SPANDIDOS PUBLICATIONS

ONCOLOGY LETTERS 14: 6259-6268, 2017

# Regulatory network involving miRNAs and genes in serous ovarian carcinoma

HAIYAN ZHAO[1], HAO XU[1,2] and LUCHEN XUE[3]

[1]College of Computer Science and Technology, Jilin University, Changchun, Jilin 130012;
[2]Zhuhai Laboratory of Key Laboratory of Symbol Computation and Knowledge Engineering of Ministry of Education, Department of Computer Science and Technology, Zhuhai College of Jilin University, Zhuhai, Guangdong 519041;
[3]College of Software, Jilin University, Changchun, Jilin 130012, P.R. China

Received December 31, 2015; Accepted May 23, 2017

DOI: 10.3892/ol.2017.6927

**Abstract.** Serous ovarian carcinoma (SOC) is one of the most life-threatening types of gynecological malignancy, but the pathogenesis of SOC remains unknown. Previous studies have indicated that differentially expressed genes and microRNAs (miRNAs) serve important functions in SOC. However, genes and miRNAs are identified in a disperse form, and limited information is known about the regulatory association between miRNAs and genes in SOC. In the present study, three regulatory networks were hierarchically constructed, including a differentially-expressed network, a related network and a global network to reveal associations between each factor. In each network, there were three types of factors, which were genes, miRNAs and transcription factors that interact with each other. Focus was placed on the differentially-expressed network, in which all genes and miRNAs were differentially expressed and therefore may have affected the development of SOC. Following the comparison and analysis between the three networks, a number of signaling pathways which demonstrated differentially expressed elements were highlighted. Subsequently, the upstream and downstream elements of differentially expressed miRNAs and genes were listed, and a number of key elements (differentially expressed miRNAs, genes and TFs predicted using the P-match method) were analyzed. The differentially expressed network partially illuminated the pathogenesis of SOC. It was hypothesized that if there was no differential expression of miRNAs and genes, SOC may be prevented and treatment may be identified. The present study provided a theoretical foundation for gene therapy for SOC.

*Correspondence to:* Dr Hao Xu, College of Computer Science and Technology, Jilin University, 2699 Qianjin Street, Changchun, Jilin 130012, P.R. China
E-mail: xuhao@jlu.edu.cn

*Abbreviations:* miRNA, microRNA; TFs, transcription factors; targets, target genes; SOC, serous ovarian carcinoma; NCBI, national center for biotechnology information; TFBSs, transcription factor binding sites; FBLs, feedback-loops

*Key words:* serous ovarian carcinoma, gene, microRNA, transcription factor, regulatory network

## Introduction

Epithelial ovarian cancer is a heterogeneous group of neoplasms that is divided into histological subgroups, each with their own underlying molecular genetic events (1). The serous type of epithelial ovarian cancer accounts for between 75 and 80% of epithelial ovarian carcinomas; it is the most common type of ovarian cancer and is the most life-threatening type of gynecological malignancy (2). However, relatively limited information is known about the molecular genetics of the initiation and progression of serous ovarian cancer (SOC).

Experimentally validated data have demonstrated that differentially expressed genes and microRNAs (miRNAs/miRs) serve key functions in the pathogenesis of SOC (1,3,4). Delineation of the underlying molecular mechanisms involved in the initiation of SOC may increase understanding of the pathogenesis of SOC, and may serve as the theoretical basis of the development of novel diagnostic tests and therapeutic strategies (2).

Transcription factors (TFs) and miRNAs are principal regulators of gene expression (5). TFs are specific proteins that may activate gene transcription independently or indirectly (6). In addition, TFs are primary and important factors that may promote or suppress gene expression at the transcriptional level (7).

miRNAs are non-coding single-stranded RNAs of 22 nucleotides in length that constitute a novel class of gene regulators. miRNAs affect the expression of genes at a post-transcriptional level by binding to complementary sequences on target mRNAs (8). A previous study demonstrated that miRNAs control a variety of biological processes, including cell differentiation, cell proliferation, apoptosis, stress-resistance and fat metabolism (9). The study of the associations between miRNAs and cancer has become an active topic in recent studies.

Genes that are regulated by miRNA are known as target genes. miRNA affects the expression of proteins by regulating target genes; therefore, identifying and validating target genes

of specific miRNAs may be a useful strategy for developing novel treatments (10). Host genes are a class of genes within which miRNAs are embedded (11). A previous study revealed that miRNAs are transcribed in parallel with host transcripts, and two transcriptional classes of miRNAs, exonic and intronic, were identified (12). Baskerville and Bartel (13) demonstrated that intronic miRNA and its host gene exhibit a close association. miRNAs and host genes may cooperate to regulate a number of biological functions; dysregulation of this system may affect the development of cancer (14).

