers in nasal-type NKTL, which is helpful to understand the pathogenesis of nasal-type NKTL patients. In addition, it may provide strong theoretical support for the early diagnosis of nasal-type NKTL patients and the development of novel therapeutic targets. However, it still has limitations:

1). Target gene prediction was only carried out for the top 10 DE-miRNAs;

2). Only the target genes of the top 10 DE-miRNAs were selected for further enrichment analysis;

3). Since there have been few studies focused on nasal-type NKTL, no dataset with a larger sample size can be found, so, 2 human normal nasal samples and 17 human nasal-type NKTL samples from the GSE313772 dataset were chosen in our study.

4). Due to a lack of experimental verification, more research should be carried out.

5. Conclusions

In conclusion, we successfully identified DE-genes and their upstream DE-miRNAs (CDC27- miR-548c-3p, FREM2- miR-373*, ARHGAP29-miR-548c-3p, QSER1-miR-548c-3p, CD3EAP-miR-149*, SF3A1-miR-548c-3p, AQP4-miR-29b, ZFP36L2-miR-142-3p, SRP72-miR-16, TSC22D2-miR-16, TSC22D2-let-7f, and DOCK5-miR-16) in nasal-type NKTL based on clinical sample tissues through bioinformatic analysis, and these molecules are highly likely to be related to nasal-type NKTL and which may serve as biomarkers in nasal-type NKTL. Undoubtedly, continued efforts to delineate the mechanism of differential genes and miRNAs will uncover novel insights into nasal-type NKTL.

Abbreviations

differentially expressed genes (DE-genes), differentially expressed microRNAs (DE-miRNAs), nasal-type NK/T-cell lymphoma (nasal-type NKTL), Cell Division Cycle 27 (CDC27), FRAS1 Related Extracellular Matrix 2 (FREM2), Rho GTPase Activating Protein 29 (ARHGAP29), Glutamine And Serine Rich 1 (QSER1), CD3e Molecule Associated Protein (CD3EAP), Splicing Factor 3a Subunit 1 (SF3A1), Aquaporin 4 (AQP4), ZFP36 Ring Finger Protein Like 2 (ZFP36L2), Signal Recognition Particle 72 (SRP72), TSC22 Domain Family Member 2 (TSC22D2), Dedicator Of Cytokinesis 5 (DOCK5)

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Appendix

Table 3. The top 20 upregulated and downregulated DE-genes (ranked by $|\log FC|$).

Genes	logFC	"t"	"P.Value"	"adj.P.Val"	expression
UBAP2L	3.879406091	7.711088382	8.31E-09	3.91E-05	upregulation
TNFRSF12A	3.65190092	5.122697428	1.37E-05	0.002386708	upregulation

Genes	logFC	"t"	"P.Value"	"adj.P.Val"	expression
HIST1H4J	3.452632998	4.705086766	4.62E-05	0.004879843	upregulation
SCTR	3.320035717	3.577358316	0.00112315	0.026257114	upregulation
CETN2	3.016183112	4.667267489	5.16E-05	0.005020758	upregulation
ADAMTS20	2.944247403	3.369083932	0.001971425	0.035561324	upregulation
LOC401565	2.931236947	4.673618746	5.06E-05	0.005020758	upregulation
TGFBR1	2.905484306	6.19925479	5.97E-07	0.000400622	upregulation
FAM3D	2.903349382	5.320153275	7.71E-06	0.001766605	upregulation
CD177	2.85437046	3.256806836	0.002656712	0.041405943	upregulation
HIST2H2AC	2.847568264	4.558287141	7.07E-05	0.006279004	upregulation
DOK5	2.818048072	3.382679659	0.001901008	0.035099561	upregulation
MGC13017	2.815718644	5.604320752	3.36E-06	0.001022668	upregulation
IL26	2.763884207	4.661045869	5.25E-05	0.005020758	upregulation
IL25	2.750375101	4.404942125	0.000109875	0.007882469	upregulation
HIST1H2BF	2.747516007	3.910023591	0.000447662	0.015875964	upregulation
SIRPG	2.736534779	5.276810906	8.75E-06	0.001868193	upregulation
SLC9A3R2	2.724778021	3.518571975	0.001317952	0.028738072	upregulation
CSF2RB	2.681546694	3.719856346	0.000759591	0.020481387	upregulation
HIST1H2BB	2.632406983	4.114378133	0.000251746	0.011829561	upregulation
KLF4	-3.29919148	-4.15919297	0.000221693	0.010960098	downregulation
SYN3	-3.11937921	-4.10098413	0.00026148	0.011929085	downregulation
ZNF207	-3.03922233	-5.26117862	9.15E-06	0.001911965	downregulation
KRTHB4	-2.99265976	-4.36352981	0.000123736	0.008075495	downregulation
ZFP36L1	-2.95271722	-4.39633941	0.000112622	0.007920838	downregulation
SLN	-2.94525138	-3.53752539	0.001251829	0.027826839	downregulation
ZBTB16	-2.89774713	-3.91918127	0.00043633	0.015750361	downregulation
FGF18	-2.86338653	-4.5475020	7.29E-05	0.006279004	downregulation
AMOTL2	-2.85713112	-6.34292943	3.94E-07	0.000320764	downregulation
NPBWR1	-2.80828507	-6.69978677	1.42E-07	1.90E-04	downregulation
EFHA2	-2.71571717	-7.24136302	3.06E-08	9.59E-05	downregulation
ZNF599	-2.67703321	-4.66520744	5.19E-05	0.005020758	downregulation
ZNF471	-2.66268816	-4.09394917	0.00026674	0.011994354	downregulation
TCAP	-2.63710513	-4.04257123	0.000308425	0.013175341	downregulation
ZFP1	-2.59412544	-5.42330123	5.70E-06	0.001531354	downregulation
ZNF503	-2.59296641	-4.74399366	4.13E-05	0.004731436	downregulation
RRBP1	0.621289108	3.768999144	0.000663049	0.019889056	downregulation
S100BPB	-2.49782697	-4.26233293	0.000165278	0.009319239	downregulation
SUSD4	-2.49727748	-4.21461472	0.000189365	0.010054514	downregulation
FAM100B	-2.48087708	-4.29613737	0.000150065	0.009099835	downregulation

DE=differentially expressed.

