RESEARCH ARTICLE

Network Analysis of microRNAs, Genes and their Regulation in Mantle Cell Lymphoma

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Abstract

The pathogenesis of mantle cell lymphoma, a special subtype of lymphoma that is invasive and indolent and has a median survival of 3 to 4 years, is still partially unexplained. Much research about genes and miRNAs has been conducted in recent years, but interactions and regulatory relations of genetic elements which may play a vital role in genesis of MCL have attracted only limited attention. The present study concentrated on regulatory relations about genes and miRNAs contributing to MCL pathogenesis. Numerous experimentally validated raw data were organized into three topology networks, comprising differentially expressed, associated and global examples. Comparison of similarities and dissimilarities of the three regulating networks, paired with the analysis of the interactions between pairs of elements in every network, revealed that the differentially expressed network illuminated the carcinogenicity mechanism of MCL and the related network further described the regulatory relations involved, including prevention, diagnosis, development and therapy. Three kinds of regulatory relations for host genes including miRNAs, miRNAs targeting genes and genes regulating miRNAs were concluded macroscopically. Regulation of the differentially expressed miRNAs was also analyzed, in terms of abnormal gene expression affecting the MCL pathogenesis. Special regulatory relations were uncovered. For example, auto-regulatory loops were found in the three topology networks, key pathways of the nodes being highlighted. The present study focused on a novel point of view revealing important influencing factors for MCL pathogenesis.

Keywords: Mantle cell lymphoma - microRNAs - transcription factors - gene network - host - target

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Introduction

Mantle cell lymphoma is a more heterogeneous and aggressive hematological malignancy than originally recognized over years of researches (Akyure et al., 2010), the prognosis of which is poorer than other small B-cell lymphomas, leading to a low rate of long-term survival. Conventional chemotherapy has little effect on this still rapidly progressing tumor MCL, but the Genetic alterations is known as important drivers of malignant lymphomas. Thus, the study of the interactions regulatory relations of the genetic elements of MCL represents an opportunity to reveal the underlying biological mechanisms.

Biological experiment demonstrated that differentially expressed miRNAs as well as differentially expressed miRNAs are vital in tumorigenesis and in the definition of possible targets for therapeutic intervention. miRNAs are a class of small non-coding RNAs that play an essential role on post-transcriptionally controlling gene expression, which can be classified into two types including intergenic miRNAs (ig-miRNAs) and intragenic miRNAs (ing-miRNAs) (Saj et al., 2011).

The genes with ing-miRNAs encoded within are referred as host genes. Studies indicated the close relationship between the miRNAs and its host genes that abnormal expression may result in dysregulation of other host genes via in-miRNAs (Baskerville et al., 2005).

Transcription factors play an essential role in promoting cell survival and proliferation, cancer development and induce tumor angiogenesis (Libermann et al., 2006).

Researches on miRNAs and genes are conducted over the years, but most of the studies are focus on one or several of the elements. For example, Kavitha et al. (2014) focus on reporting the roles miRNAs played in cancer and its potential to act as the biomarkers for cancer diagnosis and prognosis. Liu et al. (2014) summarize the latest diverse relationships between miR-29b and its target genes in malignant tumors. Meissner et al. (2013) describe the frequently mutated genes in MCL tumors. Mu et al. (2014) investigated the relationship of dysregulated of miR-193b and miR-196a with clinicopathological features and prognosis in castric cancer. These articals have emphasized the important role miRNAs or genes playing on human cancers or certain cancers, but few of them gather these important fators together to probe the significant pathways among them

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and consider the regulator relationships between them. In this paper, we analysis the pathways formed by these factors macroscopically and reveal the notable regulatory relations between them in MCL.

We collect experimentally validated raw data from databases and literature and then organized it into three topology networks. In these three networks, we can clearly see the regulate relations between these elements. Among these three networks, the differentially expressed network is the most important and can be taken as a faulty map of MCL for it partially revealing the regulatory mechanism and containing many incorrect data linkages when MCL emerges. If the differentially expressed network can be adjust to normal, the cancer may be prevented and even cured in theory. Through the overall analysis of the three networks and elements in them, the vital role the three networks played on in MCL is obvious.

