Int J Clin Exp Med 2017;10(2):2858-2865
www.ijcem.com /ISSN:1940-5901/IJCEM0045018

Original Article

Comprehensive analysis of circRNA expression patterns in small hepatocellular carcinoma by integrating circRNA and gene expression data

Minglin Ou[1], Hua Lin[1], Weiwei Gong[1], Fuhua Liu[1], Peng Chen[1], Yue Zhang[1], Jiejing Chen[1], Wen Xue[1], Weiguo Sui[1], Yong Dai[1,2]

[1]*Guangxi Key laboratory of Metabolic Diseases Research, Central Laboratory of Guilin No. 181 Hospital, Guilin, China;* [2]*Clinical Medical Research Center of Second Clinical Medical College, Jinan University, Shenzhen People's Hospital, Shenzhen, China*

Received November 24, 2016; Accepted December 26, 2016; Epub February 15, 2017; Published February 28, 2017

Abstract: Circular RNA (circRNA) is a novel type of non-coding RNA molecule with covalently closed loop structures and may be involved in the regulation of gene expression in a post-transcriptional manner. Recent studies indicated that circRNA played important roles as microRNA sponges, in pre-mRNA splicing, and in the pathogenesis of human diseases. However, the expression patterns of circRNAs and their cognate linear RNAs in the tissues of small hepatocellular carcinoma are still unknown. This paper describes the expression profiles of circRNA and genes in hepatic tissues taken from patient with small hepatocellular carcinomas, to develop a further understanding of the relationship between circRNAs and their cognate linear RNAs in human disease. Hepatic tissues were taken from patients before liver transplantation, including tumorous tissues and non-tumorous tissues that were distant from the tumorous tissues. The circRNA arrays identified 931 circRNAs and the gene expression arrays identified 19367 genes differentially expressed in tumorous tissues, of which 296 circRNAs were detected as co-expressing with their cognate linear RNA. For the changes in the expression trends, 205 circRNAs and their cognate linear RNAs were found to be similar, and 91 circRNAs and their cognate linear RNAs were found to be different. The results of the arrays were confirmed by quantitative real-time PCR. Functional annotation revealed that the genes coexpressing circRNAs and linear RNAs were involved in cell differentiation, growth, and cellular signaling networks, and some of the genes were also identified as cancer-related genes in the literature. This work indicates that some circRNAs are derived from a special splicing pattern of cancer-related genes, and that others may serve as potential diagnosis biomarkers involved in post-transcriptional regulation in the pathogenesis of small hepatocellular carcinomas.

Keywords: CircRNAs, linear RNAs, small hepatic carcinoma, array

Introduction

Hepatitis B virus (HBV) is a double-stranded DNA hepatotropic virus that causes acute and chronic hepatitis [1]. Clinically, the ultimate treatment goal of HBV infection is preventing HBV-associated hepatic diseases, including hepatic carcinoma [2]. However, hepatic carcinoma remains a significant global health problem, as currently more than 100,000 people die of this type of tumor in China [3].

Although some systemic agents have been used in recently years, surgical excision and transplantation are the main choices that offer the best chance for the cure of localized small hepatocellular carcinomas [4]. Furthermore, the usefulness of conventional screening methods are dependent on imaging technology such as ultrasound and biomarkers such as α-fetoprotein, des-γ-carboxyprothrombin, and Lens culinaris agglutinin-reactive fraction of α-fetoprotein, and these methods are still being discussed for some patients with hepatic carcinoma [5]. Therefore, novel biomarkers are needed for hepatic carcinoma.

Regulatory RNAs, including microRNA, siRNA, piRNA, and lncRNAs, have been found to be involved in several types of biological processes in human physiology and diseases [6, 7]. Circular RNAs (circRNAs) are a special type of non-coding RNA. They have been found to be closed RNA loops and unlike linear RNAs, have

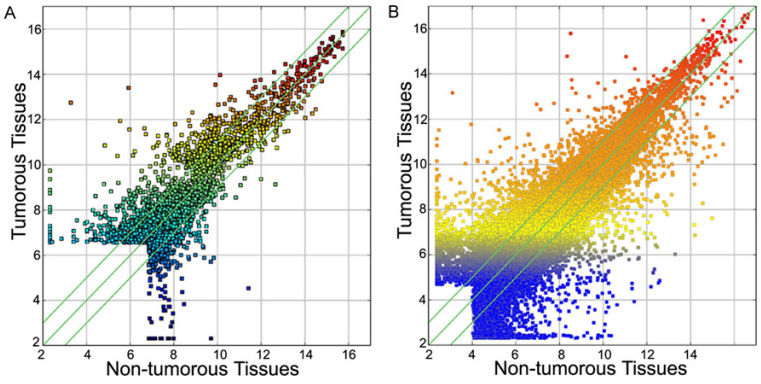

Figure 1. Scatter plot of expression data for tumorous and non-tumorous tissues. For each plot, X- and Y-axes are normalized intensity. The dots above the upper diagonal of the 3 diagonals indicate circRNAs or genes that are up-regulated expressed (fold change ≥ 2.0); the dots under the bottom diagonal of the 3 diagonals represent down-regulation (fold change ≤ -2.0). A. Scatter plot of circRNA expression data; B. Scatter plot of gene expression data.

tail structures of a terminating 5'-cap and 3'-polyadenylation [8]. The circRNAs with regulatory potency are ubiquitous and conserved in different species across the kingdoms [9]. Recent studies indicated that circRNAs played roles as sponges of cytoplasmic miRNA, sequestering agents of RNA-binding protein, and nuclear transcriptional regulators, all of which give further evidence of circRNAs participating in the gene expression regulation network [10].

Furthermore, some papers which indicated a probable link between circRNAs and human disorders aside from cancer, such as numerous neurological diseases, cardiovascular diseases, and autoimmune diseases, have been published [8]. These findings represent the initial links between circRNAs and human disorders. However, more studies that use high throughput technologies such as arrays or deep sequencing are still needed to discover the involvement of different circRNAs in various of genetic diseases. Furthermore, the relationship of the expression of circRNAs and their cognate linear RNAs and different types of human disease is still unknown to this day. Therefore, this paper attempts to comprehensively analyze the circRNA expression patterns in small hepatocellular carcinoma by integrating circRNA and gene expression data.

Materials and methods

Sample preparation

Hepatic tissues were taken from 8 patients with small hepatocellular carcinomas and who were waiting for a liver transplant at Guilin 181st Hospital, China. The diagnosis of small hepatocellular carcinoma was confirmedbyclinicalandhistopathological evidence. The criteria for eligibility for the subjects involved in this study were the following: single hepatocellular carcinomas and the presence of a tumor 5 cm or less in diameter, or multiple tumors whose diameter was less than 3 cm [11]. The non-tumorous tissues were also taken from the same 8 subjects, and they were located far away from tumorous tissue with normal structures as confirmed by light microscope. Informed written consents was obtained from all of the participant subjects, and our research was approved by the Ethics Committee of Guilin No. 181 Hospital, and abided by the ethical principles of the Helsinki Declaration for human medical research.

Appropriate hepatic tissues obtained from liver resection before liver transplant were washed in RNase-free 0.9% NaCl, and treated with RNase Inhibitor (Epicentre, USA) before storage in ultra-cold freezer (-80°C) for further use. Total RNA from the hepatic tissue was extracted by TRIzol (Invitrogen, USA) according to the instruction of the manufacturer. The quality and concentration of total RNA were measured by using a NanoDrop ND-1000 (Thermo Fisher Scientific Inc, USA) at a UV absorbance of A260/280 and confirmed by gel electrophoresis. Comparison of the pooled samples are valuable for disease studies, because the risk of a single specimen contributing bias to a group of samples may be proportionately reduced, and some shared information in each sample would be increased [12, 13]. Therefore, for the five samples with the best quality in the tumorous tissue group and the five samples with the best quality in the non-tumorous tissue group, aliquots of total RNA from each subject were respectively pooled, and subjected to circRNA and gene expression analysis by arrays and quantitative real-time PCR.