A number of genes and miRNAs have been demonstrated to be expressed at different levels in SOC compared with healthy tissue, but were identified in a dispersed form and not as part of a regulatory network. Previous studies have focused on one or a number of genes or miRNAs (1,3,4) In the present study, all genes or miRNAs and the experimentally validated associations between these molecules, including miRNA gene targeting, TF regulation of miRNAs and miRNAs located in host genes, were analyzed. Three regulatory networks were constructed: A differentially expressed network, a related network and a global network. Except for host genes, all genes and miRNAs in the differentially expressed network were differentially expressed. The signaling pathways in the differentially expressed network were extracted and compared in three networks to reveal the pathogenesis of SOC. In addition, the upstream and the downstream elements of the differentially expressed genes and miRNAs in three networks (which include genes, miRNAs and targets) were analyzed, and focus was placed on the similarities and differences between these elements to identify key elements that may affect the development of SOC.

## Materials and methods

*Material collection and data processing.* All SOC data selected were obtained from databases and relevant studies. The National Center for Biotechnology Information (NCBI) database (www.ncbi.nlm.nih.gov/gene) was used to ensure each miRNA and gene was referred to by its official name only. The experimentally validated dataset of human miRNAs and the corresponding target genes were selected from the Tarbase (diana.imis.athena-innovation.gr/DianaTools/index.php?r=tarbase/index) (15), miRTarBase (mirtarbase.mbc.nctu.edu.tw) (16) and miRecords (c1.accurascience.com/miRecords) (17), and the dataset were termed set U1. Due to increasing interest on the interactions between miRNAs and human TFs, the dataset from TransmiR, a manually built database of TF-miRNA-regulating associations (http://www.cuilab.cn/transmir), was selected, and the dataset was termed set U2. The host genes of human miRNAs were selected from NCBI and miRbase (www.mirbase.org/) (18), and the dataset were termed set U3. Differentially expressed genes of SOC were selected primarily from relevant studies (cited below where appropriate) and a limited number were selected from the NCBI Single Nucleotide Polymorphism database, and the dataset of differentially expressed genes were termed U4. Differentially expressed miRNAs of SOC were primarily selected from mir2Disease (http://www.mir2disease.org/) (19) and relevant studies (20-75), and this dataset were termed set U5. Similarly, the SOC-related miRNAs were primarily selected from relevant studies (20-75) and this dataset were termed set U7.

The SOC-associated genes were selected through three different methods. A number of SOC-associated genes were selected from the GeneCards database (www.genecards.org) and others were identified in relevant studies (20-75). In addition, there are 31 TFs predicted using the P-match method and were considered to be SOC-associated genes. The UCSC database (genome.ucsc.edu) (76) was used to download the 1,000-nt promoter region sequences of the targets of differentially expressed miRNAs, which were used as the input to predict the TFs and miRNAs they regulate. The P-match method combines pattern matching and weight matrix approaches (77). P-match was used in the present study to identify transcription factor binding sites (TFBSs) in 1,000 nt promoter region sequences and map TFBSs onto promoter region of targets. The matrix library of P-match comes from the TRANScription FACtor database (78), which enables a large variety of different TF binding sites to be searched. The dataset of the SOC-associated genes was termed set U6.

*Network construction.* The following three regulatory networks of SOC were constructed: The differentially expressed network, the related network and the global network. The differentially expressed network contained the key elements and pathways and was considered the core network. All associations between TFs, miRNAs, target genes and host genes were combined to construct the global network. All associations between differentially expressed miRNAs and the corresponding host genes in the set U3 were included in the differentially expressed network. All differentially expressed genes and differentially expressed miRNAs were mapped to the global network and their associations were combined. These associations also belong to differentially expressed network. The two parts of these associations were combined to obtain the differentially expressed network. Using the same method as that used for the related elements, the related network was constructed. Cytoscape software (version 3.0.0; Institute for Systems Biology, Seattle, WA, USA) was used to present the network graphically and in order to analyze the regulatory pathways more easily.

## Results

*Differentially expressed network of SOC.* The differentially expressed network is the core SOC network because, except for host genes, all elements were differentially expressed. As such, the differentially expressed network is the core network, which may reveal the pathogenic mechanism of SOC. This network consisted of four TFs [BRCA1, DNA repair associated (BRCA1), MYC proto-oncogene, bHLH transcription factor (MYC), phosphatase and tensin homolog (PTEN) and tumor protein p53 (TP53)], 12 differentially expressed genes (which are targets of miRNA), 65 miRNAs and 72 host genes. As presented in Fig. 1, the essential regulatory associations between significant factors were observed. The network was composed of three associations, including TFs regulating miRNAs, miRNAs targeting target genes and miRNAs located in host genes. In the differentially expressed network, a number of data linkages present special characteristics and,