Materials and Methods

From Tarbase 5.0 and miRTarBase, we collected experimentally validated dataset between miRNAs and their targets in MCL. The complete data were collated to appendix 1 which comprise of 6750 targeting interactions between miRNAs and their target genes.

From TransmiR (Wang et al., 2010), we collected experimentally validated dataset between TFs and miRNAs in MCL, which is a manually constructed database. The complete data were collated to appendix 2 which comprise of 863 regulating interactions between TFs and miRNAs.

From miRBase (Kozomara et al., 2011) and the National Centre for Biotechnology Information (NCBI) (http://www.ncbi.nlm.nih.gov/), we collected experimentally validated dataset between miRNAs and their host genes in MCL. The complete data were collated to appendix 3 which comprise of 1420 interactions relations between host genes and miRNAs.

From Cancer Genetics Web (http://www.cancerindex.org/geneweb/), single nucleotide polymorphism database of the NCBI (http://www.ncbi.nlm.nih.gov/snp/) and Kyoto Encyclopedia of Genes and Genomes, we collected the differentially expressed genes and related genes in MCL. The literature search is also a method used to collect the differentially expressed genes. The complete data were collated to appendix 4 including 22 differentially expressed genes.

From mir2Disease (Jiang et al., 2009), we collected differentially expressed miRNAs in MCL, which is a manually constructed database. Moreover, differentially expressed miRNAs from the relevant literature is a appropriate supplement. The complete data were collated to appendix 5 including 68 differentially expressed miRNAs.

From Gene Cards database, we collected 157 related genes. By using the method of P-match (Chekmenev et al., 2005), we acquired 5 predicted TFs which be taken as the related genes and we only concentrate on the TFs appeared in TransmiR. The differentially expressed genes also were taken as the parts of related genes. In total, 184 related genes in MCL were take part in this study.

From UCSC (Dreszer et al., 2012), we obtained the 1000nt promoter region sequences of the differentially expressed target genes. By using the P-match method we identified TFs binding sites in 1000nt promoter region sequences which was mapped onto targets promoter region. The P-match method is a new technique to combine pattern matching with weight matrix approaches to get a higher accuracy of recognition instead of using them by separately. Matrix library of P-match is as well as sets of known TF-binding sites collected in TRANSFAC, which make it possible to search for a large variety of different TF binding site.

After collecting the data needed we constructed the differentially expressed networks, related networks and global networks. The combination of all the regulatory relations about host genes, target genes, TFs and miRNAs form the global networks. The combination of all the regulatory relations about related elements form the related networks, while the differentially expressed networks formed by all the regulatory relations about the differentially expressed elements.