CircRNA array analysis

The expression profile of circRNA was detected by using an Arraystar Human circRNA Array (6 ×

Table 1. The primers used in the validation of circRNA by qPCR

Gene name	qRT-PCR primers	Anneal (°C)	Length (bp)
GAPDH	F: 5'GGGAAACTGTGGCGTGAT3'	60	299
	R: 5'GAGTGGGTGTCGCTGTTGA3'		
hsa_circRNA_104692	F: 5'GAGTTCATCGCCGAGACCAC3'	60	205
	R: 5'CCATTTCTGGGCCATAATCC3'		
hsa_circRNA_102046	F: 5'AGTGACGGTGGACTGCTCTT3'	60	191
	R: 5'CAGCCAGTATCAATTCTGTTCAT3'		
hsa_circRNA_104598	F: 5'TTCCTGTTTACCTCCAGTGTC3'	60	176
	R: 5'GAGTGGGTGATGGCTATTCT3'		
hsa_circRNA_102045	F: 5'ACATTGTAGAAGATGGAGGTCA3'	60	92
	R: 5'CGAATAGACAGCTCCTTCAA3'		
hsa_circRNA_104781	F: 5'CTCCCTGCTACTTACCACCTGC 3'	60	85
	R: 5'ATGGTGCTGATGACTTTGAGATTG3'		
hsa_circRNA_104137	F: 5'AACTCGTCCAACTGACAAGCC 3'	60	100
	R: 5'CCATCCTTACGGGTGACTTTC3'		
hsa_circRNA_104780	F: 5'ACAGATACCACCGCCGAACT3'	60	137
	R: 5' TCTAGCTCCTTGGCAGGGAT3'		

Table 2. The primers used in the validation of gene expression by qPCR

Gene name	qRT-PCR primers	Anneal (°C)	Length (bp)
GAPDH	F: 5'GGGAAACTGTGGCGTGAT3'	60	299
	R: 5'GAGTGGGTGTCGCTGTTGA3'		
SATB2	F: 5'GTGGCTGAATATAAGGACGA3'	60	192
	R: 5'AAAATCCTTGGACCGATGTAT3'		
PRKCB	F: 5'TGCCATCGGTCTGTTCTTCTT3'	60	293
	R: 5'CATCTTCATCCTCCCCTTCAA3'		
KAT6A	F: 5'TCCTAAGCCTCGGAACCAT3'	60	91
	R: 5'CTCTGCCAAGCCCTCAACT3'		
CFLAR	F: 5'GCCATAGCAGGAAACAGCGA3'	60	115
	R: 5'AAGTCCAATAGCCGGCACTC3'		
ASAP1	F: 5'ACGACCTCACGCCTACTCT3'	60	88
	R: 5'GTCTTCACTCGCCTCACTTT3'		
ARID3B	F: 5'CACTGTTCACCAAGTCCTACC3'	60	204
	R: 5'CACGTCCAAACTCTCAATGTC3'		
ACACA	F: 5'GAGGTGCAGATCTTAGCGGA3'	60	120
	R: 5'TGGAGTAGCAATAGTAGCAGGTG3'		
GRHPR	F: 5'TGTCCTGACAGATACCACCG3'	60	95
	R: 5'CACCATTCTTCACTTCCTCG3'		
EEF1A1	F: 5'CTGACTGTGCTGTCCTGATTG3'	60	243
	R: 5'ATGCTACTGTGTCGGGGTT3'		

7 K) (Arraystar Inc., USA) with standard protocols according to the manufacturer's instructions. Briefly, the total RNA was treated with RNase R (Epicentre, Inc., USA) for linear RNA degradation. Then, each sample was amplified and transcribed into fluorescent cRNA with an Arraystar Super RNA Labeling Kit (Arraystar Inc., USA) using a random priming method. Purification of the labeled cRNAs was performed with an RNeasy Mini Kit (Qiagen, USA). The concentration and specific activity of the labeled cRNAs (pmol Cy3/μg cRNA) were measured by NanoDrop ND-1000. One microgram of each labeled cRNA was fragmented by 5 μL of 10 × Blocking Agent and 1 μL of 25 × Fragmentation Buffer, and incubated at 60°C for 30 min. Then, the labeled cRNA was diluted with 25 μL 2 × Hybridization buffer and 50 μL of labeled cRNAs were hybridized to the probes on the circRNA array. The arrays were scanned on the Axon GenePix 4000B scanner (Axon Instruments Inc., USA) after washing; grid alignment and data extraction of the scanned images were performed by GenePix Pro 6.0 software (Axon Instruments Inc, USA); Quantile normalization and subsequent data processing were performed using the R software package. Differentially expressed circRNAs with statistical significance between two groups were identified through Volcano Plot filtering. Significantly and differentially expressed circRNAs between two groups of samples were described as a fold change.

Gene expression array analysis

The gene expression profile in the hepatic tissues used for the circRNA analyzed was detected by using Agilent Human 4 × 44 K Gene Expression Microarrays V2 (Agilent Technologies Inc., USA) according to the manufacturer's protocol. Briefly, the extracted total RNA was amplified linearly and labeled with Cy3-UTP. The purification of labeled cRNAs was performed by using the RNeasy Mini Kit (Qiagen, USA). The specific activity and concentration of

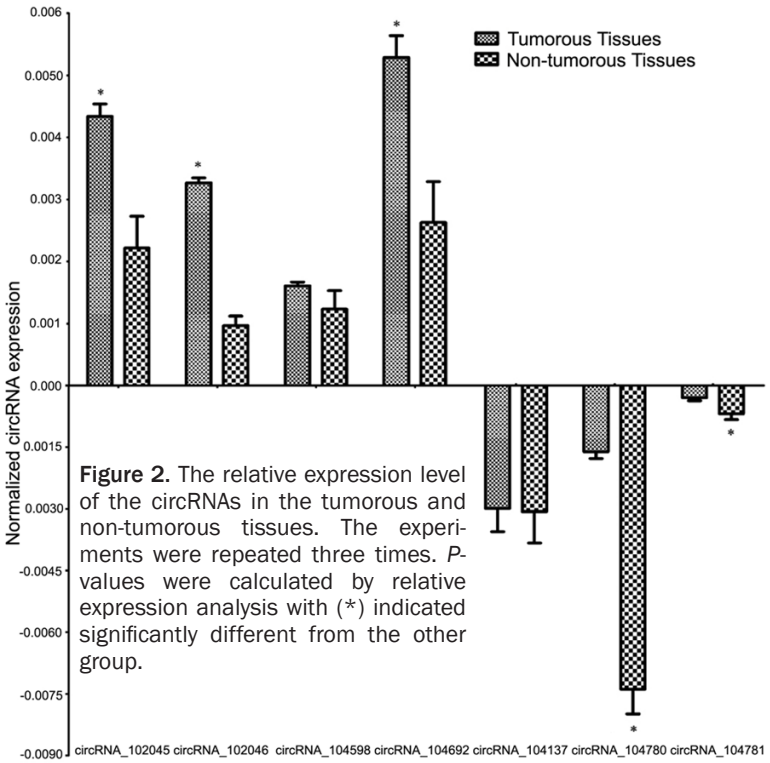

Figure 2. The relative expression level of the circRNAs in the tumorous and non-tumorous tissues. The experiments were repeated three times. *P*-values were calculated by relative expression analysis with (*) indicated significantly different from the other group.

the labeled cRNAs (pmol Cy3/μg cRNA) were measured by using the NanoDrop ND-1000. One microgram of each labeled cRNA was fragmented by adding 11 μL of 10 × Blocking Agent and 2.2 μL of 25 × Fragmentation Buffer, then heated at 60°C for 30 min, and finally 55 μL of 2 × GE Hybridization buffer was added to dilute the labeled cRNA. Approximately 100 μL of hybridization solution was dispensed into the gasket slide and assembled to the gene expression array slide. The slides were incubated for 17 hours at 65°C in an Agilent hybridization oven. The hybridized arrays were washed, fixed and scanned using the Agilent DNA Microarray Scanner (part number G2505C). Acquired array images were analyzed with Agilent Feature Extraction software (version 11.0.1.1). Quantile normalization and subsequent data processing were performed by GeneSpring GX v12.1 software package (Agilent Technologies Inc., USA). Differentially expressed genes with statistical significance between the two groups were identified by Volcano Plot filtering and described as fold change.