Table 4. The top 20 downregulated and upregulated DE-miRNAs (ranked by |logFC|).

miRNA_ID	adj.P.Val	P.Value	logFC	expression
hsa-miR-1225-5p	0.04203	0.0010752	-3.86404	downregulation
hsa-miR-373*	0.04109	0.0006506	-3.74013	downregulation
hsa-miR-647	0.03523	0.0003004	-3.48445	downregulation
hsa-miR-483-3p	0.04203	0.0009398	-3.36585	downregulation
hsa-miR-485-3p	0.04109	0.0006485	-3.35861	downregulation
hsa-miR-498	0.04203	0.0009074	-3.35428	downregulation
hsa-miR-1224-3p	0.04203	0.0007327	-3.1557	downregulation
hsa-miR-149*	0.12347	0.0091741	-3.05849	downregulation
hsa-miR-548c-3p	0.04203	0.0008541	-3.05768	downregulation
hsa-miR-1224-5p	0.22838	0.0317172	-2.98012	downregulation
hsa-miR-300	0.04109	0.0005342	-2.76202	downregulation
hsa-miR-617	0.10631	0.0071221	-2.68626	downregulation
hsa-miR-520b	0.0708	0.0030183	-2.65173	downregulation
hsa-miR-188-5p	0.18665	0.020006	-2.6094	downregulation
hsa-miR-371-5p	0.26757	0.0456272	-2.48873	downregulation
hsa-miR-557	0.22838	0.0319724	-2.3795	downregulation
hsa-miR-609	0.06622	0.0027426	-2.32371	downregulation
hsa-miR-423-5p	0.03811	0.0003713	-2.26901	downregulation
hsa-miR-939	0.19316	0.0216456	-2.15537	downregulation
hsa-miR-574-5p	0.26757	0.0453523	-2.14901	downregulation
hsa-miR-21	0.00861	2.097E-05	6.24605	upregulation
hsa-miR-142-3p	0.05704	0.0018809	4.739127	upregulation
hsa-let-7f	0.10047	0.0064858	3.887418	upregulation
hsa-miR-16	0.06261	0.0025167	3.842062	upregulation

miRNA ID	adj.P.Val	P.Value	logFC	expression
hsa-miR-29a	0.09996	0.0062097	3.812272	upregulation
hsa-let-7g	0.14563	0.0120444	3.667266	upregulation
hsa-miR-142-5p	0.05704	0.0020843	3.48577	upregulation
hsa-miR-20a	0.08195	0.0047914	3.479459	upregulation
hsa-miR-29b	0.07965	0.0045596	3.479448	upregulation
hsa-miR-451	0.14935	0.0125544	3.47876	upregulation
hsa-miR-342-3p	0.07219	0.0031656	3.423527	upregulation
ebv-miR-BART14	0.14563	0.0120354	3.351517	upregulation
ebv-miR-BART9	0.17942	0.0187394	3.257656	upregulation
hsa-miR-801	0.06261	0.0024403	3.151849	upregulation
hsa-miR-106b	0.07854	0.0042094	3.120468	upregulation
hsa-let-7a	0.17747	0.01759	3.114659	upregulation
hsa-miR-15b	0.17747	0.0180421	3.104831	upregulation
hsa-miR-26a	0.24196	0.0362505	3.081633	upregulation
ebv-miR-BART3	0.21875	0.0282662	3.048915	upregulation
hsa-miR-103	0.10743	0.0073278	3.018221	upregulation

DE=differentially expressed.