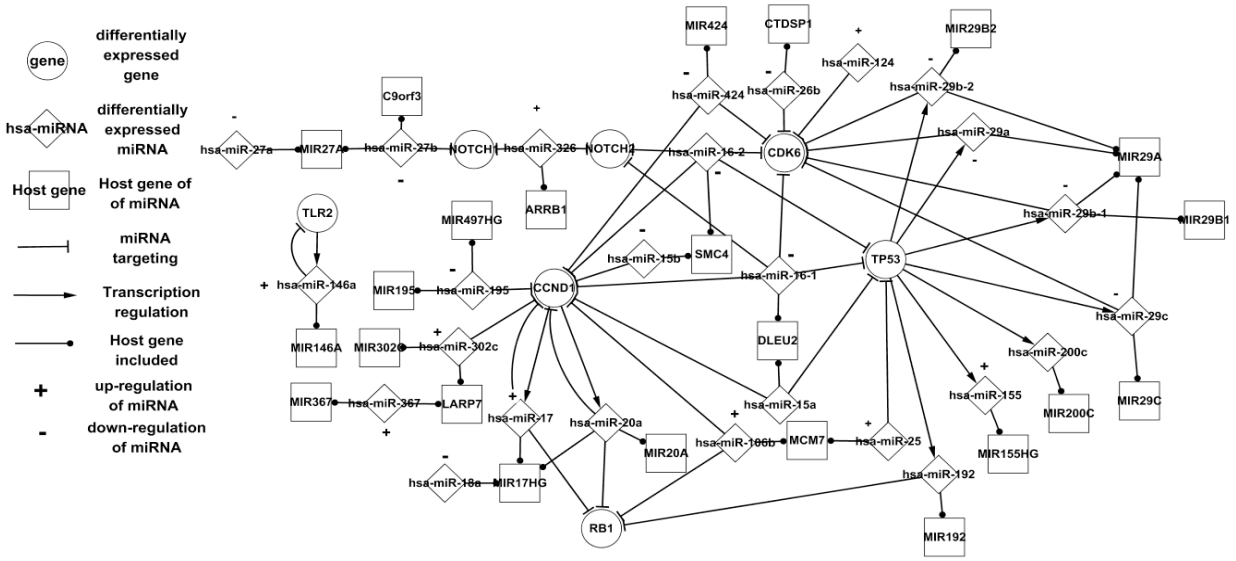

Figure 1. Differentially Expressed Network in Mantle Cell Lymphoma

Results

Differentially expressed network of mantle cell lymphoma

Four kinds of important elements and the significant regulatory pathways between them are shown clearly in the differentially expressed network. Three transcription factors, four targets of miRNAs and twenty-six miRNAs showing in Figure 1 are all differentially expressed in MCL, whereas twenty-three host genes are not differentially expressed.

All the data in differentially expressed network are experimentally validated. Three kinds of regulatory relations between them are host genes including miRNAs, miRNAs targeting genes and genes regulating miRNAs. The end of the edge in the form of circle represents the regulatory relations of gene including miRNAs, in the form of T represents miRNAs targeting at gene while arrow represents gene regulating miRNAs. These interactions between miRNAs and genes represent a complex regulation relations network.

The sub-networks formed by the relations between CCND1 and TP53 and their miRNAs are the three most notable pathways in the differentially expressed network.

For sub-network formed by CCND1, there exist several regulatory pathways. For example, CCND1 regulate hsa-miR-17 and hsa-miR-20a which both target at RB1. Both hsa-miR-17 and hsa-miR-20a form a self-adapting relations with CCND1. CCND1 was targeted by several miRNAs including hsa-miR-16-1, hsa-miR15a and hsa-miR-16-2, all of which also target at TP53. SMC4 include hsa-miR-16-2 and hsa-miR-15b, both of which target at CCND1.

For sub-network formed by TP53, there exist several regulatory pathways. For example, TP53 regulate several miRNAs including hsa-miR-29a, hsa-miR-29b-1 and hsa-miR-29b-2, all of which target at MIR29A. TP53 regulate hsa-miR-192 which locate in MIR192. TP 53 was target by hsa-miR-25 which locate in MCM7.

As is shown in Figure 1, some of the miRNAs are down-regulated in MCL such as hsa-miR-27a, hsa-miR-195 and hsa-miR-29a, while others are up-regulated in MCL such as hsa-miR-106b, hsa-miR-25 and hsa-miR-17. The dsyregulation of the miRNAs influence the expression of the genes.

Associated network of mantle cell lymphoma

Substantial relations of genes and miRNAs were shown in the related network. Overall, the differentially expressed network is a sub-network of associated network due to the differentially expressed elements being contained in associated elements. Compared with the differentially expressed network, the pathways and the regulation relations of the related network are more complicate and larger.

The related network included three differentially expressed transcription factors and thirteen associated transcription factors. Several kinds of regulatory relations in related networks are shown in the following: *i)* One miRNA can be regulating by multiple genes which were targeting by other miRNAs. For example, hsa-miR-17 was regulated by MYC and E2F1, both of which was target by hsa-miR-21; *ii)* One miRNA can target at multiple target genes and a single target gene can be targeted by multiple miRNAs. For example, hsa-miR-146a target at CCNA2, TLR4, CXCR4, TLR2 and CDKN1A.CDKN1A was targeted by hsa-miR-372, hsa-miR-106b, hsa-miR-20a and hsa-miR-17, hsa-miR-10b and hsa-miR-345; *iii)* Some self-adapting relations are formed by the genes and miRNAs.For example, hsa-miR-21 and NFKB1, hsa-miR-21 and PTEN, hsa-miR-146a and TLR2 form a self-adapting loops separately.

Global network of mantle cell cancer

All the data collected from basic source data are experimentally validated and were used to form the global regulation network which contained the differentially expressed and the related network. Massive significant pathways were uncovered in the global networks.

