RESEARCH ARTICLE

Networks of MicroRNAs and Genes in Retinoblastomas

Jie Li[1,2], Zhi-Wen Xu[1,2]*, Kun-Hao Wang[1,2], Ning Wang[1,2], De-Qiang Li[1,2], Shang Wang[1,2]

Abstract

Through years of effort, researchers have made notable progress in gene and microRNA fields about retinoblastoma morbidity. However, experimentally validated data for genes, microRNAs (miRNAs) and transcription factors (TFs) can only be found in a scattered form, which makes it difficult to conclude the relationship between genes and retinoblastoma systematically. In this study, we regarded genes, miRNAs and TFs as elements in the regulatory network and focused on the relationship between pairs of examples. In this way, we paid attention to all the elements macroscopically, instead of only researching one or several. To show regulatory relationships over genes, miRNAs and TFs clearly, we constructed 3 regulatory networks hierarchically, including a differentially expressed network, a related network and a global network, for analysis of similarities and comparison of differences. After construction of the three networks, important pathways were highlighted. We constructed an upstream and downstream element table of differentially expressed genes and miRNAs, in which we found self-adaption relations and circle-regulation. Our study systematically assessed factors in the pathogenesis of retinoblastoma and provided theoretical foundations for gene therapy researchers. In future studies, especial attention should be paid to the highlighted genes and miRNAs.

Keywords: Retinoblastoma - MicroRNA - transcription factor - network - host gene

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Introduction

Retinoblastoma (Rb) is a rapidly developing cancer that develops in the cells of retina, the light-detecting tissue of the eye.

We can conclude from the experimental data that the differentially expressed genes and differentially expressed miRNAs play a key role in the pathogenesis of Rb. The related genes and related miRNAs also play a part .

Transcription factors (TFs) and miRNAs are prominent regulator for gene expression (Hobert et al. , 2008). TFs are a special kind of proteins which promote or suppress the transcription of genes through binding to the upstream regions of genes. TFs regulate the transcription of genes in a single form and sometimes cowork with other proteins. MiRNA functions in various biological processes, including proliferation, differentiation and apoptosis. MiRNAs target at genes to regulate wide range of biological processes, which provides a plenty of experimentally validated data for the databases we retrieved.

The genes with the locations of miRNAs on it is called the host genes of the particular miRNAs. Rodriguez A et al indicated that miRNAs are transcribed in parallel with their host transcripts and two different transcription classes of miRNAs (exonic and intronic) were identified (Rodriguez et al. , 2004). Baskerville et al. (2005) indicated that intronic miRNA and its host gene have close relation. Intronic miRNA and their host gene usually coordinately express in biological progression. They usually act as potential partner to achieve biological function and affect the alteration of pathways.

Molecular biologists and medical scientists have conducted a large quantity of experiments in which many differentially expressed genes and miRNAs. However, the experiments are mostly based on a single element (gene or miRNA), which makes it complex to analyze the general nosogenesis of Rb. In this study, we focus on the relationship over all the elements in Rb instead of experiment on only several of them. There are 3 kinds of relationship between the elements in Rb. They are miRNAs locating on host genes, genes regulating miRNAs and miRNAs targeting at target genes. We also manually collected differentially expressed elements and Rb-related elements from lectures and databases. We construct 3 regulatory networks based on the relationship we picked up according to the degree of correlation between the elements and Rb, which are named the differentially expressed network, the related network and the global network. The global network is construct with all the relationship has been experimentally validated by the time the paper was written, which makes it so complex that we

*[1]Department of Computer Science and Technology, [2]Symbol Computation and Knowledge Engineer of Ministry of Education, Jilin University, Changchun, China *For correspondence: xuzw@jlu.edu.cn*

cannot draw useful information from it. So we picked up the pathways about the differentially expressed elements and popular TFs to complete our work. The differences and similarities were paid much attention to, which is of great significance in finding the key element in the pathway of Rb.

Materials and Methods

Material collection and data processing

The experimentally validated dataset of human miRNAs and their target genes were collected from the Tarbase 5. 0 and miRTarBase. The symbols used in this paper to unify each gene and miRNA are the official symbols from National Center for Biotechnology Information (NCBI) database at http://www. ncbi. nlm. nih. gov/gene/. The data strongly supports or opinion about Rb.

The experimentally validated dataset of human TFs and the miRNAs regulated by them were collected from TransmiR (Wang et al. , 2009). This dataset is a manually extracted dataset between TFs and miRNAs.