Verification by quantitative real-time PCR (qRT-PCR)

The expression levels of individual circRNAs and genes were confirmed by qRT-PCR. The qRT-PCR procedure was performed as our previously described with a minor modification [13]. In brief, individual circRNA or RNA was reverse transcribed to cDNA by either random primer (9 mer) or Oligo (dT) primer, and then amplified by the Gene Amp PCR System 9700 (Applied Biosystems, USA). Divergent primers, which were not common convergent primers, were designed for circRNA verification [14]. The primers are summarized in **Tables 1** and **2**. The cyclling parameters of the PCR reaction for circRNA amplification was 95°C for 5 min, followed by 40 cycles of a denaturing step at 95°C (10 s) and an annealing/extension step at 60°C (60 s). The GAPDH was used as an internal normalizer, and the Ct values of circRNAs and gene expression were converted to fold expression changes by the ΔCT method, and each experiment was repeated three times. Data was analyzed by SPSS using Student's t-test, and $P<0.05$ was considered as significant.

Results

In the two groups of samples, a total of 2070 circRNAs were detected after normalization of the raw data; compared with the control group (non-tumorous tissues), 599 circRNAs were significantly up-regulated, and 332 circRNAs were significantly down-regulated in the tumorous tissues (fold change cut-off: 2.0). For the gene expression profile, a total of 19367 differentially expressed genes were found, including 3047 significantly up-regulated genes and 3156 significantly down-regulated genes (fold change cut-off: 2.0) (**Figure 1**). In the combined analysis of circRNA and gene expression patterns, the product of 296 genes, including both circRNAs and linear RNAs, were different expressed between tumorous tissues and non-tumorous tissues (Table S1). For the expression change trends of the 296 genes, 205 circRNAs and their cognate linear RNAs were found to be similar, and 91 circRNAs and their cognate lin-

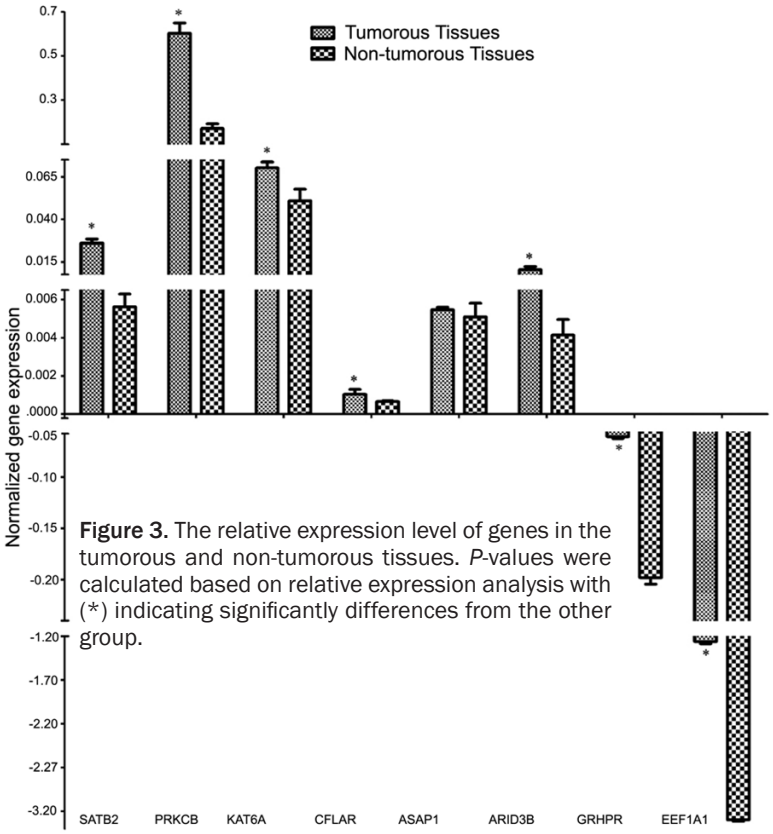

Figure 3. The relative expression level of genes in the tumorous and non-tumorous tissues. *P*-values were calculated based on relative expression analysis with (*) indicating significantly differences from the other group.

ear RNAs were found to be different. Compared with the array detection, qRT-PCR analysis confirmed a similar relative expression trend of 7 circRNAs (**Figure 2**) and 7 genes (**Figure 3**). Functional annotation such as GO and the KEGG pathway were analyzed by web-accessible DAVID (version 6.7). The genes of co-expressing circRNAs and linear RNAs produced 52 significantly enriched GO terms ($P<0.05$), including 31 GO terms related to biological processes, 8 GO terms related to cellular components, and 13 GO terms related to molecular function. Four KEGG pathways, including one carbon pool by folate, ubiquitin mediated proteolysis, propanoate metabolism and oocyte meiosis were significantly enriched ($P<0.05$). The 3 genes that were confirmed by qRT-PCR expressed circRNAs and RNAs concurrently, and they were identified as cancer-related genes in the literature [15-17]. The potential circRNA-miRNA-gene networks of interaction was constructed by using Cytoscape, of which the four circRNAs were expressed by cancer-related genes in the literature and confirmed by qRT-PCR, the miRNAs were the circRNA-targeted miRNAs predicted by TargetScan and miRanda, and the genes were the differently expressed genes identified by using arrays. [14] (**Figure 4**).

Discussion

In this paper, we tried to identify a circRNA profile and gene expression profile and revealed the expression pattern of circRNAs and their cognate linear RNAs in small hepatocellular carcinomas by arrays. Interestingly, we found two different expression patterns of circRNAs and their co-expressing cognate linear RNA.

CircRNAs are one type of non-coding RNAs that may be produced by a special form of alternative splicing as its loop is commonly formed by one exon's splice donor site ligating to its upstream exon's splice acceptor site in certain RNA sequence [18]. In our research, we found that most of the abundant circRNAs were expressed differently in tumorous tissues with similar changes in their cognate linear RNA transcript. These circRNAs may be formed to execute some regulated function in tumorous cells. For example, ASAP1 circRNA (circRNA_104692) showed up-regulated expression in our study. Some researchers have indicated that ASAP1 up-regulated expression in a variety of tumors compared with normal tissue, and ASAP1 may be a key promoter in tumorous cell motility and invasiveness. Up-regulated expression of three different splice forms of ASAP1, including rASAP1a, rASAP1b and rASAP1c, may be associated with metastatic potential in rodent tumor models [15]. Considering the up-regulated expression of circRNA_104692 in our data, ASAP1 circRNA may be another splice form correlated with metastatic potential. Additionally, the protein kinase C in cancer has been known for more than 20 years, and PRKCB is one of tumor-related genes in the protein kinase C family [19]. Interestingly, there were four PRKCB circRNAs, including circRNA_101770, circRNA_101764, circRNA_101765, and circRNA_101762 that were up-regu-