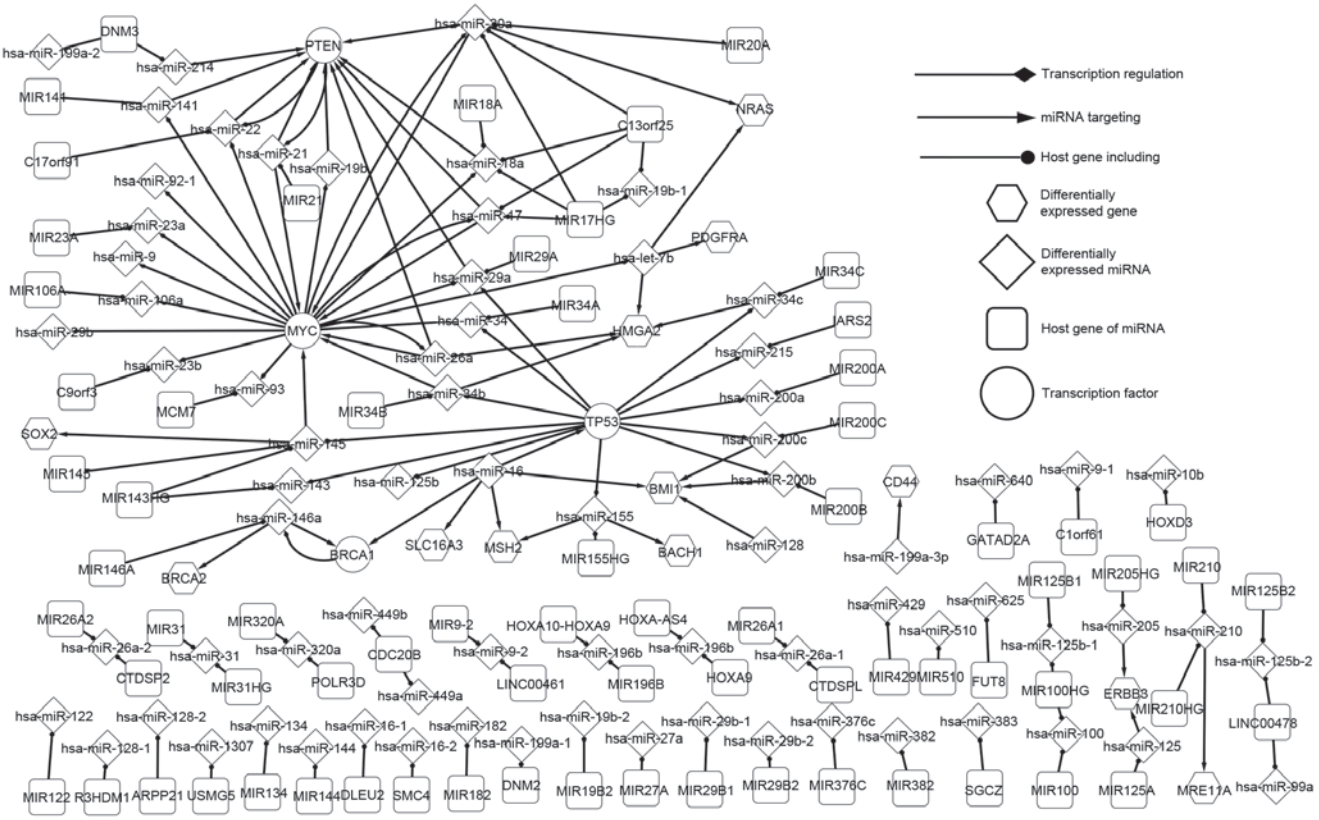


Figure 1. Differentially expressed network of genes and miRNAs in SOC. All elements are involved in various progressions of SOC. The associations between the differentially expressed genes and miRNAs are presented in this network, which partially revealed the underlying mechanism of SOC. SOC, serous ovarian carcinoma.

when SOC emerges, the network balance may be broken. The linkages between elements may provide information of the regulatory associations of SOC.

The four TF-associated pathways are marked in Fig. 1. TP53 is an extensively studied tumor-suppressor gene and it has been demonstrated that TP53 is commonly mutated in human cancers (18,79). TP53 serves a key function in the development of SOC and it has been identified that high-grade SOC is characterized by TP53 mutations in almost all tumors (96%) (80). In the differentially expressed network, human (hsa-)miR-16 targets TP53 which regulates 12 miRNAs (hsa-miR-125b, -143, -145, -155, -200a, -200b, -200c, -215, -29a, -34, -34b and -34c). MYC contributes to the genesis of a number of types of human cancer and a previous insight into the expression and function of MYC led to therapeutic opportunities (20). In the differentially expressed network, 6 miRNAs (hsa-miR-145, hsa-miR-17, hsa-miR-20a, hsa-miR-21, hsa-miR-26a and hsa-miR-34b) target MYC, which regulates 17 miRNAs (hsa-let-7b, -106a, -141, -17, -18a, -19b, -20a, -22, -23a, -23b, -26a, -29a, -29b, -34, -9, -92-1 and -93). TFs were identified to be core elements in the regulatory network.