Table 5. Target genes of top 10 upregulated differentially expressed miRNAs

miRNAs	number	genes
hsa-miR-21	42	TG2, NFIA, PDCD4, FBXO11, SPRY2, TIAM1, PCBP1, HNRNPK, WWP1, CBX4, DAXX, NTF3, COL4A1, RASA1, PIK3R1, MAP2K3, SATB1, MEF2C, CDC25A, TGF2, TIMP3, YOD1, SOCS6, DDAH1, TAP1, JAG1, ANKRD46, SMAD7, STAT3, CCL20, IL12A, TOPORS, FASLG, RTN4, PPARA, BMPR2, SOX5, RASGRP1, NFIB, RECK, MSH2, TGFB1
hsa-miR-142-3p	102	RAB2A, MMGT1, WASL, IRAK1, RAC1, AFF1, SLC37A3, TET3, C5orf24, FLVCR1, DIP2A, STAM, MANBAL, USP6NL, ROCK2, CLTA, BCLAF1, FYCO1, AKIRIN2, LCOR, ACBD5, TIPARP, COPG1, KIF5B, TWF1, ARF4, TMEM59, RICTOR, ZMYND8, GF11, ZFP36L2, GOLGA1, CCDC6, TNRC18, BOD1, MORF4L2, TMTC3, AFF4, EGR2, TMED7, TAB2, ITGAV, TGFB1, ZNF217, MTCH1, TNKS, ARHGAP12, STRN3, FBXO3, IPMK, SLC7A11, CCNT2, GNB2, SMG1, ARNTL, TFG, MRFAP1, MTMR9, HMGA2, ZCCHC14, CLOCK, PTPN23, LRRC32, SLC35F5, MARCKS, C9orf72, HECTD1, CPEB2, CLIC4, MBD6, GNAQ, EML4, FNDC3A, IL6ST, PSMB5, RGL2, TSEN34, LRRC59, PROM1, CNIH4, KMT2A, AKT1S1, NR2F6, C18orf25, BACH1, SYPL1, SUCO, BTBD7, ARL15, C16orf70, APC, HMGA1, ATG16L1, ATP2A2, TAOK1, ADCY9, SIK1, HGS, KAT7, INPP5A, KAT2B, PUM1
hsa-let-7f	120	ZNF799, SOD2, DIP2A, ITGA3, BAZ1B, PPP1R15B, MFSD8, LCOR, IRS1, EPHA4, AHR, MAP2K4, GSK3B, PANK3, ATL1, KMT2D, TXLNG, C5orf51, KLHL15, PAPOLG, CREB1, PPP2R2A, ZNF585A, ATXN1L, SMARCA1, ATG12, NRBF2, HNRNPU, RPS16, IRF2BP2, ZNF609, ARMC8, SMC1A, CCL7, GABRG1, DYRK2, NAA20, STX7, TGFB1, C1orf52, COL4A3BP, CREBZF, TRAPPC10, HMGB2, HSPE1-MOB4, CD59, DUSP6, SP1, MBNL1, TP53INP1, PLAGL2, MS12, TRIM71, FAM43A, MLLT10, ZNF800, TOR1AIP2, EIF4A2, GPRIN3, CBX5, PEG10, USP1, ZNF200, PDE12, IGF2BP3, ZNF181, DLX2, ARIH1, MOB4, BEND4, NR2F2, PRDM1, ZNF608, ZFX, ASB11, SMAD2, HNRNPA2B1, NHLRC2, TSC22D2, PMAIP1, SHOC2, HAT1, TGFB3, MXD1, NUDT4, RNF11, SEC24A, EDEM3, PDLIM5, MYADM, ZNF652, MTRF1, E2F8, MEF2D, WASL, BTG1, CDKN1B, DSG2, CASD1, AASDHPPT, LRIG3, ZNF644, GOLGA7, STX3, PHACTR4, VEZF1, SYT1, SESN3, SOCS7, RORA, ANAPC16, HDAC2, ACER2, VCL, BACH1, KLF10, SALL3, ONECUT2, STRN, SNX17
hsa-miR-16	318	RPS6KA5, GTPBP1, PDCD4, NAT8L, PPM1A, CPEB3, RICTOR, SLITRK4, AHCYL2, UBN2, DCUN1D5, CAMSAP1, PLSCR4, PAQR3, TCP1, DNAJB4, JAK2, B2M, NEGR1, PLRG1, FAM122B, ITGA2, CBX2, RFK, EIF4E, USP15, CBX4, CEP63, IPPK, PURA, CFL2, TBL1XR1, CMTM4, TSPYL1, SPTBN2, RNF111, EN2, SOX6, CA8, ZCCHC2, CHIC1, HELZ, FNDC3B, LIN7C, SESTD1, SAV1, CHPT1, SLC39A14, RAPH1, CHEK1, PHC3, PAG1, PRKAA1, SLC12A2, RAB23, PHF19, CD226, OMA1, NUP50, IFRD1, PABPC4L, GABPA, PTAR1, KIF3B, TMEM67, IVNS1ABP, NUS1, USP31, TOX4, AXIN2, PSAT1, FGF2, TMCC1, SLC38A1, FZD6, CDC42SE2, TMEM168, STXB3, MIB1, LRIG2, CACNA2D1, RBPJ, MAFK, ERLIN2, INO80D, FRYL, CBX6, ASH1L, ACVR2A, LMAN2L, SLC39A9, PANK1, CNOT7, RUNX1T1, TRIM35, ARHGAP12, NAA15, BCL11B, WEE1, TNRC6B, ZFX, USP46, YRDC, TSC22D2, CCNT1, TMEM189-UBE2V1, NACC1, SYPL1, TGFB3, BAG4, N4BP1, RAB1A, COMMD3-BMI1, PAGR1, MLLT11, CNNM2, GALNT1, SBNO1, SEC24A, AMOT, KDSR, MCM8, PLAUR, SIK1, ACSL4, PDLIM5, SMNDC1, SPTLC1, DICER1, BDNF, ACOX1, KIF5B, RAB11FIP2, HSPA4L, C1orf21, PIM1, PDPR, USP25, ZMAT3, FOXK1, PHIP, SLC11A2, BCL2L11, CPEB2, MLLT6, ZBTB33, CALU, CMPK1, AIMP1, MSH2, MGAT4A, USP48, CTDSPL, CYP26B1, RAB30, VCL, LRRFIP2, CCND2, YAP1, CYB561A3, TAOK1, CASK, BTG2, ARL6IP1, RELT, SNX16, RAD23B, SSU72, TUBB, TMEM255A, EIF1AX, BCL2, SRP72, MFN2, CDK17, RBPP6, TLK1, XPO4, NOTCH2, HMBOX1, VEGFA, MYC, E2F7, ELK4, KLHL15, TNPO1, TARBP2, CLCN3, TM9SF3, PPP6R3, LURAP1L, GSG1, PTPRJ, SOCS5, RNMT, TMEM135, UBE2V1, ACTN1, BNC2, MTRF1L, AKT3, ACTR2, CDC25A, NAPG, RASEF, DYRK2, ZFH4, SENP6, RIF1, HOXA10, PEX13, SLC38A2, LRPPRC, PRRC2C, ZCCHC3, ZNRF2, CCNT2, PDIK1L, TMEM154, NCKAP1, RTN4, SLC9A6, DCUN1D1, PLAG1, IPO7, FRK, WNK3, IBTK, DPP8, C11orf24, DOCK5, AMOTL1, SYNJ1, ZNF431, SREK1, CBX5, VTI1B, SERBP1, YTHDC1, AR, ATG14, RNF44, APP, ANP32E, RNF217, YWHAQ, MCU, TASP1, ARIH1, NR2C2, ZNF275, RAB9B, MAP7, WBP11, BCAS2, PTPN14, IFT74, CDC27, ARHGAP32, NUCKS1, TMEM68, DDX31, CCPG1, CEP55, IARS, MED13, RSBN1, GLRX, FBXW7, TFAP2A, PPP6C, ENTPD1, CPS1, HOXC8, ORC4, TAF15, AKAP11, EPM2AIP1, BRWD1, PDE3B, FASN, ZNF704, BTRC, ATP13A3, TMEM161B, SYNRG, RIMS3, HIGD1A, PHKA1, CD2AP, CRIM1, GABARAPL1, EPC1, TES, SNTB2, HMGA2, IDH3A, LSM11, HSPA5, TMEM245, RECK, JARID2, PAFAH1B2, SLFN13, GOLIM4, HOXA9, CADM1, ZC3H11A, REL, TM7SF3, PTPN3, C2orf42, UBE3C, NMD3, ONECUT2, RNF6, ARMCX2, RPS6KA3
hsa-miR-	90	FSTL1, NFIA, STK17A, PXDN, QKI, ZBTB20, WDR26, GSK3B, CACNA1C, CCDC117, FOXN3, AKT2, ABL1, CALCR,