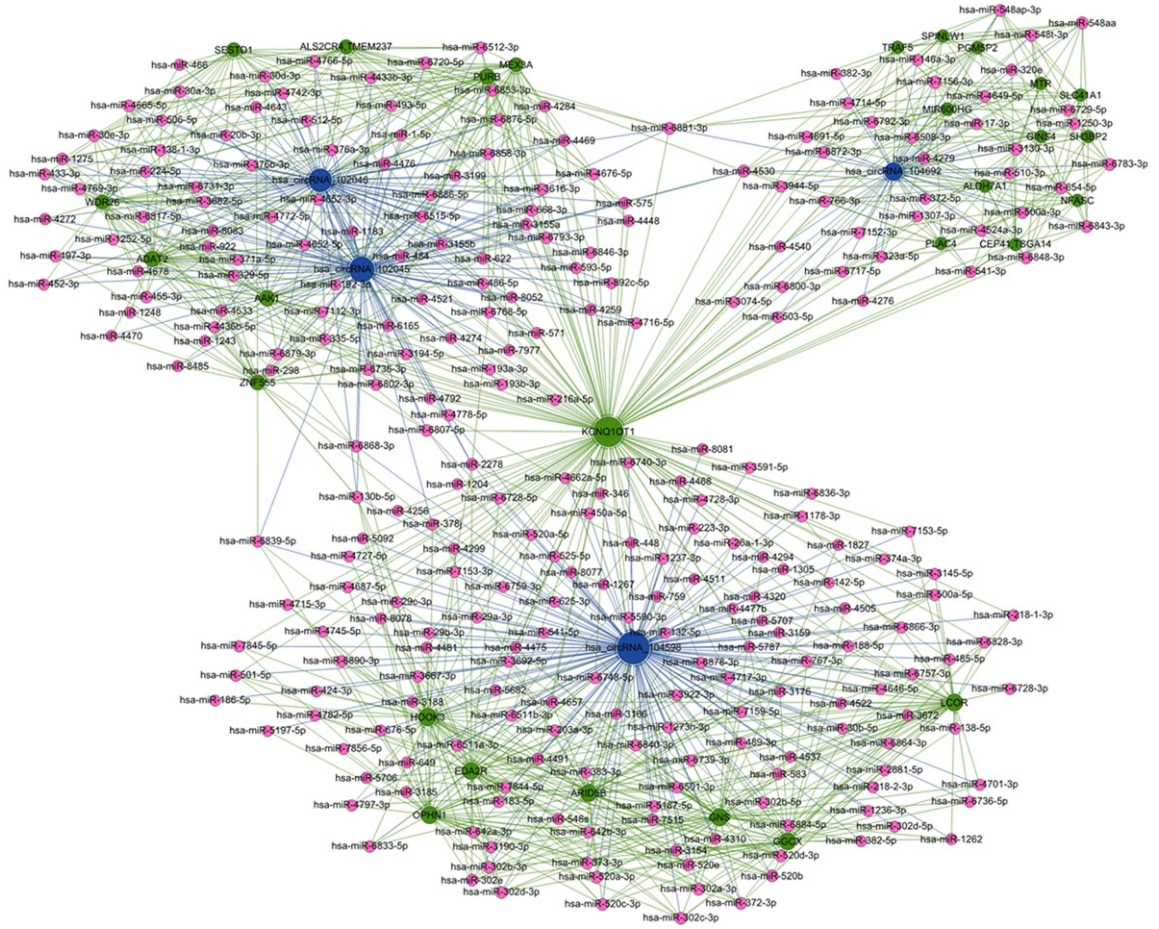

Figure 4. The biomathematically predicted circRNA-miRNA-gene network of circRNAs expressed by cancer-related genes in the literature and confirmed by qRT-PCR.

lated concomitantly with the up-regulated expression of PRKCB. This raises the question of whether these circRNAs are just random transcripts with scrambled exon order, which needs more evidence to support this hypothesis.

There is also a small portion of the abundant circRNAs expressed in tumorous tissues with differential changes of their cognate linear RNA transcript, which is consistent with these circRNAs playing a role in tumorgenesis functions. For example, ALDH1L1 expression was down-regulated and its circRNA (circRNA_103456) was up-regulated in our result. Some studies indicated that ALDH1L1 was one of the genes commonly found to be strongly down-regulated in several types of human cancers [20]. Gain, loss, or mutation of ALDH1L1 have long been known to lead to tumorigenesis, as up-regulated expression of special splice forms of ALDH1L1, such as circRNA_103456, may be another type of regulator involved in the FDH-dependent pathway which is associated with rapidly proliferating cells [21]. Similarly, PPM1D mapped to 17q23.2 is an oncogenic gene, and amplification of this gene has been found in several types of solid tumors, including liver cancer [22]. PPM1D was up-regulated expression in our tumorous tissues; however, PPM1D circRNA (circRNA_102146) was expressed in an oppositing manner. In addition, there are also some other similarly expressed patterns of genes and their circRNA pairs found in our research. This may be because linear production competes with circRNA splicing of pre-mRNA, which raises the possibility that potential function of the excision of some circRNAs could contribute to the regulation of splicing in gene expression.

Evidence indicated that circRNAs involved in the regulation of gene expression as part of

post-transcriptional modifications, and microRNA sponges may be one of the most important manners. The potential roles of circRNAs as microRNA sponges (and verified by qRT-PCR) was further analyzed by bioinformatic consideration of the expression level of circRNAs and potential microRNA targeted mRNA. Considering the mirSVR score, a great number of circRNA targeted miRNAs was found, and the miRNA targeted mRNAs were then predicted. From the network, we can find that some mRNAs are common targets of the circRNA-targeted miRNAs, such as KCNQ1OT1, SCAMP5, MYCL1, and SGCD. Interestingly, KCNQ1OT1 is a carcinogenic gene found in multiple cancers including hepatocellular carcinoma [23], and the expression level of KCNQ1OT1 was significantly up-regulated (with a fold change more than 10) in this study. These amazing findings indicate that our understanding of the regulatory network remains incomplete and remind us that exciting new transcriptional control mechanisms still await discovery.

In summary, this paper identified the circRNA profile and gene expression profile in hepatic tissues taken from patients with small hepatocellular carcinomas. By integrating the circRNA and gene expression data, we found that the genes co-expressed with circRNAs and linear RNAs were involved in many types of cellular function and that the differentially expressed circRNAs may provide a novel clue for the pathophysiology of hepatocellular carcinomas. CircRNAs may be potential biomarkers fas well as probable regulators involved in the pathogenesis of hepatocellular carcinomas. Although further research is still needed to discover the roles of identified circRNAs, our study advocates that circRNAs are involved in small hepatocellular carcinomas by combining circRNAs and cognate linear RNA analysis for the first time, which may be helpful for developing novel methods to screen and prevent hepatocellular carcinomas in the future.

Acknowledgements

We are thankful to the patients for their valuable help in this study. Funding received for this work from Science and Technology Program of Guangxi (No. 15-140-10 and No. guikegong-1598012-25).

Disclosure of conflict of interest

None.

Address correspondence to: Weiguo Sui, Guangxi Key laboratory of Metabolic Diseases Research, Central Laboratory of Guilin 181 Hospital, Guilin 541002, China. Tel: +86-773-2080681; Fax: +86-773-2080681; E-mail: suiwg@163.com; Yong Dai, Clinical Medical Research Center of the Second Clinical Medical College, Jinan University, Shenzhen People's Hospital, Shenzhen 518020, China. Tel: +86-755-25533000-2780; Fax: +86-755-256267-50; E-mail: daiyong22@aliyun.com

References

[1] Guidotti LG, Isogawa M and Chisari FV. Host-virus interactions in hepatitis B virus infection. Curr Opin Immunol 2015; 36: 61-66.

[2] Papatheodoridis GV, Chan HL, Hansen BE, Janssen HL and Lampertico P. Risk of hepatocellular carcinoma in chronic hepatitis B: assessment and modification with current antiviral therapy. J Hepatol 2015; 62: 956-967.

[3] Okuda K and Ishak KG. Neoplasms of the liver. Springer Science & Business Media 2013.

[4] Valero III V, Amini N, Spolverato G, Weiss MJ, Hirose K, Dagher NN, Wolfgang CL, Cameron AA, Philosophe B and Kamel IR. Sarcopenia adversely impacts postoperative complications following resection or transplantation in patients with primary liver tumors. J Gastrointest Surg 2015; 19: 272-281.

[5] Song P, Gao J, Inagaki Y, Kokudo N, Hasegawa K, Sugawara Y and Tang W. Biomarkers: evaluation of screening for and early diagnosis of hepatocellular carcinoma in Japan and china. Liver Cancer 2013; 2: 31-39.

[6] Sui W, Li H, Ou M, Tang D and Dai Y. Altered long non-coding RNA expression profile in patients with IgA-negative mesangial proliferative glomerulonephritis. Int J Mol Med 2012; 30: 173-178.

[7] Sui W, Ou M, Chen J, Li H, Lin H, Zhang Y, Li W, Xue W, Tang D, Gong W, Zhang R, Li F and Dai Y. MicroRNA expression profile of peripheral blood mononuclear cells of Klinefelter syndrome. Exp Ther Med 2012; 4: 825-831.