Transcriptional network of TFs and differentially expressed miRNAs

Transcriptional factors obtained previously and

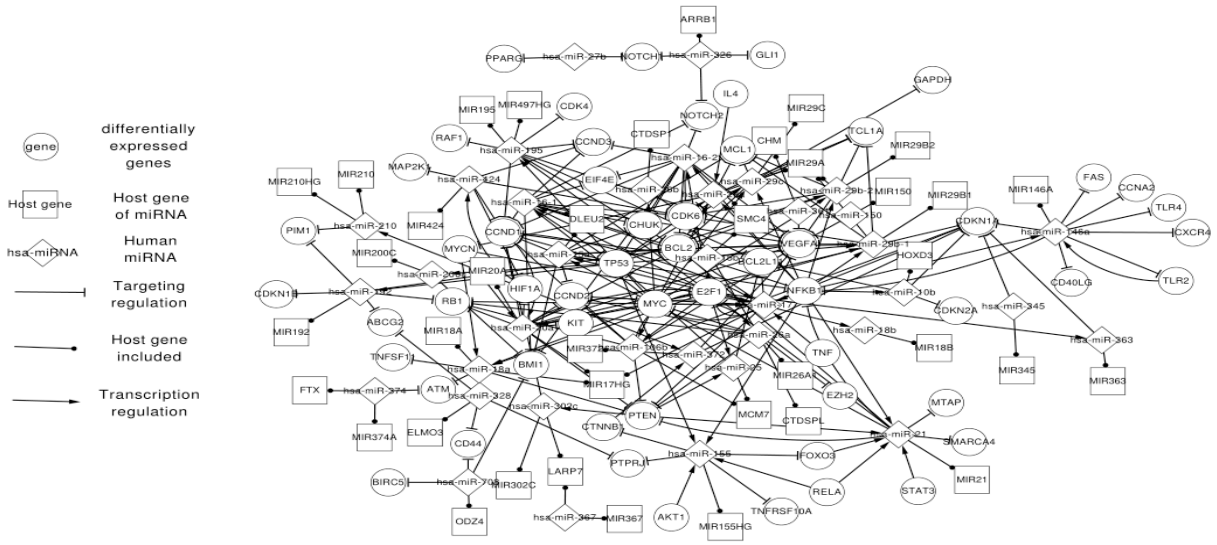

Figure 2. Associated Network in Mantle Cell Lymphoma

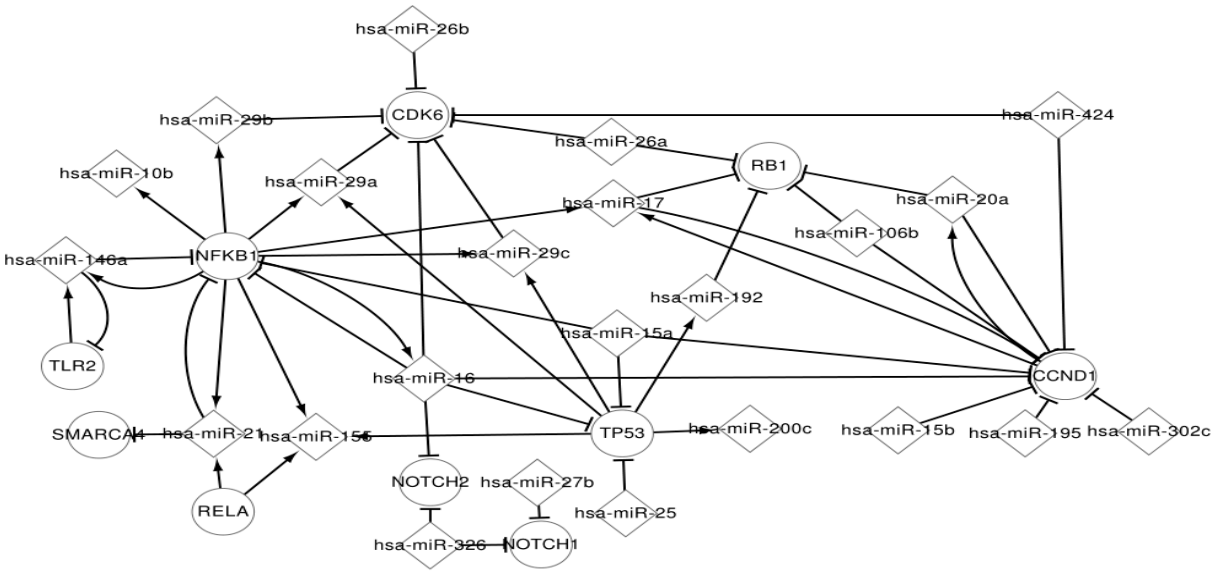

Figure 3. Transcriptional Network of TFs and Differentially Expressed miRNAs in MCL