miRNAs	number	genes
29a		LPL, AAK1, TMOD3, AKT3, HECW1, COMMD2, SH3GLB1, RCC2, HOXA10, ABCE1, ROBO1, CCNT2, IFRD1, CDC7, SEC31A, AGO1, MAPK6, IYD, ITGA11, WWTR1, FOXO3, ZBTB5, CRKL, ADAM12, IGF1, LILRB2, TET3, BBC3, CAND1, SERPINB9, DNMT3B, HLF, SOWAHB, COL5A2, DNMT3A, ITGA6, KCNN3, LIMS1, NAA40, HMGCR, KDM5B, PPP3CB, FSCN1, AMMECR1L, PHACTR2, SYNCRIP, LOX, MXD1, CLDN1, PPM1D, AMER1, PTEN, GPR180, DICER1, REST, FEM1B, NRIP1, ZCCHC24, EMP1, TMTC3, TECPR2, SLC24A2, FBN1, EPHX2, GOLGA7, BACE1, ZFP91, TET2, GLUL, RAB30, REL, NEDD9, CCND2, AGAP1, GEM, VHL
hsa-let-7g	34	CCNB1, RAB3IP, KPNA2, ABI2, RDX, KIAA0930, OLR1, ABT1, MBD2, USP38, KMT2D, HAT1, POTEM, AGPAT5, ZNF704, YOD1, ARID3A, MTUS1, MAP3K1, ABHD17C, HMGB2, HMGA2, CASP3, CLDN12, SYT1, SOCS7, MAPK6, TNFRSF10B, RAB5C, NAA30, ACER2, CBX5, WAC, APP
hsa-miR-142-5p	47	ACTN4, U2SURP, RGMB, PTEN, IGF2BP3, DDX5, RPS6KA5, SAMD12, RHOC, REST, ULK1, ATP13A3, DUSP2, ACTC1, SLITRK4, HSPA8, ZBTB20, UHMK1, ZBTB43, NFE2L2, YY1, LEPROT, EFCAB14, ROBO1, SLC30A7, FAM107B, LUZP2, TNS1, PTPN4, SLC24A2, BCOR, FIGN, TRIP10, RGPD4, FEM1C, MED17, CEP97, SOCS1, ZFYVE26, CREBRF, TGFB2, ATXN1, LZIC, EGLN3, PTP4A1, AKAP11, MFSD9
hsa-miR-20a	264	CMTR2, NHLRC3, DDX5, CHD9, MAP3K3, RPS6KA5, RUNX3, F2RL1, FAXC, CEP120, TNKS2, POLR3G, ZNF264, PLEKHM3, B2M, NF1, NFAT5, HMBOX1, KMT2B, PTPN4, PANK3, ELK4, YBX1, CCSER2, RB1CC1, RMND5A, KIAA0513, TSKU, ITGBL1, KLHL15, TNPO1, PURA, CFL2, SKI, TBL1XR1, TMEM167A, TNFRSF21, MCC, RAB22A, NABP1, GPAM, POTEM, E2F2, ZNF532, DDHD1, RBM41, TBC1D15, SOCS5, ARHGAP35, ADSS, RAB10, STX6, UGT8, AAK1, EEA1, ARSJ, PARD6B, RBM48, PSD3, KLF3, KIF26B, HECA, NUFIP2, ABL2, MECP2, MAP3K5, TMEM127, YOD1, SLC16A7, DCBLD2, KATNAL1, FYCO1, C14orf28, NACC2, PRRG4, MASTL, CROT, PDRG1, MTF1, KLF6, PITPNA, UBR5, PEAK1, WWC1, FRMD6, NAA50, STAT3, EIF5A2, CDC42, SEMA7A, ARHGEF18, EREG, SCAMP5, SMAD4, ATL3, ZBTB6, MCL1, TMEM100, ZCCHC14, FXR1, TMEM67, AGO1, RGS5, FBXO21, EZH1, BMPR2, MED17, ENPP5, GINS4, ENTPD4, TP53INP1, TSG101, RABEP1, HIF1A, WNK3, NFATC2IP, NIPAI1, TGFB2, TCF7L2, ZNF800, VANGL1, KCNB1, ANKIB1, RRAGD, RLIM, CBX5, YTHDC1, CRISPLD2, SESN2, ATG14, RBL1, APP, ATP2B1, SMAD5, FNBP1L, TET3, ATG2B, HOOK3, OTUD4, YWHAQ, OTUD3, RAB5B, ABI2, TCF4, NR2C2, FAM126B, ZNF805, SSRP1, ASXL2, VTI1A, HAS2, CNOT7, COL19A1, UBE2Q2, ITGB8, SLC5A3, ASB1, ZC3H12C, MAVS, WEE1, GPR155, SIKE1, KPNA4, FOXJ3, TFAM, HMG2, MAPK1, PIP4K2A, ZNF268, SH3BP5, SIRPA, SLAIN2, F2R, DNAJC27, PCMTD1, LYSMD3, SHOC2, PKIA, LRRC20, PPP6C, PURB, SUCO, ATXN1, CPOX, LZIC, EIF4H, DLC1, RAP2C, WDR37, DNAL1, MKRN1, AKAP11, USP28, CYBRD1, GIGYF1, ACSL4, SMIM13, TRMT5, TOMM20, AFF1, ERI1, SENP1, NUP214, ARL1, IKZF5, PTPDC1, PHLPP2, FAM129A, VPS26A, SAMD12, CNOT4, LPGAT1, ULK1, FEM1B, CADM2, SPOPL, E2F1, NPAT, TANC1, GOLGA1, PPIR3B, KIAA1147, SGTB, OSTM1, AGFG2, RBM12B, SNTB2, FAF2, DCTN6, ZMAT3, CLOCK, VEZF1, SREK1IP1, SESN3, RORA, ZNF597, BCL2L11, ATAD2, NFIB, FMNL3, ZBTB33, MXI1, MAP3K2, REEP5, ANKFY1, CKAP2, ANKRD50, ZFYVE26, FGFR1OP, DR1, GNB5, BACH1, BTBD7, CCND2, FBXO48, SSX2IP, TTPAL, ZNFX1, SALL3, VPS13C, UEVLD, PXX, TADA2B, UBXN2A
hsa-miR-29b	159	COL1A1, ZNF83, PPIL1, TPM3, WDR26, CCNA2, RDH11, KIF1B, CCDC117, MDM2, TESPA1, COL4A6, PIK3R1, TET1, ZBTB46, HSPB6, NID1, R3HDM4, AQP4, AHCY, STAT3, CREBZF, COL3A1, NUS1, C17orf58, SPI, DDX6, TRIM38, UBE4B, WWTR1, CIT, SNX24, KITLG, STX16, CAND1, CECR2, GTF3C3, OTUD4, ACTC1, CBX6, ACVR2A, NCOA3, ITGB1, DNMT3A, BBX, TNRC6B, HDAC4, SFXN1, CTNBP1, C1QTNF6, PHACTR2, DENND6A, LOX, SDE2, ELAVL1, PPIC, SLC16A1, AMER1, METTL8, CSGALNACT2, FEM1B, DHX40, MAP2K6, CDK6, TMTC3, SOX12, UBE4A, GOLGA7, LOXL2, CALU, TET2, THBS2, SRSF2, CRTC3, NEDD9, CCND2, AMD1, VHL, BTG2, EPB41L4B, PTC3, LMNB2, PPP1R15B, KDM2A, HP1BP3, TNRC18, TRAM2, RAB15, NOTCH2, VEGFA, GSK3B, TNFAIP3, PTBP3, TCERG1, NREP, PDGFRA, AKT3, HECW1, TGFB2, COMMD2, SH3GLB1, FGB, FOLR1, PDGFB, ABCE1, CDC42, NEUROD1, CCNT2, RNF138, MCL1, PIK3CG, TDG, PLAG1, ZDHHC5, C21orf91, ACVR2B, ZMIZ1, ANKRD27, PTP4A1, SPARC, COL5A1, ZBTB5, CSRN2, ADAM12, TET3, ITGA6, ENPP2, POU2F2, NAA40, HMGCR, SLC2A14, ZNF507, COL4A1, RAPGEF2, ENTPD1, FAM71F2, RAP2C, INSIG1, PTEN, ZBTB34, KCTD15, HIST1H2AE, EDC3, REST, DYNLT1, EMP1, CCSAP, ISG20L2, FBN1, CREB5, BACE1, ZFP91, RPA1, CALM3, FAM84A, REL, CERS2, MAT2A, PDGFC
hsa-miR-451	31	VEGFA, MAF, POM121C, RAB10, DCBLD2, PRKAR2A, CDKN2D, ANKRD42, VANGL2, FAM83C, OSCAR, SLU7, ARHGAP18, ADAM22, CBX6, DHCR7, SSBP2, SRP54, RHPN2, GGA3, BZW1, MAP3K1, ZMAT3, MCTS1, OSR1, ELOVL6, STEAP2, CAB39, PIP4K2C, ZBED2, MIF