[8] Andreeva K and Cooper NG. Circular RNAs: new players in gene regulation. Adv Biosci Biotechnol 2015; 6: 433.

[9] Jeck WR, Sorrentino JA, Wang K, Slevin MK, Burd CE, Liu J, Marzluff WF and Sharpless NE. Circular RNAs are abundant, conserved, and associated with ALU repeats. Rna 2013; 19: 141-157.

[10] Ebbesen KK, Kjems J and Hansen TB. Circular RNAs: Identification, biogenesis and function. Biochim Biophys Acta 2016; 1859: 163-168.

[11] Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A and Gennari L. Liver transplan-

tation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med 1996; 334: 693-699.
[12] Agrawal D, Chen T, Irby R, Quackenbush J, Chambers AF, Szabo M, Cantor A, Coppola D and Yeatman TJ. Osteopontin identified as lead marker of colon cancer progression, using pooled sample expression profiling. J Natl Cancer Inst 2002; 94: 513-521.
[13] Ou M, Zhang X, Dai Y, Gao J, Zhu M, Yang X, Li Y, Yang T and Ding M. Identification of potential microRNA-target pairs associated with osteopetrosis by deep sequencing, iTRAQ proteomics and bioinformatics. Eur J Hum Genet 2014; 22: 625-632.
[14] Wang YH, Yu XH, Luo SS and Han H. Comprehensive circular RNA profiling reveals that circular RNA100783 is involved in chronic CD28-associated CD8 (+) T cell ageing. Immun Ageing 2015; 12: 1.
[15] Muller T, Stein U, Poletti A, Garzia L, Rothley M, Plaumann D, Thiele W, Bauer M, Galasso A, Schlag P, Pankratz M, Zollo M and Sleeman JP. ASAP1 promotes tumor cell motility and invasiveness, stimulates metastasis formation in vivo, and correlates with poor survival in colorectal cancer patients. Oncogene 2010; 29: 2393-2403.
[16] Talebi A, Dehairs J and Swinnen J. De novo lipogenesis and membrane remodeling in cancer. Biomedical Research-India 2012; 23: 49-53.
[17] Ivey BT, Guest S and Ethier SP. A chromatin modifier from the 8p11 amplicon in luminal breast cancer. Cancer Res 2014; 74: 5135-5135.
[18] Conn SJ, Pillman KA, Toubia J, Conn VM, Salmanidis M, Phillips CA, Roslan S, Schreiber AW, Gregory PA and Goodall GJ. The RNA binding protein quaking regulates formation of circRNAs. Cell 2015; 160: 1125-1134.
[19] Wallace JA, Pitarresi JR, Sharma N, Palettas M, Cuitino MC, Sizemore ST, Yu L, Sanderlin A, Rosol TJ, Mehta KD, Sizemore GM and Ostrowski MC. Protein kinase C Beta in the tumor microenvironment promotes mammary tumorigenesis. Front Oncol 2014; 4: 87.
[20] Krupenko SA and Oleinik NV. 10-formyltetrahydrofolate dehydrogenase, one of the major folate enzymes, is down-regulated in tumor tissues and possesses suppressor effects on cancer cells. Cell Growth Differ 2002; 13: 227-236.
[21] Oleinik NV, Krupenko NI and Krupenko SA. Epigenetic silencing of ALDH1L1, a metabolic regulator of cellular proliferation, in cancers. Genes Cancer 2011; 2: 130-139.
[22] Li GB, Zhang XL, Yuan L, Jiao QQ, Liu DJ and Liu J. Protein phosphatase magnesium-dependent 1δ (PPM1D) mRNA expression is a prognosis marker for hepatocellular carcinoma. PLoS One 2013; 8: e60775.
[23] Wan J, Huang M, Zhao H, Wang C, Zhao X, Jiang X, Bian S, He Y and Gao Y. A novel tetranucleotide repeat polymorphism within KCNQ1OT1 confers risk for hepatocellular carcinoma. DNA Cell Biol 2013; 32: 628-634.

Table S1. The combined analysis of circRNA and gene expression patterns in small hepatocellular carcinoma and non-tumorous tissues

CircRNAs Expression Pattern				mRNA Expression Pattern		
CircRNA	GeneSymbol	Fold Change	Regulation	GeneSymbol	Fold Change	Regulation
hsa_circRNA_101992	TRIM16L	2.65	Up	TRIM16L	2.35	Down
hsa_circRNA_101868	IST1	5.30	Up	IST1	2.50	Down
hsa_circRNA_103248	FBLN1	2.02	Up	FBLN1	2.01	Down
hsa_circRNA_102661	SLC30A6	10.62	Up	SLC30A6	3.61	Up
hsa_circRNA_103039	UQCC	9.70	Up	UQCC	2.04	Down
hsa_circRNA_100147	EIF3I	2.67	Up	EIF3I	2.32	Down
hsa_circRNA_103852	ADAMTS6	23.84	Up	ADAMTS6	12.87	Up
hsa_circRNA_101213	RAN	4.00	Up	RAN	2.02	Up
hsa_circRNA_103985	NDST1	3.59	Up	NDST1	2.07	Up
hsa_circRNA_100365	NTRK1	3.49	Up	NTRK1	3.56	Down
hsa_circRNA_104598	KAT6A	5.73	Up	KAT6A	3.16	Up
hsa_circRNA_103992	FAM114A2	2.02	Up	FAM114A2	2.40	Up
hsa_circRNA_103993	FAM114A2	2.63	Up	FAM114A2	2.40	Up
hsa_circRNA_104873	SUSD1	2.59	Up	SUSD1	3.13	Up
hsa_circRNA_103128	DYRK1A	2.17	Up	DYRK1A	2.52	Up
hsa_circRNA_001826	DYRK1A	5.80	Up	DYRK1A	2.52	Up
hsa_circRNA_100566	PIP4K2A	2.01	Up	PIP4K2A	2.26	Up
hsa_circRNA_102063	ERBB2	3.05	Up	ERBB2	4.07	Down
hsa_circRNA_103137	C2CD2	6.38	Up	C2CD2	2.41	Up
hsa_circRNA_000482	SLC45A4	28.64	Up	SLC45A4	23.15	Up
hsa_circRNA_100989	FLI1	84.46	Up	FLI1	2.80	Up
hsa_circRNA_100988	FLI1	31.22	Up	FLI1	2.80	Up
hsa_circRNA_104589	RAB11FIP1	3.23	Up	RAB11FIP1	2.41	Up
hsa_circRNA_101344	BAZ1A	5.64	Up	BAZ1A	2.62	Up
hsa_circRNA_104658	STK3	10.57	Up	STK3	2.23	Up
hsa_circRNA_104657	STK3	2.24	Up	STK3	2.23	Up
hsa_circRNA_103947	SEC24A	2.21	Up	SEC24A	2.91	Up
hsa_circRNA_103947	SEC24A	2.21	Up	SEC24A	2.27	Up
hsa_circRNA_103846	DEPDC1B	5.04	Up	DEPDC1B	2.44	Up
hsa_circRNA_103405	ABHD6	3.30	Up	ABHD6	3.14	Down
hsa_circRNA_101208	SLC15A4	4.79	Up	SLC15A4	3.74	Up
hsa_circRNA_104365	ADCY1	2.77	Up	ADCY1	22.94	Down
hsa_circRNA_100085	EIF4G3	2.18	Up	EIF4G3	3.38	Down
hsa_circRNA_100085	EIF4G3	2.18	Up	EIF4G3	10.72	Up
hsa_circRNA_103456	ALDH1L1	4.22	Up	ALDH1L1	168.29	Down
hsa_circRNA_101879	WDR59	2.34	Up	WDR59	2.41	Down
hsa_circRNA_103529	YEATS2	2.03	Up	YEATS2	2.85	Up
hsa_circRNA_102895	BMPR2	5.02	Up	BMPR2	10.51	Up
hsa_circRNA_100479	TTC13	3.82	Up	TTC13	3.04	Up
hsa_circRNA_104581	LEPROTL1	2.79	Up	LEPROTL1	2.15	Up
hsa_circRNA_102241	FOXK2	2.61	Up	FOXK2	2.48	Up
hsa_circRNA_103002	SNX5	2.47	Up	SNX5	2.18	Up
hsa_circRNA_103001	SNX5	2.81	Up	SNX5	2.18	Up
hsa_circRNA_104878	PTBP3	5.99	Up	PTBP3	2.49	Up
hsa_circRNA_104880	PTBP3	8.14	Up	PTBP3	2.49	Up
hsa_circRNA_104879	PTBP3	8.79	Up	PTBP3	2.49	Up