acquired based on the evaluation of 1,000 nt sequences, paired with the differentially expressed miRNAs act as the main elements of the transcriptional networks. The five transcriptional factors shown in Fig.3 are RELA, NFKB1, CCND1, TP53 and TLR2, which have regulatory relations with differentially expressed miRNAs. Pathways centered on NFKB1 and TP53 played a vital role in the progression of MCL are more significant than other genes. There are several kinds of regulatory relations between miRNAs and TFs which show in the following part: *i)* One TF can regulate multiple miRNAs at the same time and can be target by several miRNAs. For example, hsa-miR-17 and hsa-miR-20a were regulated by CCND1,which was target by hsa-miR-15b, hsa-miR-195 and hsa-miR-302c; *ii)* One miRNA can indirectly influence other miRNAs via TFs. For example, hsa-miR-15a indirectly affect hsa-miR-192 via TP53; *iii)* TFs can indirectly influence other genes via miRNAs. For example,TLR2 regulate hsa-miR-146a, which target at NFKB1; *iv)* TFs can cooperate with other TFs regulate the same miRNAs thus influence the same genes. For example, NFKB1 and TP53 regulate hsa-miR-29a,which target at CDK6; NFKB1 and CCND1 regulate hsa-miR-17, which target at RB1; *v)* TFs can cooperate with other TFs regulating difference miRNAs while influencing the same genes. For example, NFKB1 regulate hsa-miR-17, TP53 regulate hsa-miR-192,CCND1 regulate hsa-miR-20a. hsa-miR-17, hsa-miR-192 and hsa-miR-20a all target at RB1; *vi)* TFs can indirectly influence other TFs via miRNAs. For example, NFKB1 indirectly affect TLR2 via hsa-miR-146a. NFKB1 indirectly affect TP53 via hsa-miR-16; *vii)* TFs can regulate several miRNAs and were target by several miRNAs. For example, hsa-miR-192, hsa-miR-200c and hsa-miR-29c and hsa-miR-155 was regulated by TP53, which was target by hsa-miR-15a, hsa-miR-16 and hsa-miR-25; *viii)* TFs and miRNAs can form a self-adapting loop means TFs indirectly influence themselves via miRNAs. For example, NFKB1 indirectly influence itself via hsa-miR-16, hsa-miR-146a andhsa-miR-21. CCND1 indirectly influence itself via hsa-miR-20a.

Comparison and analysis about feature of differentially expressed genes in MCL

The three networks have indicated the role for the interaction relationship of miRNAs, TFs and genes in the development of MCL. It is difficult to understand the massive relations concluded in the three networks due to the large-scale and complication of the networks. Extraction of the upstream and downstream information and comparison of the pathways about the differentially expressed elements contribute to a better comprehension of the regulation relations of the three networks. We list the adjacency nodes including precursor and successor of the differentially expressed genes in three networks. The complete data is shown in appendix 6. Half of the eighteen differentially expressed genes have no adjacent nodes. There exists four differentially expressed TFs (CCND1, TP53, RB1, TLR2) which can be classified into two types; *i)* The first type of the TFs have six kinds of adjacency nodes including three precursors and three successors, such as CCND1, TP53 and TLR2; *ii)* The second type of the TFs have four kinds of adjacency nodes containing three precursors and one successor, such as RB1.

There are fourteen differentially expressed non-TFs genes which can be concluded into three types: *i)* The first type of the genes have three adjacency nodes including three precursors and zero successor, such as ATM, SMARCA4, CDK6; *ii)* The second type of the genes have one adjacency nodes containing one precursor and zero successor, such as BIRC3; *iii)* The third type of the genes have no adjacency nodes such as TRAF2, TET2 and CHEK2.