Table 6. Target genes of top 10 downregulated differentially expressed miRNAs

miRNAs	Number	predicted target genes
hsa-miR-1225-5p	5	SEMA4D, DCX, ZNF107, SEMA6D, ASPH
hsa-miR-373	16	HOOK3, EIF4E, TRIM66, PDP2, SUZ12, FGF5, RNPS1, DNAL1, SPIB, SATB2, LIMA1, SGTB, FREM2, RPF2, TTC31, GTF2IRD2
hsa-miR-647	8	NCOA1, ZNF609, NFIX, HNRNPF, SECISBP2L, NIPBL, IL5, MG1
hsa-miR-483-3p	4	IGF1, MAPKAPK2, RAB5B, CNOT6L
hsa-miR-485-3p	1	RORA
hsa-miR-498	69	EP300, PPP1R15B, KLHL36, EPHA4, LIN28B, LIMD2, PLEKHM3, GK5, EPB41L3, GALNT10, ELK4, CBX4, ZFP36L1, UBE2H, C16orf72, MSMO1, PDIA6, ZNF689, IRF2BP2, SFPQ, YOD1, PAG1, MID1, MATN3, ZNF134, KCTD20, MYO1F, CDV3, DSN1, VTA1, TOB1, ATP2B1, PELI2, IKZF3, PALM2, CRCP, HYPK, SLC7A11, S100A16, SAMD5, GPR155, FOXJ3, SLC2A14, IL17RD, MEX3A, COL4A1, SERF2, PLEKHG1, LACTB, SCO1, TRDN, DICER1, CAPZA2, WT1, CDK6, MORF4L2, SYNRG, FRAT2, ZKSCAN4, PDCD10, CHAC1, MCTS1, ASXL3, LOXL2, WIPF2, CYP20A1, KLHL8, MED28, FAM217B