hsa_circRNA_101692	GLIS2	2.26	Up	GLIS2	2.24	Up
hsa_circRNA_100770	ANO5	7.95	Up	ANO5	7.32	Up
hsa_circRNA_100719	DOCK1	94.89	Up	DOCK1	2.06	Up
hsa_circRNA_103966	UBE2D2	3.51	Up	UBE2D2	2.07	Up
hsa_circRNA_103967	UBE2D2	2.08	Up	UBE2D2	2.07	Up
hsa_circRNA_102817	SAP130	2.07	Up	SAP130	2.41	Up
hsa_circRNA_104766	UBAP2	5.06	Up	UBAP2	3.03	Down
hsa_circRNA_104758	UBAP2	2.06	Up	UBAP2	3.03	Down
hsa_circRNA_104759	UBAP2	3.73	Up	UBAP2	3.03	Down
hsa_circRNA_104762	UBAP2	3.20	Up	UBAP2	3.03	Down
hsa_circRNA_104755	UBAP2	2.84	Up	UBAP2	3.03	Down
hsa_circRNA_104764	UBAP2	2.81	Up	UBAP2	3.03	Down
hsa_circRNA_100405	RASAL2	2.29	Up	RASAL2	5.66	Up
hsa_circRNA_100405	RASAL2	2.29	Up	RASAL2	9.33	Up
hsa_circRNA_103169	YPEL1	2.44	Up	YPEL1	2.32	Down
hsa_circRNA_101043	LRRK2	4.80	Up	LRRK2	2.15	Down
hsa_circRNA_101322	HAUS4	5.73	Up	HAUS4	2.30	Down
hsa_circRNA_102795	UXS1	2.68	Up	UXS1	2.47	Up
hsa_circRNA_101063	CSRNP2	5.80	Up	CSRNP2	2.56	Up
hsa_circRNA_100499	MTR	9.25	Up	MTR	2.19	Up
hsa_circRNA_100499	MTR	9.25	Up	MTR	2.79	Up
hsa_circRNA_100500	MTR	9.94	Up	MTR	2.19	Up
hsa_circRNA_100500	MTR	9.94	Up	MTR	2.79	Up
hsa_circRNA_104253	TMEM181	2.28	Up	TMEM181	4.82	Up
hsa_circRNA_103890	FAM169A	4.13	Up	FAM169A	11.26	Up
hsa_circRNA_103890	FAM169A	4.13	Up	FAM169A	4.15	Up
hsa_circRNA_103893	FAM169A	2.07	Up	FAM169A	11.26	Up
hsa_circRNA_103893	FAM169A	2.07	Up	FAM169A	4.15	Up
hsa_circRNA_103891	FAM169A	5.25	Up	FAM169A	11.26	Up
hsa_circRNA_103891	FAM169A	5.25	Up	FAM169A	4.15	Up
hsa_circRNA_104293	FBXL18	3.96	Up	FBXL18	2.56	Up
hsa_circRNA_104401	GTF2I	4.03	Up	GTF2I	3.07	Up
hsa_circRNA_104400	GTF2I	2.49	Up	GTF2I	3.07	Up
hsa_circRNA_103727	PDE5A	11.09	Up	PDE5A	4.28	Up
hsa_circRNA_103317	UBP1	2.15	Up	UBP1	2.12	Up
hsa_circRNA_104645	STAU2	2.47	Up	STAU2	3.21	Up
hsa_circRNA_103676	FRAS1	2.50	Up	FRAS1	26.47	Up
hsa_circRNA_103748	ARHGAP10	2.43	Up	ARHGAP10	6.22	Down
hsa_circRNA_104138	SENP6	2.36	Up	SENP6	3.22	Up
hsa_circRNA_104139	SENP6	2.52	Up	SENP6	3.22	Up
hsa_circRNA_103519	ZNF639	2.65	Up	ZNF639	2.07	Up
hsa_circRNA_102919	ZNF142	5.07	Up	ZNF142	2.04	Up
hsa_circRNA_104694	ZFAT	2.66	Up	ZFAT	2.20	Up
hsa_circRNA_002044	ZEB1	2.47	Up	ZEB1	2.18	Up
hsa_circRNA_100302	LRIG2	2.64	Up	LRIG2	22.72	Up
hsa_circRNA_102158	TLK2	2.05	Up	TLK2	2.92	Up
hsa_circRNA_100168	KIAA0319L	2.65	Up	KIAA0319L	4.15	Down
hsa_circRNA_104223	MTHFD1L	7.51	Up	MTHFD1L	2.43	Down
hsa_circRNA_102600	PPP1R12C	2.44	Up	PPP1R12C	2.44	Down
hsa_circRNA_100525	WDR37	2.57	Up	WDR37	10.62	Up

hsa_circRNA_101707	RSL1D1	2.40	Up	RSL1D1	2.02	Down
hsa_circRNA_103570	LRCH3	4.48	Up	LRCH3	2.38	Down
hsa_circRNA_103572	LRCH3	2.42	Up	LRCH3	2.38	Down
hsa_circRNA_102329	TTC39C	2.60	Up	TTC39C	3.35	Down
hsa_circRNA_102328	TTC39C	2.81	Up	TTC39C	3.35	Down
hsa_circRNA_100339	SNX27	8.19	Up	SNX27	2.93	Up
hsa_circRNA_100339	SNX27	8.19	Up	SNX27	3.78	Up
hsa_circRNA_104938	FNBP1	6.17	Up	FNBP1	3.18	Up
hsa_circRNA_100412	SOAT1	2.55	Up	SOAT1	3.73	Up
hsa_circRNA_100751	STIM1	3.11	Up	STIM1	2.10	Up
hsa_circRNA_100750	STIM1	2.34	Up	STIM1	2.10	Up
hsa_circRNA_100748	STIM1	12.53	Up	STIM1	2.10	Up
hsa_circRNA_102391	ZNF236	3.89	Up	ZNF236	2.04	Up
hsa_circRNA_104801	TLE1	2.07	Up	TLE1	2.51	Up
hsa_circRNA_102226	NPLOC4	19.55	Up	NPLOC4	16.22	Up
hsa_circRNA_102224	NPLOC4	7.30	Up	NPLOC4	16.22	Up
hsa_circRNA_103915	MCTP1	3.24	Up	MCTP1	3.97	Up
hsa_circRNA_103916	MCTP1	2.27	Up	MCTP1	3.97	Up
hsa_circRNA_104538	LMBR1	3.75	Up	LMBR1	17.32	Up
hsa_circRNA_104538	LMBR1	3.75	Up	LMBR1	4.73	Up
hsa_circRNA_104540	LMBR1	2.81	Up	LMBR1	17.32	Up
hsa_circRNA_104540	LMBR1	2.81	Up	LMBR1	4.73	Up
hsa_circRNA_104163	HACE1	3.21	Up	HACE1	3.58	Up
hsa_circRNA_104163	HACE1	3.21	Up	HACE1	3.80	Up
hsa_circRNA_104161	HACE1	16.04	Up	HACE1	3.58	Up
hsa_circRNA_104161	HACE1	16.04	Up	HACE1	3.80	Up
hsa_circRNA_101748	C16orf62	3.47	Up	C16orf62	2.27	Up
hsa_circRNA_101741	C16orf62	2.41	Up	C16orf62	2.27	Up
hsa_circRNA_101744	C16orf62	2.70	Up	C16orf62	2.27	Up
hsa_circRNA_101740	C16orf62	2.82	Up	C16orf62	2.27	Up
hsa_circRNA_100469	PSEN2	2.90	Up	PSEN2	2.09	Up
hsa_circRNA_100470	PSEN2	3.04	Up	PSEN2	2.09	Up
hsa_circRNA_104203	REPS1	3.42	Up	REPS1	2.35	Down
hsa_circRNA_101615	CIB2	4.48	Up	CIB2	5.68	Up
hsa_circRNA_102894	CFLAR	3.38	Up	CFLAR	5.36	Up
hsa_circRNA_104141	PHIP	5.30	Up	PHIP	2.10	Up
hsa_circRNA_104204	AIG1	5.20	Up	AIG1	2.24	Down
hsa_circRNA_102045	ACACA	3.72	Up	ACACA	3.21	Up
hsa_circRNA_102046	ACACA	5.90	Up	ACACA	3.21	Up
hsa_circRNA_103709	TET2	3.54	Up	TET2	2.24	Down
hsa_circRNA_100173	EIF2C3	3.92	Up	EIF2C3	2.93	Down
hsa_circRNA_102949	AGAP1	6.39	Up	AGAP1	2.10	Down
hsa_circRNA_102949	AGAP1	6.39	Up	AGAP1	2.65	Up
hsa_circRNA_100068	PLEKHM2	2.41	Up	PLEKHM2	8.21	Up
hsa_circRNA_102889	SATB2	2.35	Up	SATB2	3.36	Up
hsa_circRNA_102888	SATB2	2.31	Up	SATB2	3.36	Up
hsa_circRNA_100832	FADS1	24.99	Up	FADS1	14.29	Up
hsa_circRNA_102333	ZNF521	2.39	Up	ZNF521	4.05	Up
hsa_circRNA_100205	GPBP1L1	2.22	Up	GPBP1L1	2.05	Down
hsa_circRNA_102993	CDS2	3.29	Up	CDS2	2.76	Up