In the following part, we only concentrate on CCND1 to proceed the analysis.

Table 1 shows the upstream and downstream information of CCND1 in the three networks of Mantle cell lymphoma. The data of the left three columns is the precursors of CCND1 in the three networks, which are miRNAs targeting at CCND1, while the data of the right three columns is the successors of CCND1 in the three networks, which are miRNAs regulating by CCND1. The

number 0 in table1 means no data in the corresponding pathway.

From Table 1 we can see, ten miRNAs are targeting at CCND1 and CCND1 regulate two miRNAs in differentially expressed networks and related networks. Twenty-nine miRNAs are targeting at CCND1 and CCND1 regulate four miRNAs in the global network. The expression of miRNAs on the left columns indirectly affect the expression of miRNAs on the right columns via CCND1. miRNAs appeared on both sides of table1 form a self-adapting loops with CCND1. Both of hsa-miR-17 and hsa-miR-20a are in such relation with CCND1. The interaction between them may be vital in MCL pathogenesis.

Comparison and analysis about feature of differentially expressed miRNAs

The regulation relations are obviously shown in the extraction information. Some miRNAs can indirectly influence other miRNAs via TFs. Some genes can indirectly influence other genes via miRNAs. The complete data is shown in appendix 7.

Forty-six miRNAs have adjacent nodes among sixty-seven miRNAs which can be classified into six types: *i)* The first type of miRNAs have only one adjacent nodes including one precursor or zero successor. For example, hsa-miR-367 has only one precursor and zero successor while hsa-miR-135a is just opposite to hsa-miR-367. In differentially expressed networks and related networks, there has no TFs regulating hsa-miR-367 and hsa-miR-367 targeting at no genes. There exist TFs regulating hsa-miR-367 and hsa-miR-367 target at no genes in global networks. hsa-miR-135a has only one successor which means that hsa-miR-135a only target at genes in one networks but regulated by no genes in the three networks. In differentially expressed networks and related networks, there has no TFs regulating hsa-miR-135a and hsa-miR-135a target at no genes. There has no TFs regulating hsa-miR-135a and hsa-miR-135a target at two genes in global networks. *ii)* The second type of miRNAs have two adjacent nodes including one precursor and one successor or zero precursor and two successors. For example, hsa-miR-27a has one precursor and one successor while hsa-miR-328 has zero precursor and two successors. There is no TF regulating hsa-miR-27a and hsa-miR-27a target at no genes in the former two networks. There exists genes regulating and being targeted by hsa-miR-27a in the global networks. There is no genes regulating hsa-miR-328 in the three networks and hsa-miR-328 target at no genes in the former networks, but hsa-miR-328 target at genes in the last two networks; *iii)* The third type of miRNAs have three adjacent nodes including one precursor and two successors or zero precursor and three precursor successors or two precursors and one successor. For example, hsa-miR-374 has one precursor and two successors. There is no genes regulating hsa-miR-374 and hsa-miR-374 target at no genes in the first networks. There is no genes regulating hsa-miR-374 and hsa-miR-374 target at one gene in related networks. However in the global one, hsa-miR-374 was regulating

Table 1. The Upstream and Downstream Information of CCND1 in the three Networks of MCL

Upstream miRNAs of Ded genes			Ded genes	Downstream miRNAs of Ded genes		
Ded miRNAs	Related miRNAs	Global miRNAs		Ded miRNAs	Related miRNAs	Global miRNAs
miR-106b	miR-106b	miR-106b	CCND1	miR-17	miR-17	miR-17
miR-424	miR-424	miR-424		miR-20a	miR-20a	miR-20
miR-15a	miR-15a	miR-15a		0	0	miR-20a
miR-15b	miR-15b	miR-15b		0	0	miR-91
miR-16-1	miR-16-1	miR-16-1		0	0	0
miR-16-2	miR-16-2	miR-16-2		0	0	0
miR-17	miR-17	miR-17		0	0	0
miR-195	miR-195	miR-195		0	0	0
miR-20a	miR-20a	miR-20a		0	0	0
miR-302c	miR-302c	miR-302c		0	0	0
0	0	let-7b		0	0	0
0	0	let-7e		0	0	0
0	0	miR-19a		0	0	0
0	0	miR-19b-1		0	0	0
0	0	miR-20		0	0	0
0	0	miR-16		0	0	0
0	0	miR-302		0	0	0
0	0	miR-302a		0	0	0
0	0	miR-91		0	0	0
0	0	miR-322		0	0	0
0	0	miR-34		0	0	0
0	0	miR-34a		0	0	0
0	0	miR-34b		0	0	0
0	0	miR-365a		0	0	0
0	0	miR-193b		0	0	0
0	0	miR-449		0	0	0
0	0	miR-449a		0	0	0
0	0	miR-503		0	0	0
0	0	miR-520b		0	0	0