miRNAs	Number	predicted target genes
hsa-miR-1224-3p	27	HAUS2, ATF6B, GSTCD, KIAA0232, KMT2B, HLCS, PXMP4, C16orf58, TAF8, TFPD2, SLCO3A1, SCD, GOSR1, NDUFV3, ORAI2, FANCA, TGIF2, GPR182, BCL11B, MKNK2, HNRNPA2B1, BBS5, ZNF500, PLK1, MIS18A, ZNF708, GATAD2B NTSR1, RRP7A, CCL22, ITGA3, EFN1, LMNB2, NCOR2, DUSP4, ANGPT4, NPR1, TMEM59, TLCD2, CACNB1, HCFC1, NRF1, ENTPD7, SAMD10, KLHL21, BTBD9, FAM129B, NFAT5, ELL, F2RL2, KMT2D, KRT80, PNMA2, SH3TC2, TSKU, MDM2, FZD5, DNPEP, HOXC4, NUDT19, SKI, HM13, TSPYL1, PSKH1, KIF1A, FBXL16, DTD2, MARCKSL1, SH3BP1, KLHL26, PDGFRA, KLC2, SLC25A45, ZBTB7B, PDE1B, TRAF3IP2, CTNBL1, RHOF, TMEM127, SLC35F6, RAP1GAP2, NOVA2, UBLCP1, SLCO3A1, ZBTB2, IFFO2, PACS2, SLC47A1, TBXA2R, RBMS2, MSII, RNF2, PTPNA, PEAK1, RASA4, EMID1, HOXA10, SCD, ARHGEF39, ATN1, DPYSL5, GPRC5A, NFIC, ATL3, IL6, CREBL2, AGO1, FASLG, DUSP19, VPS37C, PSAP, STX1A, ZNF491, SNX27, NFIX, EIF5, GCFC2, KHSRP, ORAI2, TCTN2, TOR1AIP2, ULK2, AKT1, USP22, PPM1F, PTC1, PRR12, GP5, STRN4, ZNF490, COL5A1, FBXL18, DCTN2, NPTXR, CNOT6L, ANKRD45, AHDC1, ANKRD13B, FGFR1, BBC3, S1PR2, CLCC1, TMEM63C, IP6K1, ATP1B4, TSPYL4, CRIPT, PNPLA6, YWHAZ, ANKRD52, FAM83H, PGAM1, BVES, PEX26, SLC25A34, NAV2, VPS53, AQP6, MAVS, ARL8A, GCDH, PLXND1, FN3K, AAR2, SBF1, CLEC7A, MARK2, GGCX, RNF24, TNNI1, TP53, PURB, FAM71F2, IQSEC3, UBE2D4, SPRY4, CAPN15, ZBTB3, TOLLIP, SREBF1, TMTC1, SYNGR1, CAPZB, CD3EAP, MYADM, ZNF500, MTHFR, GPR173, TGFB3, MYH9, MGAT5B, ZCCHC24, SLC19A3, C17orf75, STARD3, FEM1A, GNG4, PFKFB3, M6PR, MAZ, RPRD2, FOXK1, PHACTR4, GIT1, CARM1, HES6, ZNF674, HDAC2, CYP2W1, C1orf35, ZCCHC8, IRGQ, MLEC, PGAM4, CDCP1, ZNF385A, SLC38A7, PGPEP1 USP6NL, PDCD4, FAXC, CDCA4, METTL21A, UBE2W, ARHGEF26, ANKRD40, EPB41L3, UNKL, CRLF3, GSR, MRAS, PIK3C2B, PURA, TBL1XR1, HCFC2, PRDM10, CALCR, PPP1CB, ZBTB10, ZNF99, TPPP, DPPA4, TPR, SESTD1, CCT6A, ATXN7L1, IRF2BP2, GTF2E1, SKP1, OSTF1, RIPPLY3, ENAH, MAML3, STYX, ELP3, GDPD1, FXR1, LYPD6, DSC3, LYN, RREB1, FGF2, HNRNPAB, TMCC1, SMU1, CDKN2AIP, EDEM1, WDR76, RNF219, TGFB2, KCNB1, CANX, ZFH3, FZD6, TRPS1, ANP32B, SCN9A, BTG3, TRA2B, HS3ST1, EMP2, MZT1, ZNF805, CCDC6, NCOA3, PANK1, KCNN3, LIX1L, TNRC6B, ASB11, KPNA4, SF3A1, PGAP1, CEP85L, GGF5, CLIP4, SDE2, LAMP2, CTNND1, NUDT4, NXT2, GALNT1, AGO3, ZNF652, EXOC5, ACAD8, PROK2, FOPNL, MYEF2, UHMK1, CDK6, TLL2, TMTC3, ZNF792, IL1RAP, TJP1, PTCH1, ELOVL4, ATF7IP, ICK, GOLGA7, OGT, CPEB2, ZBTB33, SIX4, FAT3, NAA30, ZNF708, SRSF2, SPATA13, SEMA5A, DPY19L1, RPS6KB1, DIP2A, TRPM6, TIAL1, CARD8, RBBP6, PARG, SET, EIF2S1, MKLN1, PPFIBP1, KDELR1, GK5, FKBP5, GSK3B, ST6GALNAC3, ELK4, PHAX, CCSER2, SH3BP2, TLE3, NDST3, TMC5, ARHGAP29, THBS1, TNFRSF21, ZDHHC21, TM9SF3, PTPRJ, C16orf70, HNRNPU, KCNE4, ABLIM1, HECW1, RAPIA, CLN8, SKP2, FAM102B, GRSF1, SMAD4, TRIAP1, ELMOD2, MSANTD3-TMEFF1, SHMT1, MTX3, BMRP2, PDZD8, IGF1R, ZNF319, MON2, TNFRSF10B, QSER1, TMEFF1, ZNF28, OLA1, ATAD5, TMED4, PTGIS, UBE2G1, MTF, IGF2BP3, S1PR2, KPNA3, YTHDF1, NUP37, FXN, ZNF711, SCN1A, SPCS3, KCTD10, RANBP1, LUZP2, ANAPC1, NFATC3, PNISR, CDC27, NUCKS1, FOXJ3, ZIC5, PIP4K2A, CPSF6, NFE2L1, SLC25A36, TGIF1, PAXBP1, PURB, LZIC, NSUN7, CERS6, CALM1, BRWD1, PGK1, WASL, GPR180, SNTG1, REST, ATP13A3, SPOPL, CNN3, PPP1CC, LEPROT, LRIG3, AFF4, ITGAV, CD2AP, CWC27, NEDD1, ZBTB8A, TMPPRS15, ELAVL4, SLC7A5, NFIB, TTC28, SRSF1, CPNE3, DNAJB9, FGFR1OP, B4GALT7, FAM84A, STAT2, REL, GNA14, GXYLT1, ZNF845, SNAI2, FCHO2
hsa-miR-149	191	
hsa-miR-548c-3p	240	
hsa-miR-1224-5p	3	KLHL15, CREB1, PPP1R9B