hsa_circRNA_102485	PGPEP1	3.08	Up	PGPEP1	6.73	Down
hsa_circRNA_100841	SLC3A2	4.48	Up	SLC3A2	2.72	Down
hsa_circRNA_102093	KIAA1267	2.43	Up	KIAA1267	2.64	Up
hsa_circRNA_102535	WTIP	6.08	Up	WTIP	4.14	Up
hsa_circRNA_104692	ASAP1	26.29	Up	ASAP1	5.61	Up
hsa_circRNA_103269	LMF2	2.93	Up	LMF2	2.73	Down
hsa_circRNA_103269	LMF2	2.93	Up	LMF2	2.41	Down
hsa_circRNA_101674	LMF1	2.33	Up	LMF1	3.89	Up
hsa_circRNA_104703	PTK2	3.50	Up	PTK2	2.06	Up
hsa_circRNA_104704	PTK2	3.44	Up	PTK2	2.06	Up
hsa_circRNA_104705	PTK2	5.05	Up	PTK2	2.06	Up
hsa_circRNA_104707	PTK2	2.25	Up	PTK2	2.06	Up
hsa_circRNA_101461	CYFIP1	2.55	Up	CYFIP1	2.19	Up
hsa_circRNA_101545	USP3	4.37	Up	USP3	2.17	Up
hsa_circRNA_101548	USP3	5.45	Up	USP3	2.17	Up
hsa_circRNA_101128	CORO1C	2.25	Up	CORO1C	3.70	Up
hsa_circRNA_105051	PRKY	4.01	Up	PRKY	2.37	Up
hsa_circRNA_101163	MED13L	18.94	Up	MED13L	2.02	Up
hsa_circRNA_104511	SLC37A3	2.03	Up	SLC37A3	2.01	Up
hsa_circRNA_104803	UBQLN1	13.11	Up	UBQLN1	2.08	Up
hsa_circRNA_102101	CDC27	3.26	Up	CDC27	2.26	Down
hsa_circRNA_102100	CDC27	2.04	Up	CDC27	2.26	Down
hsa_circRNA_100757	ST5	4.56	Up	ST5	2.05	Up
hsa_circRNA_102924	SERPINE2	2.72	Up	SERPINE2	8.65	Up
hsa_circRNA_101957	UBE2G1	5.85	Up	UBE2G1	2.86	Up
hsa_circRNA_101958	UBE2G1	5.40	Up	UBE2G1	2.86	Up
hsa_circRNA_102676	LTBP1	2.26	Up	LTBP1	2.42	Up
hsa_circRNA_103999	MAT2B	3.27	Up	MAT2B	3.22	Down
hsa_circRNA_103999	MAT2B	3.27	Up	MAT2B	3.14	Down
hsa_circRNA_104982	TXLNG	5.96	Up	TXLNG	8.38	Up
hsa_circRNA_104610	HOOK3	2.20	Up	HOOK3	4.81	Up
hsa_circRNA_101762	PRKCB	2.27	Up	PRKCB	5.68	Up
hsa_circRNA_101764	PRKCB	20.39	Up	PRKCB	5.68	Up
hsa_circRNA_101765	PRKCB	4.80	Up	PRKCB	5.68	Up
hsa_circRNA_101770	PRKCB	705.73	Up	PRKCB	5.68	Up
hsa_circRNA_103008	XRN2	2.82	Up	XRN2	2.26	Up
hsa_circRNA_103035	GGT7	2.28	Up	GGT7	3.43	Down
hsa_circRNA_100422	DENND1B	2.01	Up	DENND1B	4.05	Up
hsa_circRNA_100421	DENND1B	3.52	Up	DENND1B	4.05	Up
hsa_circRNA_102936	TRIP12	3.05	Up	TRIP12	2.18	Down
hsa_circRNA_104812	AGTPBP1	2.64	Up	AGTPBP1	2.12	Up
hsa_circRNA_100621	PPP3CB	2.25	Up	PPP3CB	3.40	Up
hsa_circRNA_100621	PPP3CB	2.25	Up	PPP3CB	2.40	Up
hsa_circRNA_102216	ENGASE	3.71	Up	ENGASE	4.78	Down
hsa_circRNA_104342	BBS9	8.17	Up	BBS9	6.85	Up
hsa_circRNA_101591	ARID3B	3.72	Up	ARID3B	5.67	Up
hsa_circRNA_101258	KIAA0564	2.50	Up	KIAA0564	2.52	Down
hsa_circRNA_001747	MCU	19.14	Up	MCU	2.36	Up
hsa_circRNA_100882	STARD10	-4.23	Down	STARD10	5.89	Down
hsa_circRNA_104780	GRHPR	-2.23	Down	GRHPR	3.14	Down