As presented in Fig. 1, PTEN regulates hsa-miR-21 and hsa-miR-21 targets PTEN in return, which is an association known as a feedback-loop (FBL). Other FBLs were identified in the differentially expressed network including PTEN and hsa-miR-22, MYC and hsa-miR-20a (hsa-miR-17), and BRCA1 and hsa-miR-146a. It was identified that hsa-miR-200b is regulated by TP53 and targets BMI1 proto-oncogene, polycomb ring finger (BMI1). Therefore, the mutation of TP53 may influence the expression of BMI1 indirectly. The results of the present study indicate that precursors influence their successors in an orderly manner (e.g., hsa-miR-200b is regulated by TP53, and hsa-miR-200b also targets BMI1. When TP53 is differentially expressed, hsa-miR-200b will be differentially expressed which may affect the expression of BMI1). Furthermore, targets of miRNAs, including BTB domain and CNC homolog 1 and BMI1, do not regulate any miRNA, and some miRNAs such as hsa-miR-125b, hsa-miR-215 which are regulated by TFs do not target any gene in the networks outlined in the present study. These factors may be the last actors in the network (elements which are regulated by other genes but not regulate any other elements in the SOC network) and may affect the tumorigenesis of SOC. The core transcriptional network partially revealed the mechanism of SOC and the present study may contribute to the development of cancer prevention and gene therapy.

*SOC-related network*. The SOC-related network included differentially expressed genes and miRNAs and associated genes and miRNAs. As can be observed in Fig. 1, the differentially expressed network is part of the related network because the SOC-related network contains an increased number of elements and pathways, which may influence the development of SOC, and it is complicated compared with the differentially expressed network. In the related network, there were 38 TFs including 4 differentially expressed TFs, 110 miRNAs and a number of targets of miRNAs. Due to the complexity of the related network, primary focus was placed on the regulatory

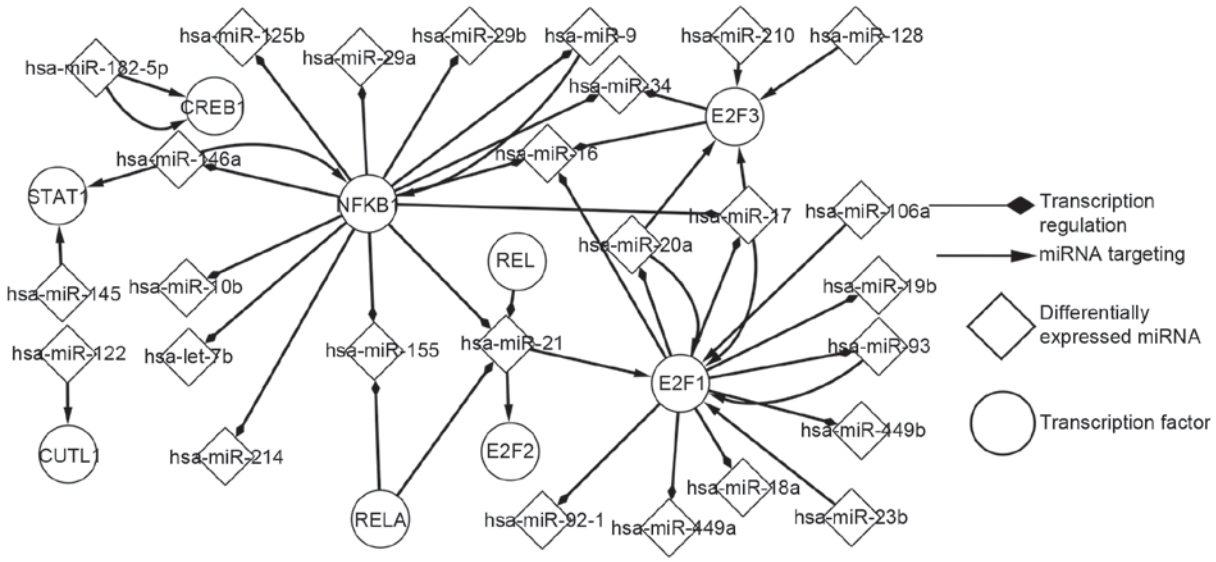


Figure 2. Network of predicted TFs and differentially expressed miRNAs in SOC. The associations between popular TFs and differentially expressed miRNAs are presented in this network, these TFs are typically involved in the transcriptional progression of cancer. SOC, serous ovarian carcinoma; TF, transcription factor.

associations between differentially expressed elements and associated elements.