by one gene meanwhile target at four genes; *iv)* The fourth type of miRNAs have four adjacent nodes including one precursor and three successors or two precursors and two precursor successors. For example, hsa-miR-27b has one precursor and three successors. Only in the global network exist genes regulating hsa-miR-27b, but there exist genes target by hsa-miR-27b in all three networks. hsa-miR-372 has two precursors and two successors. There has no gene regulating hsa-miR-372 and hsa-miR-372 target at no genes in the first networks while in the last two networks exist genes regulating hsa-miR-372 and targeting by hsa-miR-372. *v)* The fifth type of miRNAs have five adjacent nodes including two precursors and three successors. For example, hsa-miR-15b has two precursors and three successors. There is no gene regulating hsa-miR-15b and hsa-miR-15b target at one gene in the first networks. But There exist genes regulating and being targeted by hsa-miR-15b in the last two networks; *vi)* The sixth type of miRNAs have six adjacent nodes including three precursors and three successors. For example, hsa-miR-29b-1 has three precursors and three successors. There exist genes regulating hsa-miR-29b-1 and hsa-miR-29b-1 target at genes in all three networks.

In the following part, we only concentrate on TF CCND1 to proceed the analysis.

In Table 2, the number 0 means no data in the corresponding pathway.

There are no TFs regulating hsa-miR-15b which target at CCND1 in differentially expressed networks. E2F1 regulate hsa-miR-15b which target at CCND1, BCL2 and VEGFA in related work, which can be concluded that E2F1 can indirectly influence CCND1, BCL2 and VEGFA via hsa-miR-15b. There are four TFs regulate hsa-miR-15b and hsa-miR-15b target at eight genes in global networks.

Comparison and analysis about feature of popular TFs

We analysis the popular TFs using the same method above. The complete data is shown in appendix 8. The TFs can be classified into several types. The first type of TFs have no adjacent nodes such as NFE2.The second type

Table 2. The Upstream and Downstream Information of miR-15b in the three Networks of MCL

Upstream TFs of Ded miRNAs			Ded miRNAs	Downstream targets of Ded miRNAs		
Ded TFs	Related TFs	Global TFs		Ded targets	Related targets	Global targets
0	E2F1	BRD2	miR-15b	CCND1	BCL2	BCL2
0	0	E2F1		0	CCND1	VEGFA
0	0	E2F3		0	VEGFA	CCND1
0	0	STAT5B		0	0	CCNE1
0	0	0		0	0	DMTF1
0	0	0		0	0	EIF4A1
0	0	0		0	0	RECK
0	0	0		0	0	TMEM184B

Table 3. The Detail Information About The Upstream And Downstream Information of NFKB1 in the three Networks of MCL

Upstream miRNAs of Ded genes			TFs	Downstream miRNAs of Ded genes		
Ded miRNAs	Related miRNAs	Global miRNAs		Ded miRNAs	Related miRNAs	Global miRNAs
miR-21	miR-21	miR-21	NFKB1	miR-21	miR-21	miR-21
miR-16	miR-16	miR-16		miR-16	miR-16	miR-16
miR-15a	miR-15a	miR-15a		miR-29b	miR-29b	miR-29b
miR-146a	miR-146a	miR-146a		miR-146a	miR-146a	miR-146a
0	miR-29c	miR-29c		miR-29c	miR-29c	miR-29c
0	0	let-7a-2		miR-29a	miR-29a	miR-29a
0	0	miR-146b		miR-155	miR-155	miR-155
0	0	let-7a-3		miR-17	miR-17	miR-17
0	0	let-7a		miR-10b	miR-10b	miR-10b
0	0	let-7a-1		0	0	let-7a-3
0	0	miR-9		0	0	let-7b
0	0	miR-9-1		0	0	miR-125b
0	0	miR-9-2		0	0	miR-199a-2
0	0	miR-9-3		0	0	miR-214
0	0	0		0	0	miR-34
0	0	0		0	0	miR-365
0	0	0		0	0	miR-365a
0	0	0		0	0	miR-365b
0	0	0		0	0	miR-448
0	0	0		0	0	miR-224
0	0	0		0	0	miR-34a
0	0	0		0	0	miR-9
0	0	0		0	0	miR-91
0	0	0		0	0	miR-9-1
0	0	0		0	0	miR-9-2
0	0	0		0	0	miR-9-3