Table 7. Top 20 clusters with their representative enriched terms of upregulated and downregulated DE-genes (one per cluster).

GO	Category	Description	Count	%	Log10 (P)	DE-genes
R-HSA-912446	Reactome Gene Sets	Meiotic recombination	12	4.43	-9.64	upregulated
GO:0060142	GO Biological Processes	regulation of syncytium formation by plasma membrane fusion	5	1.85	-4.79	upregulated
R-HSA-5689901	Reactome Gene Sets	Metalloprotease DUBs	5	1.85	-4.25	upregulated
hsa04060	KEGG Pathway	Cytokine-cytokine receptor interaction	12	4.43	-4.23	upregulated
R-HSA-5688426	Reactome Gene Sets	Deubiquitination	12	4.43	-3.84	upregulated
GO:0002476	GO Biological Processes	antigen processing and presentation of endogenous peptide antigen via MHC class Ib	3	1.11	-3.8	upregulated
R-HSA-202733	Reactome Gene Sets	Cell surface interactions at the vascular wall	8	2.95	-3.77	upregulated
GO:0097191	GO Biological Processes	extrinsic apoptotic signaling pathway	10	3.69	-3.63	upregulated
GO:0051549	GO Biological Processes	positive regulation of keratinocyte migration	3	1.11	-3.55	upregulated
GO:0045217	GO Biological Processes	cell-cell junction maintenance	3	1.11	-3.55	upregulated
GO:0030099	GO Biological Processes	myeloid cell differentiation	14	5.17	-3.48	upregulated
GO:0060603	GO Biological Processes	mammary gland duct morphogenesis	4	1.48	-3.36	upregulated
R-HSA-391160	Reactome Gene Sets	Signal regulatory protein family interactions	3	1.11	-3.15	upregulated
M5885	Canonical Pathways	NABA MATRISOME ASSOCIATED	19	7.01	-3.04	upregulated
GO:0050708	GO Biological Processes	regulation of protein secretion	14	5.17	-2.85	upregulated
R-HSA-69618	Reactome Gene Sets	Mitotic Spindle Checkpoint	6	2.21	-2.78	upregulated

GO	Category	Description	Count	%	Log10 (P)	DE-genes
GO:0051496	GO Biological Processes	positive regulation of stress fiber assembly	4	1.48	-2.56	upregulated
hsa04144	KEGG Pathway	Endocytosis	9	3.32	-2.55	upregulated
GO:0006968	GO Biological Processes	cellular defense response	4	1.48	-2.53	upregulated
GO:0008625	GO Biological Processes	extrinsic apoptotic signaling pathway via death domain receptors	5	1.85	-2.52	upregulated
GO:0070838	GO Biological Processes	divalent metal ion transport	14	6.7	-3.95	downregulated
GO:0008298	GO Biological Processes	intracellular mRNA localization	3	1.44	-3.88	downregulated
GO:0048820	GO Biological Processes	hair follicle maturation	3	1.44	-3.48	downregulated
GO:0017145	GO Biological Processes	stem cell division	4	1.91	-3.29	downregulated
GO:0070371	GO Biological Processes	ERK1 and ERK2 cascade	10	4.78	-3.22	downregulated
hsa03060	KEGG Pathway	Protein export	3	1.44	-3	downregulated
GO:0050727	GO Biological Processes	regulation of inflammatory response	12	5.74	-2.78	downregulated
R-HSA-5218920	Reactome Gene Sets	VEGFR2 mediated vascular permeability	3	1.44	-2.7	downregulated
GO:1901661	GO Biological Processes	quinone metabolic process	3	1.44	-2.54	downregulated
R-HSA-418594	Reactome Gene Sets	G alpha (i) signalling events	10	4.78	-2.52	downregulated
GO:0019228	GO Biological Processes	neuronal action potential	3	1.44	-2.5	downregulated
GO:0060047	GO Biological Processes	heart contraction	8	3.83	-2.47	downregulated
GO:0001525	GO Biological Processes	angiogenesis	12	5.74	-2.24	downregulated
GO:0001667	GO Biological Processes	ameboidal-type cell migration	10	4.78	-2.08	downregulated
GO:0030029	GO Biological Processes	actin filament-based process	14	6.7	-2.06	downregulated
GO:0034620	GO Biological Processes	cellular response to unfolded protein	5	2.39	-2.06	downregulated
GO:0060711	GO Biological Processes	labyrinthine layer development	3	1.44	-2.06	downregulated

"Count" is the number of genes in the user-provided lists with membership in the given ontology term. "%" is the percentage of all of the user-provided genes that are found in the given ontology term (only input genes with at least one ontology term annotation were included in the calculation). "Log10 (P)" is the p-value in log base 10. "Log10 (q)" is the multi-test adjusted p-value in log base 10. DE=differentially expressed.