The present study found that MYC, a differentially expressed gene, regulates 2 SOC-associated miRNAs (hsa-let-7a and hsa-miR-146a) in the related network. In the differentially expressed network, hsa-miR-34c targeted HMGA2. hsa-miR-34c targets 3 genes in the related network, enhancer of zeste 2 polycomb repressive complex 2 subunit (EZH2), MYB proto-oncogene like 2 (MYBL2) and B cell lymphoma 2. It has been suggested that miR-34c may suppress the expression of EZH2 and MYBL2 in SOC (79). Hsa-miR-31 is a differentially expressed miRNA in SOC (81). In the differentially expressed network, hsa-miR-31 is only located in 2 host genes. No genes regulate hsa-miR-31 and it target no genes; however, in the related network, it targets several genes. Creighton *et al* (81) identified that functional overexpression of miR-31, the most under-expressed miRNA in serous ovarian cancer, repressed predicted miR-31 gene targets including the cell cycle regulator E2F2, miR31 and cyclin dependent kinase inhibitor 2A. Furthermore, miR-31 overexpression may affect many genes underlying SOC disease progression (81). Without differentially expressed factors, the regulatory associations between elements may influence the tumorigenesis of SOC. Yang *et al* (82) suggested that miR-506 expression was associated with decreased Snail family transcriptional repressor 2 and vimentin, elevated epithelial-cadherin, and improved prognosis for patients with SOC. The related network enables the underlying molecular mechanism of SOC to be explored.

*Global network of SOC*. A global network is an experimentally validated biological network in the human body, which contains all the experimentally validated interactions between miRNAs and genes. Therefore, the differentially expressed and the related networks were included in the global network. The global network was used as the reference when the two other networks were constructed and studied.

*Host genes and miRNAs in SOC*. If miRNAs were differentially expressed, their corresponding host genes were considered to be differentially expressed genes, as mutation of the host gene may make the miRNAs located within it similarly differentially expressed. The host genes and corresponding miRNAs demonstrate important characteristics. A host gene includes a number of miRNAs that target genes, either alone or together. MIR17HG is a cluster host gene that includes four miRNAs (hsa-miR-17, hsa-miR-18a, hsa-miR-19b-1 and hsa-miR-20a), of which three (hsa-miR-17, hsa-miR-18a, hsa-miR-20a) together target PTEN (Fig. 1). Furthermore, the three miRNAs are regulated by MYC. Therefore, miRNA may locate in several host genes. In addition, hsa-miR-20a and hsa-miR-18a locate in MIR20A and MIR18, respectively. Hsa-miR-31 locates in MIR31 and MIR31HG (Fig. 1). It has been hypothesized that overexpression of miR-31 results in decreased cell proliferation, clonogenic potential, cell migration and invasion in SOC (83). Hsa-miR-21 and hsa-miR-22, which form a self-adaption association with PTEN locate in MIR21 and C17orf91, respectively (Fig. 1).

*Network of predicted TFs and differentially expressed miRNAs in SOC*. Using the P-match algorithm enabled the predicted TFs to be determined. Regulatory associations between predicted TFs and differentially expressed miRNAs were analysed (Fig. 2). As presented in Fig. 2, E2F1 and nuclear factor-κB subunit 1 (NFKB1) were identified to be more marked, compared with other elements, in the development of SOC. E2F1 regulates 10 miRNAs and it is regulated by 6 miRNAs. NFKB1 regulates 13 miRNAs and it is regulated by 2 miRNAs. The differential expression of a miRNA may indirectly influence a different miRNA, by targeting TFs; for example, hsa-miR-128 targets E2F3, which regulates hsa-miR-34. Similarly, the differential expression of a predicted TF may indirectly influence a predicted TF, by regulating a differentially expressed miRNA. Additionally, this network consisted of a number of FBLs; for instance, E2F1 separately forms FBLs with hsa-miR-106a, hsa-miR-20a, hsa-miR-17 and hsa-miR-93. NFKB1 separately form FBLs with hsa-miR-9 and hsa-miR-146a. In addition, CAMP responsive element

Table I. Upstream and downstream of MYC in three networks of serous ovarian cancer.