hsa_circRNA_104781	GRHPR	-7.60	Down	GRHPR	3.14	Down
hsa_circRNA_104014	FBXW11	-3.49	Down	FBXW11	2.01	Up
hsa_circRNA_100396	RFWD2	-3.19	Down	RFWD2	2.53	Up
hsa_circRNA_103370	MAP4	-2.61	Down	MAP4	2.12	Down
hsa_circRNA_102164	CCDC47	-2.98	Down	CCDC47	2.21	Down
hsa_circRNA_104666	PABPC1	-2.22	Down	PABPC1	2.88	Up
hsa_circRNA_103578	GAK	-2.65	Down	GAK	2.37	Down
hsa_circRNA_104048	NQO2	-2.24	Down	NQO2	2.38	Down
hsa_circRNA_104575	EPHX2	-2.02	Down	EPHX2	4.76	Down
hsa_circRNA_101673	LMF1	-2.30	Down	LMF1	3.89	Up
hsa_circRNA_101997	SPECC1	-3.15	Down	SPECC1	2.33	Up
hsa_circRNA_103251	ATXN10	-2.19	Down	ATXN10	2.41	Up
hsa_circRNA_100705	OAT	-2.22	Down	OAT	3.06	Down
hsa_circRNA_102205	TNRC6C	-2.51	Down	TNRC6C	2.30	Down
hsa_circRNA_102205	TNRC6C	-2.51	Down	TNRC6C	2.89	Down
hsa_circRNA_103010	ABHD12	-4.76	Down	ABHD12	3.27	Up
hsa_circRNA_100597	SGMS1	-3.09	Down	SGMS1	2.41	Up
hsa_circRNA_100548	UPF2	-2.76	Down	UPF2	6.44	Down
hsa_circRNA_101379	SMOC1	-2.38	Down	SMOC1	2.22	Down
hsa_circRNA_100636	FAM190B	-2.36	Down	FAM190B	2.09	Down
hsa_circRNA_102001	USP22	-3.82	Down	USP22	2.35	Up
hsa_circRNA_104030	CANX	-2.57	Down	CANX	2.55	Up
hsa_circRNA_104031	CANX	-4.35	Down	CANX	2.55	Up
hsa_circRNA_104029	CANX	-2.16	Down	CANX	2.55	Up
hsa_circRNA_104057	RREB1	-2.04	Down	RREB1	4.17	Down
hsa_circRNA_104137	EEF1A1	-5.44	Down	EEF1A1	5.09	Down
hsa_circRNA_104137	EEF1A1	-5.44	Down	EEF1A1	4.28	Down
hsa_circRNA_104137	EEF1A1	-5.44	Down	EEF1A1	2.77	Down
hsa_circRNA_104137	EEF1A1	-5.44	Down	EEF1A1	2.40	Down
hsa_circRNA_104137	EEF1A1	-5.44	Down	EEF1A1	2.07	Up
hsa_circRNA_100145	EIF3I	-2.45	Down	EIF3I	2.32	Down
hsa_circRNA_102146	PPM1D	-2.28	Down	PPM1D	2.73	Up
hsa_circRNA_101697	ABAT	-4.40	Down	ABAT	6.09	Down
hsa_circRNA_100345	C1orf43	-2.64	Down	C1orf43	2.74	Down
hsa_circRNA_101101	CCT2	-2.36	Down	CCT2	2.04	Up
hsa_circRNA_103984	NDST1	-2.11	Down	NDST1	2.07	Up
hsa_circRNA_104205	PHACTR2	-2.11	Down	PHACTR2	5.37	Up
hsa_circRNA_104205	PHACTR2	-2.11	Down	PHACTR2	3.79	Up
hsa_circRNA_100179	MFSD2A	-2.01	Down	MFSD2A	179.07	Down
hsa_circRNA_104936	PPP2R4	-2.26	Down	PPP2R4	2.87	Down
hsa_circRNA_100948	ACAT1	-166.04	Down	ACAT1	2.24	Down
hsa_circRNA_100948	ACAT1	-166.04	Down	ACAT1	2.71	Down
hsa_circRNA_104252	TMEM181	-2.20	Down	TMEM181	4.82	Up
hsa_circRNA_102990	SLC23A2	-2.53	Down	SLC23A2	3.75	Down
hsa_circRNA_104110	CNPY3	-4.66	Down	CNPY3	4.99	Down
hsa_circRNA_104733	UHRF2	-3.24	Down	UHRF2	2.42	Down
hsa_circRNA_100497	NID1	-2.29	Down	NID1	3.50	Up
hsa_circRNA_101921	TCF25	-2.53	Down	TCF25	3.28	Down
hsa_circRNA_101921	TCF25	-2.53	Down	TCF25	3.67	Down
hsa_circRNA_101917	TCF25	-2.12	Down	TCF25	3.28	Down
hsa_circRNA_101917	TCF25	-2.12	Down	TCF25	3.67	Down

hsa_circRNA_104222	PLEKHG1	-3.17	Down	PLEKHG1	11.02	Up
hsa_circRNA_104701	PTK2	-2.69	Down	PTK2	2.06	Up
hsa_circRNA_100461	CAPN2	-2.55	Down	CAPN2	2.24	Up
hsa_circRNA_104060	SIRT5	-3.01	Down	SIRT5	2.54	Down
hsa_circRNA_104060	SIRT5	-3.01	Down	SIRT5	2.44	Down
hsa_circRNA_104868	KIAA0368	-13.94	Down	KIAA0368	5.60	Up
hsa_circRNA_101112	ACSS3	-2.44	Down	ACSS3	3.56	Down
hsa_circRNA_101664	PCSK6	-7.88	Down	PCSK6	11.64	Up
hsa_circRNA_101663	PCSK6	-9.21	Down	PCSK6	11.64	Up
hsa_circRNA_102986	C20orf194	-2.63	Down	C20orf194	3.76	Up
hsa_circRNA_104120	MCM3	-2.60	Down	MCM3	2.29	Up
hsa_circRNA_104870	PTGR1	-3.06	Down	PTGR1	2.10	Down
hsa_circRNA_105035	IDS	-3.42	Down	IDS	2.48	Down
hsa_circRNA_102401	POLR2E	-23.04	Down	POLR2E	3.18	Down
hsa_circRNA_101817	AMFR	-4.05	Down	AMFR	4.20	Down
hsa_circRNA_101817	AMFR	-4.05	Down	AMFR	4.08	Up
hsa_circRNA_104656	STK3	-2.19	Down	STK3	2.23	Up
hsa_circRNA_104659	STK3	-2.38	Down	STK3	2.23	Up
hsa_circRNA_102643	DTNB	-3.62	Down	DTNB	4.45	Down
hsa_circRNA_103612	SEPSECS	-9.35	Down	SEPSECS	2.43	Down
hsa_circRNA_103280	RPUSD3	-2.34	Down	RPUSD3	2.31	Down
hsa_circRNA_101638	ABHD2	-4.62	Down	ABHD2	3.33	Down
hsa_circRNA_101637	ABHD2	-2.79	Down	ABHD2	3.33	Down
hsa_circRNA_101096	MDM2	-7.78	Down	MDM2	2.22	Up
hsa_circRNA_104963	ANAPC2	-2.19	Down	ANAPC2	7.77	Up
hsa_circRNA_101751	NPIPL3	-42.44	Down	NPIPL3	2.27	Down
hsa_circRNA_101991	SHMT1	-24.74	Down	SHMT1	5.05	Down
hsa_circRNA_101991	SHMT1	-24.74	Down	SHMT1	9.50	Down
hsa_circRNA_101991	SHMT1	-24.74	Down	SHMT1	4.75	Down
hsa_circRNA_101370	GPHN	-2.06	Down	GPHN	2.85	Down
hsa_circRNA_103445	HGD	-2.93	Down	HGD	9.24	Down
hsa_circRNA_101137	KCTD10	-2.17	Down	KCTD10	3.91	Up
hsa_circRNA_103948	SEC24A	-2.10	Down	SEC24A	2.91	Up
hsa_circRNA_103948	SEC24A	-2.10	Down	SEC24A	2.27	Up
hsa_circRNA_100257	DNAJC6	-3.34	Down	DNAJC6	3.71	Up
hsa_circRNA_102649	EPT1	-2.37	Down	EPT1	8.08	Up
hsa_circRNA_102772	KCMF1	-28.14	Down	KCMF1	3.29	Up
hsa_circRNA_100530	WDR37	-2.66	Down	WDR37	10.62	Up
hsa_circRNA_100204	AKR1A1	-16.54	Down	AKR1A1	3.90	Down
hsa_circRNA_104143	BCKDHB	-33.34	Down	BCKDHB	2.96	Down
hsa_circRNA_104143	BCKDHB	-33.34	Down	BCKDHB	2.04	Down
hsa_circRNA_100246	FGGY	-43.94	Down	FGGY	5.13	Down
hsa_circRNA_102579	SLC1A5	-2.08	Down	SLC1A5	6.22	Down
hsa_circRNA_100188	HIVEP3	-2.02	Down	HIVEP3	9.91	Up
hsa_circRNA_101974	EIF4A1	-7.99	Down	EIF4A1	2.21	Down
hsa_circRNA_101954	ANKFY1	-3.61	Down	ANKFY1	2.20	Up
hsa_circRNA_100923	PICALM	-2.24	Down	PICALM	2.15	Down
hsa_circRNA_100921	PICALM	-2.36	Down	PICALM	2.15	Down
hsa_circRNA_105024	TMEM164	-2.16	Down	TMEM164	8.79	Up

CircRNA expression pattern, the expression of circRNAs analyzed by circRNA array; gene expression pattern, the expression of gene analyzed by gene expression array (Fold change cut-off: 2.0).