The host genes of human miRNAs were extract from miRbase (Kozomara et al. , 2011) and NCBI. We used official symbol and official ID to sign each host gene.

We collected differentially expressed genes in Rb from Cancer Genetics Web which can be accessed at http:// www. cancerindex. org/geneweb/index. html/, NCBI SNP database at http://www. ncbi. nlm. nih. gov/snp/ and pertinent literatures. We collected Rb-related genes from GeneCards database (Safran et al. , 2010) and pertinent literatures including those genes which affect tumor growth, migration, radial therapy and clinical outcome of Rb. Furthermore, we extracted the popular TFs by P-match method (Chekmenev et al. , 2005). We considered them as Rb-related genes and only focused on these TFs that appear in transmiR. We downloaded 1000nt promoter region sequences of the targets of differentially expressed genes from UCSC database (Fujita et al. , 2011). We used P-match method that combines pattern matching and weight matrix approaches to identify transcription factor binding sites (TFBSs) in 1000 nt promoter region sequences and mapped TFBSs onto promoter region of targets. Matrix library of P-match is also sets of known TF-binding sites collected in TRANSFAC, so it provides the possibility to search for a large variety of different TF binding sites. We used the vertebrate matrix and restricted high quality criterion for the matrix.

We extracted differentially expressed miRNAs from pertinent literatures and mir2Disease (Bao et al. , 2012), which is a manually created database about differentially expressed miRNAs in various human diseases. We collected Rb-related miRNAs manually from permanent literatures.

Three networks construction

We constructed three regulatory networks of Rb, which are differentially expressed network, Rb-related network and global network. We extracted all regulatory relations on host genes, target genes, miRNAs and TFs. After combining all these relations, we got the global regulatory network. We extracted differentially expressed elements, and selected the relations with both differentially expressed elements from global network. That's how we got the differentially expressed network. In the same way, we got the Rb-related network.

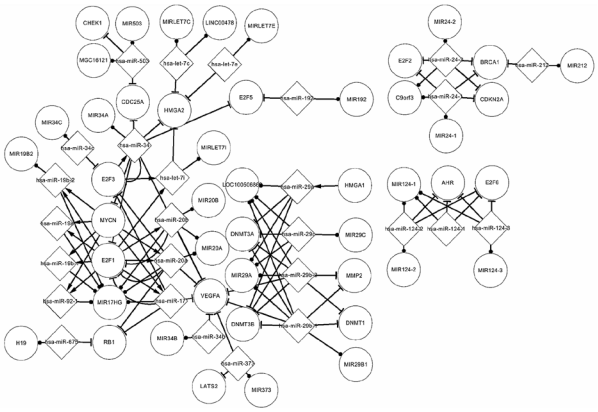

Figure 1. Differentially Expressed Network about Genes and Mirnas in Retinoblastoma

Results

Differentially expressed network of Rb

There are many significant regulatory pathways and important elements about Rb in Figure 1. This network is composed of 8 TFs, 20 targets of miRNAs, 47 miRNAs and their host genes. Besides the host genes, all the other elements are differentially expressed in Rb. There are several kinds of regulatory relations between miRNAs and genes in Figure 1. There are three kinds of relations between the elements in Rb, which are miRNAs targeting at target genes, host genes including miRNAs and genes regulates miRNAs. Some special features of host genes and their miRNAs are highlighted in this Figure. A host gene may include one or several miRNAs meanwhile the miRNAs may target at other genes. For example, MIR373 includes hsa-miR-373 while hsa-miR-373 targets at VEGFA and LATS2. A miRNA may locate in one or several genes. For example hsa-miR-181b-1 locates in MIR181B1 and LOC100131234. We also found some regulatory circuits in this network. For example, hsa-miR-34 regulates and locates in E2F3 at the same time. This differentially expressed network partly revealed the regulatory mechanism of Rb.

Related network of Rb

The Rb-related network contains a large quantities of relations between genes and miRNAs. In our opinion, the differentially expressed elements are included in the related Rb-related elements, which leads to the result that the differentially expressed regulatory network is part of the Rb-related network. There are 8 differentially expressed TFs, 11 additional TFs, 42 miRNAs and much more target genes. Related network shows many additional pathways about genes and miRNAs. Rb-related network shows more topology relations than the differentially expressed network and contributes to further understand the pathogenesis of Rb.