| Upstream | | | | Downstream | | |
|---|---|---|---|---|---|---|
| Differentially expressed network | Related network | Global network | Gene | Differentially expressed network | Related network | Global network |
| miR-145 | miR-145 | let-7a | MYC | let-7b | let-7b | let-7 |
| miR-17 | miR-17 | let-7c | | miR-106a | miR-106a | let-7a |
| miR-20a | miR-20a | let-7g | | miR-141 | miR-141 | let-7a-1 |
| miR-21 | miR-21 | miR-145 | | miR-17 | miR-17 | let-7a-2 |
| miR-26a | miR-26a | miR-17 | | miR-18a | miR-18a | let-7a-3 |
| miR-34b | miR-34b | miR-20a | | miR-19b | miR-19b | let-7b |
| | miR-34a | miR-21 | | miR-20a | miR-20a | let-7c |
| | | miR-24 | | miR-22 | miR-22 | let-7d |
| | | miR-26a | | miR-23a | miR-23a | let-7e |
| | | miR-34a | | miR-23b | miR-23b | let-7f |
| | | miR-34a-5p | | miR-26a | miR-26a | let-7f-1 |
| | | miR-34b | | miR-29a | miR-29a | let-7f-2 |
| | | miR-34b* | | miR-29b | miR-29b | let-7g |
| | | miR-34c-5p | | miR-34 | miR-34 | let-7i |
| | | miR-371a-3p | | miR-9 | miR-9 | miR-106 |
| | | miR-373-3p | | miR-92-1 | miR-92-1 | miR-106a |
| | | miR-378 | | miR-93 | miR-93 | miR-106b |
| | | miR-451a | | | miR-34a | miR-141 |
| | | miR-98 | | | | miR-15a |
| | | | | | | miR-16-1 |
| | | | | | | miR-17 |
| | | | | | | miR-18a |
| | | | | | | miR-195 |
| | | | | | | miR-19a |
| | | | | | | miR-221 |
| | | | | | | miR-29b-2 |

miR, microRNA.

binding protein 1 and hsa-miR-182-5p form FBLs. The transcription network of predicted TFs and miRNAs is important for the analysis of the pathogenesis of SOC.

*Regulatory pathways of differentially expressed genes*. In order to analyze the network of SOC, the focus was placed on the core elements and adjacent nodes. The upstream and downstream elements of differentially expressed genes, miRNAs and predicted TFs in three networks (differentially expressed network, related network and global network), were extracted and listed separately to analyze the characteristics.

The precursors and successors of differentially expressed genes are listed in three levels. The precursors are miRNAs that target genes and the successors are miRNAs that are regulated by genes. PTEN and MYC are the much more marked compared with other genes. As presented in Table I, the upstream and downstream elements of MYC and the regulatory associations were observed (some miRNAs in the global network are omitted as they are not associated with SOC). MYC has 6 types of adjacent nodes (three successors and three predecessors). In the differentially expressed network, 6 miRNAs target MYC, MYC regulates 17 miRNAs, and hsa-miR-17, hsa-miR-20a and hsa-miR-26a separately form FBLs with MYC. In the related network, seven miRNAs target MYC and MYC regulates 18 miRNAs. In the global network, 19 miRNAs target MYC which regulates 57 miRNAs. The precursors may regulate successors indirectly by influencing MYC. For example, the mutation of hsa-miR-21 may influence the expression of hsa-miR-18a by up- or downregulating the expression of MYC. As presented in Fig. 1, MYC may influence the expression of a number of other genes by regulating its successors. MYC regulates hsa-miR-20a and hsa-miR-20a targets neuroblastoma RAS viral oncogene homolog (NRAS); therefore, MYC may affect NRAS. BMI1 only has 3 types of predecessors and it does not regulate any miRNA; therefore, BMI1 may be the last actor in the network of SOC.

*Regulatory pathways of differentially expressed miRNAs*. Similarly, the pathways of each differentially expressed

Table II. Upsteam and downstream of hsa-miR-17 in three networks of serous ovarian cancer.

| Upstream | | | | Downstream | | |
|---|---|---|---|---|---|---|
| Differentially expressed network | Related network | Global network | miRNA | Differentially expressed network | Related network | Global network |
| MYC | CCND1 | CCND1 | miR-17 | PTEN | CCND1 | APP |
| | E2F1 | E2F1 | | MYC | BCL2 | BCL2 |
| | ESR1 | ESR1 | | | RUNX1 | BCL2L11 |
| | MYC | MYC | | | CCND2 | BIM |
| | MYCN | MYCN | | | CDKN1A | BMPR2 |
| | NFKB1 | NFKB1 | | | E2F1 | CCL1 |
| | TNF | NKX2-5 | | | CXCL8 | CCND1 |
| | | SPI1 | | | SMAD4 | CCND2 |
| | | STAT5B | | | MYC | CDKN1A |
| | | TLX1 | | | PTEN | DNAJC27 |
| | | TLX3 | | | RB1 | E2F1 |
| | | TNF | | | TGFBR2 | E2F3 |
| | | | | | THBS1 | S1PR1 |
| | | | | | VEGFA | FBXO31 |
| | | | | | VIM | GAB1 |
| | | | | | E2F3 | GPR137B |
| | | | | | | ICAM1 |
| | | | | | | CXCL8 |
| | | | | | | JAK1 |
| | | | | | | MAP3K12 |
| | | | | | | MAPK9 |
| | | | | | | MEF2D |
| | | | | | | MUC17 |
| | | | | | | MYC |
| | | | | | | NCOA3 |
| | | | | | | NPAT |
| | | | | | | NABP1 |
| | | | | | | PKD2 |
| | | | | | | PRKD1 |
| | | | | | | PRKD2 |
| | | | | | | PTEN |
| | | | | | | PTPRO |
| | | | | | | RB1 |
| | | | | | | RBL1 |
| | | | | | | YES1 |
| | | | | | | ZNFX1 |

