Analysis and construction of an exosome derived competing endogenous RNA network for small cell lung cancer in the exoRbase database

Kangle Zhu
Nantong University
Lian Wang
Xuyi county people's Hospital
Zanhao Chen
Nantong University
Jianing Ding
Nantong University
Jixuan Dong
Nantong University
Jinliang Chen (chenjinliang@163.com)
Nantong first people's Hospital

Research Article

Keywords: Small cell lung cancer, Exosome, Competing RNA endogenous networks, Enrichment analysis

Posted Date: March 11th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1430050/v1

Abstract

A competing endogenous RNA (ceRNA) regulatory network in the blood exosomes of small cell lung cancer (SCLC) patients was constructed by bioinformatics methods to explore the pathogenesis. Blood exosomal gene sequencing data of SCLC patients and normal controls were downloaded from the exorbase 2.0 database, and the expression profiles of exosomal mRNAs, long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs) were differentially analyzed using the R language, miRNAs binding to differentially expressed lncRNAs were predicted using the miRcode database, and miRNAs binding to differentially expressed circRNAs were predicted using the Starbase database. The associated mRNAs, circRNAs, lncRNAs, and their corresponding miRNA prediction data were imported into the cytoscape software to visualize the ceRNA network. Enrichment analysis of Go and KEGG was performed and visualized using the R language and Kobas. Cytohubba has used Plug-in identified hub genes. 13 differentially expressed mRNAs, 59 differentially expressed circRNAs, and 40 differentially expressed lncRNAs were filtered out. A ceRNA network was constructed by cytoscape software, and a total of 5 mRNA nodes, 5 lncRNA nodes, 7 circRNA nodes, and 41 miRNA nodes were identified. KEGG enrichment analysis showed that the differentially expressed mRNAs in the regulatory network were mainly enriched on non-small cell lung cancer pathways, and rassf3 was the pathway Among the key genes. Cytohubba to find the most critical hub gene oip5-as.in this study, we successfully constructed a ceRNA regulatory network in the blood exosomes of SCLC patients to provide exact targets for the diagnosis and treatment of SCLC.

Introduction

Lung cancer is one of the most common malignant tumors. Every year, about 1.8 million people are diagnosed with lung cancer and 1.6 million people die from lung cancer [1, 2]. Its morbidity and mortality are the first among malignant tumors [3], which has posed a serious threat to human life and health. Among them, small cell lung cancer(SCLC) accounts for 13–15% of all lung cancers [4]. It belongs to poorly differentiated neuroendocrine carcinoma and has the characteristics of aggressive growth and easy extensive metastasis. Therefore, most patients have distant metastasis when it is found. At present, traditional chemoradiotherapy commonly used in clinical practice has poor treatment effects on SCLC and is prone to relapse. The five-year survival rate in patients with localized SCLC is 20–25%, while the five-year survival rate in patients with extensive SCLC is only 3–8% [5, 6]. Therefore, exploring the mechanism of occurrence and metastasis of SCLC and finding more accurate and sensitive early diagnostic markers and therapeutic targets of SCLC are important goals to improve the prognosis of patients with SCLC.

Exosomes are extracellular disc-shaped vesicles with a diameter of 40 ~ 100nm, which are secreted specifically by various active cells and distributed in body fluids such as saliva, milk, serum, and plasma. Exosomes contain bioactive substances such as protein, lipids, DNA, and non-coding RNA, and play an important role in the regulation of physiological functions [7–8]. The exosomes derived from SCLC cells, as an important carrier for cell-to-cell communication and genetic material transfer, participate in the

development process of breast cancer such as proliferation, invasion, metastasis, angiogenesis, immunosuppression, and so on by changing the biochemical components, signal transduction pathways and gene regulation of recipient cells [9].The hypothesis of competitive endogenous RNA (ceRNA) was first put forward by SALMENA of Harvard Medical School in the United States. According to this hypothesis, long non-coding RNA (lncRNA), mRNA, circular RNA (circRNA), and other non-coding RNA can competitively bind to miRNA and reduce the inhibition of its target gene mRNA, thus further regulating a series of biological behaviors such as proliferation, growth, differentiation, and apoptosis of tumor cells [10]. At present, research shows that ceRNA may be involved in the development of SCLC [11], but the regulatory mechanism of ceRNA in the exosomes of SCLC patients is still unclear.

In this study, we analyzed the exosome sequencing data of SCLC patients and normal controls in the exoRBase database, and found the differential expression profiles of mRNA, lncRNA, and circRNA, and constructed a ceRNA network, which will provide a theoretical basis for exploring new targets for the diagnosis and treatment of SCLC.