Table 1. The Upstream and Downstream Information of E2F1 in the Three Networks of GCT

hsa-miR-106b	/	/	PTEN	hsa-miR-19a	hsa-miR-302	hsa-miR-302
hsa-miR-141	/	/	PTEN	hsa-miR-21	hsa-miR-302b	hsa-miR-302b
hsa-miR-17	/	/	PTEN	hsa-miR-22	hsa-miR-302d	hsa-miR-302d
hsa-miR-18a	/	/	PTEN	hsa-miR-25	/	/
hsa-miR-19a	/	/	PTEN	hsa-miR-302	/	/
hsa-miR-19b	/	/	PTEN	hsa-miR-302a	/	/
hsa-miR-19b-1	/	/	PTEN	hsa-miR-302b	/	/
hsa-miR-19b-2	/	/	PTEN	hsa-miR-302c	/	/
hsa-miR-20	/	/	PTEN	hsa-miR-302d	/	/
hsa-miR-20a	/	/	PTEN	hsa-miR-302f	/	/
hsa-miR-21	/	/	PTEN	/	/	/
hsa-miR-214	/	/	PTEN	/	/	/
hsa-miR-216	/	/	PTEN	/	/	/
hsa-miR-216a	/	/	PTEN	/	/	/
hsa-miR-217	/	/	PTEN	/	/	/
hsa-miR-221	/	/	PTEN	/	/	/
hsa-miR-222	/	/	PTEN	/	/	/
hsa-miR-26a	/	/	PTEN	/	/	/
hsa-miR-26a-1	/	/	PTEN	/	/	/
hsa-miR-26a-2	/	/	PTEN	/	/	/
hsa-miR-494	/	/	PTEN	/	/	/
hsa-miR-91	/	/	PTEN	/	/	/

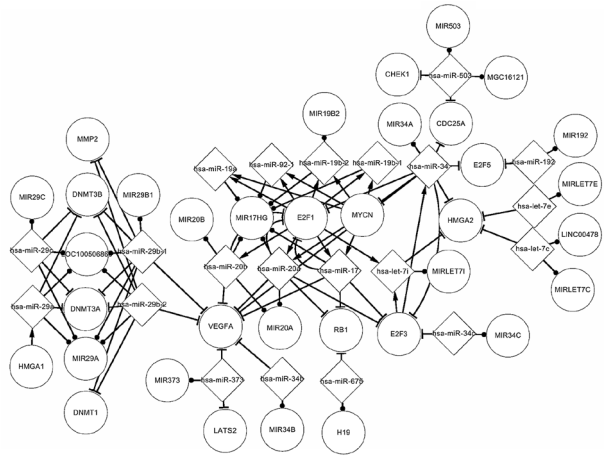

Figure 2. Host Genes and miRNAs in the Differentially Expressed Network of Retinoblastoma

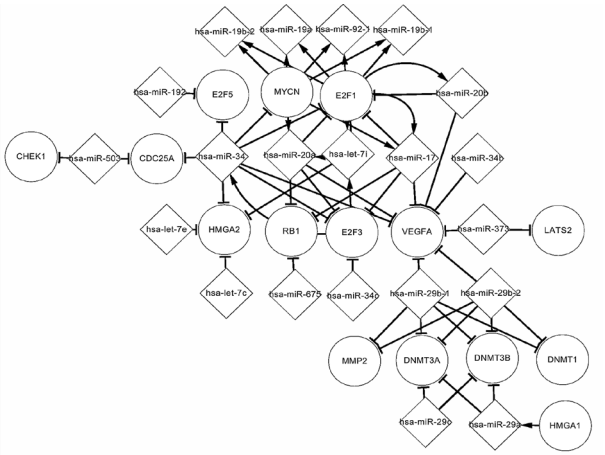

Figure 3. Transcription Factors and miRNAs in the Differentially Expressed Network of Retinoblastoma

Global network of Rb

The global network includes more comprehensive regulatory relations that are from the three sets. It is an experimentally validated biological network in human body. Indeed it includes differentially expressed network and related network.

Host gene and its miRNA in Rb

Host genes and its miRNAs show some important characteristics in this study. As we can see in the differentially expressed network, the elements in this network are all differentially expressed elements except for the host genes. We considered the host genes as differentially expressed genes as long as the miRNAs are differentially expressed. In the differentially expressed network, we found that some host genes and their miRNAs show the feature, which is a host gene includes several miRNAs that alone or together target some genes. They are shown in Figure 2.