hsa, human; miRNA, microRNA; APP, amyloid beta precursor protein; BCL2, apoptosis regulator; BCL2L11, BCL2 like 11; BMPR2, bone morphogenetic protein receptor type 2; CCL1, C-C motif chemokine ligand 1; CCND1, cyclin D1; CCND2, cyclin D2; CDKN1A, cyclin dependent kinase inhibitor 1A; DNAJC27, DnaJ heat shock protein family (Hsp40) member C27; E2F1, E2F transcription factor 1; E2F3, E2F transcription factor 3; S1PR1, sphingosine-1-phosphate receptor 1; ESR1, estrogen receptor 1; FBXO31, F-box protein 31; GAB1, GRB2 associated binding protein 1; GPR137B, G protein-coupled receptor 137B; ICAM1, intercellular adhesion molecule 1; CXCL8, C-X-C motif chemokine ligand 8; JAK1, Janus kinase 1; MAP3K12, mitogen-activated protein kinase kinase kinase 12; MAPK9, mitogen-activated protein kinase 9; MEF2D, myocyte enhancer factor 2D; MUC17, mucin 17, cell surface associated; MYC, MYC proto-oncogene, bHLH transcription factor; MYCN, MYCN proto-oncogene, bHLH transcription factor; NCOA3, nuclear receptor coactivator 3; NFKB1, nuclear factor-κB subunit 1; NKX2-5, NK2 homeobox 5; NPAT, nuclear protein, coactivator of histone transcription; NABP1, nucleic acid binding protein 1; PKD2, polycystin 2, transient receptor potential cation channel; PRKD1, protein kinase D1; PRKD2, protein kinase D2; PTEN, phosphatase and tensin homolog; PTPRO, protein tyrosine phosphatase, receptor type O; RB1, RB transcriptional corepressor 1; RBL1, RB transcriptional corepressor like 1; RUNX1, runt related transcription factor 1; SMAD4, SMAD family member 4; SPI1, Spi-1 proto-oncogene; STAT5B, signal transducer and activator of transcription 5B; TGFBR2, transforming growth factor beta receptor 2; THBS1, thrombospondin 1; TLX1, T-cell leukemia homeobox 1; TLX3, T-cell leukemia homeobox 3; TNF, tumor necrosis factor; VEGFA, vascular endothelial growth factor A; VIM, vimentin; YES1, YES proto-oncogene 1, Src family tyrosine kinase; ZNFX1, zinc finger NFX1-type containing 1.

Table III. Upstream and downstream of NFKB1 in three networks of serous ovarian carcinoma.

| Upstream | | | | Downstream | | |
|---|---|---|---|---|---|---|
| Differentially expressed network | Related network | Global network | NFKB1 | Differentially expressed network | Related network | Global network |
| miR-146a | miR-146a | miR-let-7a | NFKB1 | miR-let-7b | miR-let-7b | miR-let-7a-3 |
| miR-9 | miR-9 | miR-146a | NFKB1 | miR-10b | miR-10b | miR-let-7b |
| | | miR-146b-5p | NFKB1 | miR-125b | miR-125b | miR-10b |
| | | miR-15a | NFKB1 | miR-146a | miR-146a | miR-125b |
| | | miR-16-5p | NFKB1 | miR-155 | miR-155 | miR-125b-1 |
| | | miR-21-5p | NFKB1 | miR-16 | miR-16 | miR-125b-2 |
| | | miR-9 | NFKB1 | miR-17 | miR-17 | miR-146a |
| | | miR-9-5p | NFKB1 | miR-21 | miR-21 | miR-155 |
| | | | NFKB1 | miR-214 | miR-214 | miR-16 |
| | | | NFKB1 | miR-29a | miR-29a | miR-16-1 |
| | | | NFKB1 | miR-29b | miR-29b | miR-16-2 |
| | | | NFKB1 | miR-34 | miR-34 | miR-17 |
| | | | NFKB1 | miR-9 | miR-34a | miR-199a-2 |
| | | | NFKB1 | | miR-9 | miR-21 |
| | | | NFKB1 | | | miR-214 |
| | | | NFKB1 | | | miR-224 |
| | | | NFKB1 | | | miR-29a |
| | | | NFKB1 | | | miR-29b |
| | | | NFKB1 | | | miR-29b-1 |
| | | | NFKB1 | | | miR-29b-2 |
| | | | NFKB1 | | | miR-29c |
| | | | NFKB1 | | | miR-34 |
| | | | NFKB1 | | | miR-34a |
| | | | NFKB1 | | | miR-365 |
| | | | NFKB1 | | | miR-365-1 |
| | | | NFKB1 | | | miR-365-2 |
| | | | NFKB1 | | | miR-365a |
| | | | NFKB1 | | | miR-365b |
| | | | NFKB1 | | | miR-448 |
| | | | NFKB1 | | | miR-9 |
| | | | NFKB1 | | | miR-91 |
| | | | NFKB1 | | | miR-9-1 |
| | | | NFKB1 | | | miR-9-2 |
| | | | NFKB1 | | | miR-9-3 |