Materials And Methods

Data download and screening of differentially expressed mRNA, lncRNA, circRNA

The exosome gene sequencing data of the blood of SCLC patients and the normal control group are downloaded from the exoRBase 2.0 database (http://www.exorbase.org/). The corresponding gene annotation file is also downloaded. The data deadline is October 20, 2021. A total of 154 sets of sample data were downloaded, including 36 sets of SCLC exosome gene sequencing data and 118 sets of normal sample exosome gene sequencing data. The SCLC data were used as the experimental group and the normal sample data as the control to separately analyze the differential expression of mRNA, lncRNA, and circRNA in exosome. The screening condition for differential expression was $|log2FC| > 0$, and the screening condition after correction was P value < 0.05.

RNA prediction of interaction and construction of ceRNA network

TargetScan (http://www.targetscan.org/vert_71/) and miRanda (http://www.micro

-rna.org/) databases were used to jointly predict and differentially express mRNA-bound miRNAs. The miRcode database was used to predict miRNA binding to differentially expressed lncRNA, and the starBase database was used to predict miRNA binding to differentially expressed circRNA. Finally, the related mRNA, circRNA, lncRNA, and their corresponding miRNA prediction data were imported into Cytoscape (version 3.8.2) software to visualize the ceRNA network.

Functional enrichment analysis of differentially expressed mRNA

Differentially expressed mRNA was converted from Gene Symbol to entrez ID using R package "org.Hs.eg.db", followed by GO enrichment analysis and visualization of differentially expressed mRNA using R packages "clusterProfiler", "org.Hs.eg.db", "enrichplot" and "ggplot2". KEBAS (http://kobas.cbi.pku.edu.cn/) was also used for KEGG enrichment analysis and visualization of differentially expressed mRNA to explore potential roles or potential pathways of influence for differentially expressed mRNA.

Hub gene screening

The obtained gene network information was imported into Cytospace software, and the connectivity score of each protein node was calculated by CytoHubba plug-in. The top 10 genes with the scores were identified as Hub genes.

Statistical analysis

Data were organized using the Perl (version strawbuerry-Perl-5.32.) programming language, and data analysis and drawing were performed using RStudio (version 4.1.0). Measurement data were expressed as mean standard deviation, and a statistical test was conducted using a T-test or analysis of variance. $P < 0.05$ indicated statistically significant.

Results

Data download and difference analysis

Exosome sequencing data from 36 groups of SCLC patients and sequencing data from 118 groups of the normal population were downloaded from the exoRBase 2.0 database. The corresponding mRNA expression profile, lncRNA expression profile, and circRNA expression profile matrix were integrated. Differential analysis of mRNA, lncRNA and circRNA was performed using the R language, and 13 differentially expressed mRNA, 40 differentially expressed lncRNA, and 59 differentially expressed circRNA were screened out. Information on the most significantly differentially expressed mRNA, lncRNA, and circRNA (Table 1), and heat map of the differentially expressed genes (Fig. 1-ABC).

Table 1
Differentially expressed genes

Gene name	ConMean	TreatMean	LogFC	P-value	Gene type
YBX1	3683.383531	4296.887304	0.222260314	0.002017195	mRNA
HIST1H1E	1978.121861	2334.745157	0.23913378	0.007224538	mRNA
HNRNPAB	178.0694415	200.7087535	0.172663581	0.011522177	mRNA
EHBP1L1	220.989895	259.9908699	0.234480559	0.022740253	mRNA
ANXA2	206.9705566	236.4051464	0.191835896	0.023325696	mRNA
RASSF3	559.4317647	630.2201839	0.171893787	0.030722551	mRNA
HIST1H1C	1913.370042	2188.940531	0.194116845	0.033622972	mRNA
ID2	123.6389667	144.9075005	0.228998769	0.034361332	mRNA
CX3CR1	126.4755853	149.6717007	0.242942553	0.034647911	mRNA
RAB13	35.09026937	44.04097176	0.32777528	0.037705976	mRNA
AC092069.1	12.05662822	34.95575791	1.53570362	6.70E-07	lncRNA
AC022150.4	26.24046299	44.13219849	0.750038443	7.78E-07	lncRNA
AC009779.2	11.76834663	19.17564383	0.704363371	0.000653026	lncRNA
TTTY15	4.517461115	7.713278751	0.771832067	0.005364037	lncRNA
AC125807.2	11.42835854	17.45351427	0.610899349	0.005891972	lncRNA
OIP5-AS1	33.43425041	39.17048468	0.228440207	0.005964902	lncRNA
LINC00989	446.0513809	338.0074264	-0.40015496	0.006920439	lncRNA
AL355816.2	15.91372014	26.56502573	0.739256977	0.007852757	lncRNA
LINC01133	1.523648291	2.995376812	0.975207583	0.008131795	lncRNA
HCP5	83.75544412	100.9643744	0.269591449	0.010322913	lncRNA
hsa_circ_0001953	393.2728066	860.2315051	1.129194537	2.00E-05	circRNA
hsa_circ_0002360	2416.039893	1544.784058	-0.645239095	0.000102943	circRNA
hsa_circ_0000437	4546.675171	2883.705124	-0.656888289	0.000124244	circRNA
hsa_circ_0005615	619.810798	1100.558477	0.828336009	0.000141833	circRNA
hsa_circ_0000711	665.8038431	1265.097498	0.926079471	0.000188089	circRNA
hsa_circ_0002711	981.9400653	584.8103927	-0.74766602	0.00025046	circRNA
hsa_circ_0004771	1324.648038	814.0209902	-0.702471182	0.001893693	circRNA