of TFs have one adjacent nodes containing one precursor and zero successor, such as containing and NR2F2.The third type of TFs have four adjacent nodes, which have three precursors and three successors, such as RELA. The fourth type of TFs have six adjacent nodes which have one precursor and three successors, such as NFKB1.

In the following part, we only concentrate on NFKB1 to proceed the analysis.

Table 3 shows the detail information about the upstream and downstream information of NFKB1 in the three networks of Mantle cell lymphoma. The data of the left three columns is the precursors of NFKB1 in the three networks, which are miRNAs regulating NFKB1. while the data of the right three columns is the successors of NFKB1 in the three networks, which are miRNAs targeting at NFKB1. The number 0 in Table 3 means no data in the corresponding pathway.

There are four miRNAs targeting at NFKB1 which regulate nine miRNAs in differentially expressed networks, five miRNAs target at NFKB1which regulate nine miRNAs in related networks, while in global networks, fourteen miRNAs target at NFKB1 which regulate multiple miRNAs.

In differentially expressed networks, miRNAs separately forming self-adapting loops with NFKB1 are hsa-miR-21, hsa-miR-16 and hsa-miR-146a. In related networks, four hsa-miRNAs separately forming self-adapting loops with NFKB1 are hsa-miR-21, hsa-miR-16, hsa-miR-146a and hsa-miR-29c.

Analysis of host genes and miRNAs in MCL

Host genes are not differentially expressed in MCL but it was considered to be differentially expressed when their miRNAs are differentially expressed. Important feature and the role of the relations of host gene and their miRNAs playing on were uncovered in this study. Part of figure 1 is indicated the pathways between host genes and their miRNAs.

The following part shows the special relationship between host genes and their miRNAs, host genes and the TFs: *i)* Host genes can be host of several miRNAs means that a host gene can containing one or several miRNAs. For example, MIR29A contains hsa-miR-29a, hsa-miR-29b-1, hsa-miR-29b-2 and hsa miR-29c. An miRNA can be included in one or several host genes. For example, hsa-miR-195 can located in MIR497HG and MIR195; *ii)* Host genes can contain miRNAs that regulated by other genes. For example, MIR17HG contains hsa-miR-17 and hsa-miR-20a, both of form self-adapting relations with CCND1. The analysis demonstrates that miRNAs cooperate with its host gene have an effect on the MCL progression.

Discussion

In this study, the regulatory relations about differentially expressed genes, differentially expressed genes, miRNAs and predicted TFs in MCL are highlighted and elements playing an important role in MCL are known to us. We constructed three networks including differentially expressed networks, related networks and global networks. The dissimilarity and similarity of the three networks are compared and analyzed in the three networks. We extract and analyzed the upstream and downstream information of differentially expressed miRNAs, differentially expressed gene and TFs to make the networks more obvious. The differentially expressed networks and related networks are the most important for the pathogenesis mechanism and therapy of MCL whereas the global network not only influence MCL but also have effect on other cancers.

Multiple significant pathways are found in the three networks. For example, differentially expressed miRNAs can form self-adapting relations with differentially expressed genes or TFs. All those regulatory pathways indicate the fact that miRNAs can be taken as regulators to other miRNAs and genes, and genes can also be the regulators to miRNAs and genes. It is important for the prevention, diagnosis, development and therapy of MCL. The TFs predicted by the use of *p*-match methods indicate the potential regulatory relations between differentially expressed miRNAs and TFs meanwhile offer some topics for future study. Our study offer some reference for future study in MCL.

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