NFKB1, nuclear factor-κB subunit 1; miR, microRNA.

miRNA were extracted, compared and analyzed in the same way to the method by which the regulatory pathways of differentially expressed genes were analyzed. The precursors and successors of differentially expressed miRNAs were listed in three levels. To describe the results, hsa-miR-17 is used as an example. Table II presents the upstream and downstream elements of hsa-miR-17 and the regulatory associations. In the differentially expressed network, it was indicated that MYC regulates hsa-miR-17 and hsa-miR-17 targets PTEN and MYC. In addition, hsa-miR-17 and MYC form FBLs. In the related network, six more genes regulate hsa-miR-17, which itself targets 14 more genes. Cyclin D1 (CCND1) and E2F1 separately form FBLs with hsa-miR-17 in the related network, and CCND1 and E2F1 are TFs in the related network. Therefore, it is indicated that the mutation of hsa-miR-17 may influence a number of other elements. In the global network, there are 12 genes regulating hsa-miR-17 which, itself, targets 47 genes. The results of the present study suggested that hsa-miR-17 is a crucial miRNA in the progression of SOC. hsa-miR-128 deserves more attention because it is not regulated by any gene. That is to say hsa-miR-128 is the 'starter' in the network of SOC (it regulates elements but is not regulated by elements in the SOC network) and it is the switch of SOC. The regulation of those switches would be a notable issue.

*Regulatory pathways of predicted TFs in SOC*. The same method as that used to analyze the regulatory pathways of differentially expressed genes was used to extract, compare and analyze the pathways of TFs predicted using the P-match method in SOC. The miRNAs associated with these TFs were listed in three networks and not all TFs have precursors and successors. Here, the focus is on NFKB1 as a representative example because its precursors and successors are uniformly distributed in three networks. Table III presents the upstream and downstream elements of hsa-miR-17 and the regulatory associations. In the differentially expressed network, 2 miRNAs target NFKB1, NFKB1 regulates 13 miRNAs, and hsa-miR-146a and hsa-miR-9 separately form FBLs with NFKB1. In the related network, NFKB1 only regulates one additional miRNA compared with the differentially expressed network. In the global network, NFKB1 was the target of 8 miRNAs and it regulates 34 miRNAs. The results of the present study indicated that NFKB1 exhibits an increased likelihood to influence the development of SOC. A number of TFs, including E2F4, do not have precursors or successors and these TFs exhibit small effects on the development of SOC.

## Discussion

In the present study, differentially expressed genes, differentially expressed miRNAs, TFs predicted using the P-match method and the interactions between them were focused on. From the aforementioned networks, a number of signaling pathways include ≥3 elements. For example, hsa-miR-16 targets TP53 and TP53 regulates hsa-miR-29a. All these pathways have important functions in SOC as elements within them are differentially expressed in SOC, but some pathways are only proposed notionally and their functions remain unclear in SOC. In other types of carcinoma, miRNAs serve a key role; for example, in human breast cancer, miR-145 exhibited a pro-apoptotic effect, dependent on TP53 activation, and that TP53 activation may, in turn, stimulate miR-145 expression (84). Data from the present study suggests that TFs that are predicted using the P-match method exhibit potential associations with differentially expressed miRNAs. However, whether they are closely associated with SOC remains unknown.

In conclusion, the present study constructed 3 regulatory networks, the differentially expressed network, the related network and the global network, to analyze the associations between genes and miRNAs in SOC. Certain signaling pathways and elements were highlighted to analyze the potential regulation mechanism of SOC. The results of the present study identified pathways associated with SOC and may be used to assist gene therapy of SOC. The function of a number of elements and signaling pathways remain unknown.

## Acknowledgements

The present study was supported by the Science and Technology Development Project of Jilin Province (grant no. 20160414009GH), the National Natural Science Foundation of China (grant nos. 61300147 and 61472159), the China Postdoctoral Science Foundation (grant no. 2014M551185), the Electronic Commerce Engineering Laboratory Project of Jilin Province (grant no. 2014N143), the Science and Technology Program of Changchun (grant no. 14GH014), the Premier-Discipline Enhancement Scheme supported by Zhuhai Government and the Premier Key-Discipline Enhancement Scheme supported Guangdong Government Funds.

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