Table 8. Top 20 clusters with their representative enriched terms of downregulated and upregulated DE-miRNAs (one per cluster).

GO	Category	Description	Count	%	Log10 (P)	DE-miRNAs
O:0016569	GO Biological Processes	covalent chromatin modification	33	6.04	-7.79	downregulated
hsa05200	KEGG Pathway	Pathways in cancer	28	5.13	-6.93	downregulated
R-HSA-9006925	Reactome Gene Sets	Intracellular signaling by second messengers	24	4.4	-6.83	downregulated
GO:0034248	GO Biological Processes	regulation of cellular amide metabolic process	32	5.86	-6.7	downregulated
GO:0006476	GO Biological Processes	protein deacetylation	13	2.38	-6.6	downregulated
GO:0006403	GO Biological Processes	RNA localization	20	3.66	-6.32	downregulated
R-HSA-9022692	Reactome Gene Sets	Regulation of MECP2 expression and activity	8	1.47	-6.26	downregulated
GO:2000147	GO Biological Processes	positive regulation of cell motility	34	6.23	-6.24	downregulated
GO:0044380	GO Biological Processes	protein localization to cytoskeleton	10	1.83	-6.2	downregulated
hsa04110	KEGG Pathway	Cell cycle	14	2.56	-6.07	downregulated
GO:0010498	GO Biological Processes	proteasomal protein catabolic process	29	5.31	-5.73	downregulated
R-HSA-1368082	Reactome Gene Sets	RORA activates gene expression	6	1.1	-5.72	downregulated
GO:0045600	GO Biological Processes	positive regulation of fat cell differentiation	10	1.83	-5.48	downregulated
GO:0031647	GO Biological Processes	regulation of protein stability	21	3.85	-5.47	downregulated
hsa04520	KEGG Pathway	Adherens junction	10	1.83	-5.31	downregulated
GO:0010256	GO Biological Processes	endomembrane system organization	27	4.95	-5.28	downregulated
GO:0061061	GO Biological Processes	muscle structure development	35	6.41	-5.26	downregulated
R-HSA-170834	Reactome Gene Sets	Signaling by TGF-beta Receptor Complex	10	1.83	-5.26	downregulated
GO:1903827	GO Biological Processes	regulation of cellular protein localization	30	5.49	-5.24	downregulated
GO:0048598	GO Biological Processes	embryonic morphogenesis	32	5.86	-5.12	downregulated
GO:0001568	GO Biological Processes	blood vessel development	91	9.01	-18.31	upregulated
GO:0007265	GO Biological Processes	Ras protein signal transduction	53	5.25	-12.86	upregulated

GO	Category	Description	Count	%	Log10 (P)	DE-miRNAs
GO:0007507	GO Biological Processes	heart development	78	7.72	-18.84	upregulated
GO:0008285	GO Biological Processes	negative regulation of cell proliferation	83	8.22	-14.5	upregulated
GO:0009896	GO Biological Processes	positive regulation of catabolic process	55	5.45	-12.53	upregulated
GO:0010638	GO Biological Processes	positive regulation of organelle organization	72	7.13	-13.61	upregulated
GO:0030099	GO Biological Processes	myeloid cell differentiation	54	5.35	-12.52	upregulated
GO:0030335	GO Biological Processes	positive regulation of cell migration	70	6.93	-15.6	upregulated
GO:0045596	GO Biological Processes	negative regulation of cell differentiation	79	7.82	-13.09	upregulated
GO:0045786	GO Biological Processes	negative regulation of cell cycle	70	6.93	-12.78	upregulated
GO:0048589	GO Biological Processes	developmental growth	73	7.23	-12.79	upregulated
GO:0061061	GO Biological Processes	muscle structure development	82	8.12	-17.43	upregulated
GO:0070848	GO Biological Processes	response to growth factor	84	8.32	-16.23	upregulated
GO:0071407	GO Biological Processes	cellular response to organic cyclic compound	64	6.34	-13.07	upregulated
GO:0071900	GO Biological Processes	regulation of protein serine/threonine kinase activity	66	6.53	-14.74	upregulated
GO:0080135	GO Biological Processes	regulation of cellular response to stress	82	8.12	-14.29	upregulated
R-HSA-5663202	Reactome Gene Sets	Diseases of signal transduction by growth factor receptors and second messengers	52	5.15	-13.52	upregulated
R-HSA-9006925	Reactome Gene Sets	Intracellular signaling by second messengers	44	4.36	-12.08	upregulated
hsa05200	KEGG Pathway	Pathways in cancer	59	5.84	-16.79	upregulated
hsa05206	KEGG Pathway	MicroRNAs in cancer	43	4.26	-11.82	upregulated

"Count" is the number of genes in the user-provided lists with membership in the given ontology term. "%" is the percentage of all of the user-provided genes that are found in the given ontology term (only input genes with at least one ontology term annotation are included in the calculation). "Log10 (P)" is the p-value in log base 10. "Log10 (q)" is the multi-test adjusted p-value in log base 10.

DE=differentially expressed.

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