Gene name	ConMean	TreatMean	LogFC	P-value	Gene type
hsa_circ_0007637	78.87445448	171.7960704	1.12306701	0.002030439	circRNA
hsa_circ_0001492	2854.323427	2019.834745	-0.498911556	0.002664035	circRNA
hsa_circ_0027464	2178.246911	1499.746316	-0.538449009	0.003393619	circRNA

Construction of miRNA-related ceRNA regulatory network

A total of 39 miRNAs combined with differentially expressed mRNA were predicted using TargetScan and miRanda databases, 520 miRNAs combined with differentially expressed lncRNA were predicted using miRcode database, and 337 miRNAs combined with differentially expressed circRNA were predicted using the starBase database. A ceRNA network of five mRNA nodes, five lncRNA nodes, seven circRNA nodes, and 41 miRNA nodes was constructed using Cytoscape software (Fig. 2).

KEGG pathway enrichment analysis

The R packages "clusterProfiler", "org.Hs.eg.db", "enrichplot", and "ggplot2" were used for GO enrichment analysis and visualization of differentially expressed mRNA, while Kobas (http://kobas.cbi.pku.edu.cn/) was used for KEGG enrichment analysis and visualization of differentially expressed mRNA. GO enrichment analysis showed that mRNA was mainly enriched in "melon", "banana", "late endosome membrane" (Fig. 3-AB). The KEGG enrichment analysis showed that the mRNA differentially expressed in the regulatory network were mainly enriched in "Non-small cell lung cancer", "Leucocyte transendothelial migration ", "cellular aging", "Rap1 signaling pathway", "Ras signaling pathway", "MAPK signaling pathway" (Table 2). Among them, the most critical RASSF3 was mainly enriched in the "Non-small cell lung cancer" pathway (Fig. 4). These results indicate that the ceRNA regulatory network constructed by blood exosomes of SCLC patients plays an important role in the development of SCLC.

Table 2
KEGG enrichment analysis of mRNA in the blood exosomal ceRNA regulatory network in SCLC patients

#Term	Database	ID	P-Value	Input
Non-small cell lung cancer	KEGG PATHWAY	hsa05223	0.008506591	RASSF3
Leukocyte transendothelial migration	KEGG PATHWAY	hsa04670	0.014313345	RASSF3
Cellular senescence	KEGG PATHWAY	hsa04218	0.020343528	RASSF3
Rap1 signaling pathway	KEGG PATHWAY	hsa04015	0.026593549	RASSF3
Ras signaling pathway	KEGG PATHWAY	hsa04014	0.029333433	RASSF3
MAPK signaling pathway	KEGG PATHWAY	hsa04010	0.037145348	MAP4K4
Pathways in cancer	KEGG PATHWAY	hsa05200	0.065842555	RASSF3

Hub gene screening

The top 10 hub genes scored were filtered out by the cytospace software and included 6 miRNAs: hsa-mir-23b-3p, hsa-mir-137, hsa-mir-613, hsa-mir-320a, hsa-mir-320b, hsa-mir-206; 1 lncRNA: oip5-as1; 2 mRNAs: anxa2, map4k4; 1 circrna: hsa_ circ_ 0000437 to construct the corresponding hub gene network map, we suggested that the genes closely related to the development and progression of SCLC are: hsa-mir-23b-3p, oip5-as1, map4k4, hsa-mir-137 see Fig. 5.