We can find many special relations between host genes and other elements in Figure 2. MIR29A includes 4 miRNAs (hsa-miR-29a, hsa-miR-29b-1, hsa-miR-29b-2 and hsa-miR-29c) that together target at DNMT3A and DNMT3B. Hsa-miR-34 is regulated by E2F3 and E2F1. Hsa-miR-34 and ESF3 form a self-adaption relation. MIR17HG includes 4 miRNAs (hsa-miR-92-1, and hsa-miR-19a, hsa-miR-19b-1 and hsa-miR-19b-2) that are regulated by E2F1 and MYCN, meanwhile, all the 4 miRNAs do not target at any differentially expressed genes. HMGA2 is targeted by 4 miRNAs (hsa-miR-7c, hsa-miR-7e, hsa-miR-7i and hsa-miR-34) but does not regulates any miRNAs . It is suggested that host genes and their miRNAs could help us to understand the pathogenesis of Rb.

Transcriptional network of popular TFs

We further analyzed 21 differentially expressed miRNAs that are regulated by popular TFs. Figure 3 shows regulatory relations between popular TFs and miRNAs as well as targets in Rb. These elements influence their successors by targeting at or regulating them. Figure 3 shows E2F1 regulates 8 miRNAs and it is

Table 2. The Upstream and Downstream Information of Hsa-Mir-17 in The Three Networks of Retinoblastoma

E2F1	CCND1	CCND1	hsa-miR-17	E2F1	BCL2	APP
MIR17HG	E2F1	E2F1	hsa-miR-17	E2F3	CCND1	BCL2
MYCN	MIR17HG	ESR1	hsa-miR-17	RB1	CDKN1A	BCL2L11
/	MYC	MIR17HG	hsa-miR-17	VEGFA	E2F1	BMPR2
/	MYCN	MYC	hsa-miR-17	/	E2F3	CCL1
/	NFKB1	MYCN	hsa-miR-17	/	MYC	CCND1
/	NKX2-5	NFKB1	hsa-miR-17	/	PTEN	CCND2
/	SPI1	NKX2-5	hsa-miR-17	/	RB1	CDKN1A
/	/	SPI1	hsa-miR-17	/	RBL1	DNAJC27
/	/	STAT5B	hsa-miR-17	/	RBL2	E2F1
/	/	TLX1	hsa-miR-17	/	RUNX1	E2F3
/	/	TLX3	hsa-miR-17	/	SMAD4	FBXO31
/	/	TNF	hsa-miR-17	/	TGFBR2	GPR137B
/	/	/	hsa-miR-17	/	VEGFA	GPX2
/	/	/	hsa-miR-17	/	/	ICAM1
/	/	/	hsa-miR-17	/	/	JAK1
/	/	/	hsa-miR-17	/	/	
MAP3K12						
/	/	/	hsa-miR-17	/	/	MAPK9
/	/	/	hsa-miR-17	/	/	MEF2D
/	/	/	hsa-miR-17	/	/	MUC17
/	/	/	hsa-miR-17	/	/	MYC
/	/	/	hsa-miR-17	/	/	NCOA3
/	/	/	hsa-miR-17	/	/	NPAT
/	/	/	hsa-miR-17	/	/	OBFC2A
/	/	/	hsa-miR-17	/	/	PKD2
/	/	/	hsa-miR-17	/	/	PTEN
/	/	/	hsa-miR-17	/	/	PTPRO
/	/	/	hsa-miR-17	/	/	RB1
/	/	/	hsa-miR-17	/	/	RBL1
/	/	/	hsa-miR-17	/	/	RBL2
/	/	/	hsa-miR-17	/	/	RUNX1
/	/	/	hsa-miR-17	/	/	SELE
/	/	/	hsa-miR-17	/	/	SMAD4
/	/	/	hsa-miR-17	/	/	SOD2
/	/	/	hsa-miR-17	/	/	TGFBR2
/	/	/	hsa-miR-17	/	/	THBS1
/	/	/	hsa-miR-17	/	/	TNFSF12
/	/	/	hsa-miR-17	/	/	TXNRD2
/	/	/	hsa-miR-17	/	/	VEGFA
/	/	/	hsa-miR-17	/	/	VIM
/	/	/	hsa-miR-17	/	/	WEE1
/	/	/	hsa-miR-17	/	/	YES1
/	/	/	hsa-miR-17	/	/	ZNFX1

targeted at by 4 miRNAs. Hsa-miR-17 and E2F1 form a self-adaption relation. E2F1 regulates hsa-miR-20a that targets at VEGFA, RB1 and E2F3. In this Figure, we can see that a differentially expressed miRNA may target at one or several TFs, and a TF may regulate one or several differentially expressed miRNAs. The transcription network about popular TFs and miRNAs will contribute to understand the pathogenesis of Rb.

Regulatory pathways about differentially expressed genes

To describe the network of Rb more clearly, we extracted the upstream and downstream information of the important elements (differentially expressed genes, differentially expressed miRNAs and popular TFs from the P-match method).

Here, we see E2F1 as an example . In Table 1, we listed the precursors and successors of E2F1 in differentially expressed network, related network and global network. We extracted the successor nodes and precursor nodes of the differentially expressed genes of Rb from the three networks (differentially expressed network, related network and global network). Some pathways were highlighted after the list was made because we can see some special pathways more obviously. Among these genes, E2F1 and E2F3 showed a special characteristic that the precursor nodes and successor nodes have some elements in common which means the gene and miRNA form a self-adaption relation.

We firstly focused on the TFs

The first class of TF has 2 kinds of adjacent nodes (three kinds of successors and three kinds of predecessors). These TFs include E2F1, E2F3 and MYCN. We only focused on E2F1 as following part. In Table 1, we listed the precursors and successors of E2F1 in differentially expressed network, related network and global network. There are 4 miRNAs target at E2F1 which regulates 7 miRNAs in differentially expressed network. There are 4

Table 3. The Upstream and Downstream Information of Zeb1 in The Three Networks of Retinoblastoma

0	hsa-miR-141	hsa-miR-141	ZEB1	0	hsa-let-7c	hsa-let-7
/	hsa-miR-200a	hsa-miR-200a	ZEB1	/	hsa-let-7e	hsa-let-7a
/	hsa-miR-200b	hsa-miR-200b	ZEB1	/	hsa-let-7i	hsa-let-7a-1
/	hsa-miR-200c	hsa-miR-200c	ZEB1	/	hsa-miR-141	hsa-let-7a-2
/	hsa-miR-429	hsa-miR-205	ZEB1	/	hsa-miR-200a	hsa-let-7a-3
/	/	hsa-miR-429	ZEB1	/	hsa-miR-200b	hsa-let-7b
/	/	/	ZEB1	/	hsa-miR-200c	hsa-let-7c
/	/	/	ZEB1	/	hsa-miR-34	hsa-let-7d
/	/	/	ZEB1	/	hsa-miR-34b	hsa-let-7e
/	/	/	ZEB1	/	hsa-miR-429	hsa-let-7f
/	/	/	ZEB1	/	/	hsa-let-7f-1
/	/	/	ZEB1	/	/	hsa-let-7f-2
/	/	/	ZEB1	/	/	hsa-let-7g
/	/	/	ZEB1	/	/	hsa-let-7i
/	/	/	ZEB1	/	/	hsa-miR-141
/	/	/	ZEB1	/	/	hsa-miR-200a
/	/	/	ZEB1	/	/	hsa-miR-200b
/	/	/	ZEB1	/	/	hsa-miR-200c
/	/	/	ZEB1	/	/	hsa-miR-34
/	/	/	ZEB1	/	/	hsa-miR-34a
/	/	/	ZEB1	/	/	hsa-miR-34b
/	/	/	ZEB1	/	/	hsa-miR-429

miRNAs target E2F1 which regulates 7 miRNAs in related network. There are 23 miRNAs target at E2F1 which regulates 39 miRNAs in global network. The successors of E2F1 are indirectly regulated by the precursors through E2F1. Hsa-miR-20a and hsa-miR-20b target at E2F1 and E2F1 regulates them in return, which form a self-adaption relation. Table supplement file 9 shows that E2F1 indirectly influences other genes by some miRNAs. For example, E2F1 regulates hsa-miR-17 which targets at RB1. Some TFs also indirectly influence E2F1 by some miRNAs. For example, E2F3 hsa-miR-34 which targets at E2F1.

The second class of TF has 4 kinds of adjacent nodes (3 kinds of successors and 1 kinds of predecessors), for example HGMA1. HGMA1 regulates 1 differentially expressed miRNA and is targeted by no miRNAs.

The third class of TF has 4 kinds of adjacent nodes (1 kinds of successors and 3 kinds of predecessors), for example RB1. RB1 regulates 1 global miRNA and is targeted by 13 global miRNAs.

We secondly focused on the rest of genes that do not regulate any miRNAs.

There is only 1 kind of non-TF genes, which has 3kinds of adjacent nodes (3 kinds of successors and 0 kinds of predecessors). They are target genes of miRNAs.

Regulatory pathways about differentially expressed miRNAs

we extracted, compared and analyzed the pathways of each differentially expressed miRNA by the same method as Regulatory pathways about differentially expressed genes. Here we see hsa-miR-17 as an example. In Table 2, we listed the precursors and successors of hsa-miR-17 in differentially expressed network, related network and global network.

The first class of miRNA has 6 kinds of adjacent nodes (three kinds of predecessors and three kinds of successors), such as hsa-miR-34a, hsa-miR-17, hsa-miR-192 and hsa-miR-20a. We only focused on hsa-miR-17 . We listed the precursors and successors of hsa-miR-17 in differentially expressed network, related network and global network. There are 3 genes regulating hsa-miR-17, which targeting at 4 genes in differentially expressed network. There are 8 genes regulating hsa-miR-17, which targeting at 14 genes in related network. There are 13 genes regulating hsa-miR-17, which targeting at 43 genes in global network. We can see that MYC, E2F1 and hsa-miR-17 form a self-adaption relation. Table supplement file 10 shows hsa-miR-17 indirectly influences other miRNAs by some TFs. For example, hsa-miR-17 targets at E2F1 that regulates hsa-miR-20a. Some miRNAs also indirectly influence hsa-miR-20a by targeting at some TFs, for example hsa-miR-34 targets at MYCN which regulates hsa-miR-17.

The second class of miRNA has five kinds of adjacent nodes (2 kinds of successors and 3 kinds of predecessors), for example hsa-miR-19a.

The third class of miRNA has four kinds of adjacent nodes (1 kind of successors and 3 kinds of predecessors), such as hsa-miR-10b, hsa-miR-198, hsa-miR-320, hsa-miR-494, hsa-miR-513-1 and hsa-miR-513-2.

The fourth class of miRNA has three kinds of adjacent nodes (0 kinds of successors and 3 kind of predecessor), for example hsa-miR-129b, hsa-miR-142 and hsa-miR-492.

Regulatory pathways about popular Transcription factor

With the method we used above, we processed the data of popular Transcription factor form p-match method. Here we see ZEB1 as an example. In Table 3, we listed the precursors and successors of ZEB1 in differentially expressed network, related network and global network. The first class of TF has 4 kinds of adjacent nodes (2 kinds of successors and 2 kinds of predecessors). These TFs include ZEB1, YY1, RUNX1 and CREB1. We only focused on ZEB1 . We listed the precursors and successors of ZEB1 in differentially expressed network, related network and global network. . There are 5 differentially expressed miRNAs target at ZEB1 which regulates 10

related miRNAs. There are 6 differentially expressed miRNAs target at ZEB1 which regulates 22 global miRNAs. All the related genes of Rb form a self-adaption relation in differentially expressed network.

The second class of TF has 3 kinds of adjacent nodes (2 kinds of successors and 1 kind of predecessors, 1 kind of successor and 2 kinds of predecessors), such as NFKB1 and RUNX1.

The third class of TF has 2 kinds of adjacent nodes (2 kinds of successors), such as NKX2-5.

The fourth class of TF has 1 kinds of adjacent nodes (1 kind of successor), such as IRF1.

Discussion

In this section, we discuss about the pathways from the differentially expressed network.

In our study, there are many pathways including 3 our more elements. For example, hsa-miR-149 targets at E2F3 and E2F3 regulates hsa-let-7i. These pathways play a key biological function in Rb.

Some of the functions of the pathways have not been found in the Rb, but the function of these pathways did lead to other carcinoma. It suggested that RB1 pathway should be paid attention to in the research of Rb in future. In this way we can expand the relations between genes from one kind of carcinoma to another, and highlight the blind spots of research on pathology of Rb.

What should be paid more attention to is that the TFs from the P-match method suggest the potential relations between the differentially expressed miRNAs and TFs. These relations remain to be experimentally validated being in close relation with Rb.

In conclusion, in this study, we constructed three regulatory topological networks of elements about Retinoblastoma. Then we extracted three Figures from the networks to highlight some of the important pathways and elements. To describe the network more clearly, we focus on the successors and precursors of the elements in the three networks. The whole experimentally validated data of Retinoblastoma were involved in our work. Besides, we made some predictions with the P-match method, which provides some topics for further study of Retinoblastoma.

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