Discussion

SCLC is extremely malignant and often metastasizes extensively when diagnosed [12]. Early diagnosis and treatment of SCLC are therefore paramount. In recent years, some progress has been made in the study of the molecular mechanism and treatment of SCLC, but there is still a lack of reliable specific markers in the early diagnosis and treatment of SCLC. The exosome is an extracellular vesicle that can be secreted by almost all cells. It contains complex RNA and protein and is characterized by high concentration, easy enrichment, and stable biological activity. Therefore, exosome has great clinical diagnostic value. Recent studies have shown that exosome-derived lncRNA-mediated intercellular signal transduction plays an important role in the occurrence and development of tumors [13]. In recent years, the ceRNA hypothesis has proved that lncRNA can competitively bind to miRNA to regulate the expression of target genes [14], which provides important clues for studying the occurrence and development mechanism of tumors as well as new ideas for early diagnosis and treatment of tumors. The regulatory network of ceRNA has been proved to play an important role in tumors such as gastric cancer, liver cancer, and prostate cancer [15–18]. The proposal of the ceRNA hypothesis and its verification in many other cancers have provided a reliable reference for exploring the mechanisms of the ceRNA regulatory network in SCLC.

In this study, the exosome exoRBase database was used to analyze the genetic data of exosomes in the normal population and peripheral blood of SCLC patients. 13 differentially expressed mRNA, 40 differentially expressed lncRNA, and 59 differentially expressed circRNA were screened out. A ceRNA network consisting of 5 mRNA nodes, 5 lncRNA nodes, 7 circRNA nodes, and 41 miRNA nodes was constructed using Cytoscape software. GO annotation enrichment analysis showed that mRNA was mainly enriched in "melanosome", "pigment granule", "late endosome membrane". The KEGG enrichment analysis showed that the mRNA differentially expressed in the regulatory network were mainly enriched in "Non-small cell lung cancer", "Leucocyte transendothelial migration r", "cell sentinel", "Rap1 signaling pathway", Among them, the most important differential gene RASSF3 was enriched in the "Non-small cell lung cancer" related pathway on "Ras signaling pathway" and "MAPK signaling pathway". RASF3 is the smallest protein gene in the C-terminal members of the RASSF family. RASSF3 plays a role in tumor inhibition by regulating apoptosis, p53-dependent DNA repair, and cell cycle [19]. Studies by Fukatsu1[20] et al. have shown that the expression level of RASSF3 is down-regulated in non-small cell lung cancer. The down-regulation of gene expression is closely related to the progressive phenotype of NSCLC, and in vitro studies have also shown that the down-regulation of RASSF3 increases the mobility of lung cancer

cells. Kudo et al. [21] showed that RASSF3 expression induced p53-dependent apoptosis, and its consumption weakened DNA damage-induced apoptosis. The Cytospace software screened out the Hub genes with the top 10 scores, indicating that the genes closely related to the occurrence and development of breast cancer were: HSA-MIRI-23B-3P, OIP5-AS1, MAP4K4, and HSA-MIRI-137. A literature search of the Hub gene revealed that the gene OIP5-AS1 was closely related to the occurrence and development of SCLC. OIP5-AS1, a gene reverse transcription product of OIP 5, is located on human chromosome 15q15.1. It is a newly discovered lncRNA that shows abnormal expression in malignant tumors such as lung cancer, cervical cancer, osteosarcoma, glioma, and melanoma, regulates malignant biological behaviors such as tumor proliferation, migration, and invasion, and is closely related to lymphatic metastasis and patient prognosis [22]. Wang et al. [23] found that the expression of OIP5-AS1 in lung cancer was increased and was closely related to the tumor size and prognosis of patients. The results showed that OIP5- AS1, as ceRNA, binds to MIRI-378A-3P and inhibits the expression of cyclin-dependent kinase 4/6 (CDK4 /6) downstream of MIRI-378A-3P, thereby promoting the proliferation of tumor cells. In the latest research, Zhang et al. [24] adopted the qRT-PCR method to detect the expression levels of OIP5-AS1 and miR-511-3p, and adopted MTT and Transwell methods to detect the cell proliferation, migration, and invasion. At the same time, the western blot method was used to detect the protein expression levels of CyclinD1 and MMP-2, and a double luciferase reporting experiment was used to detect the targeting relationship between OIP5-AS1 and miR-511-3p. The results showed that LncRNA OIP5-AS1 inhibited the proliferation, migration, and invasion of lung cancer cells by targeting and regulating the expression of miR-511-3p. Esfandi et al. [25] studied the expression of OIP5-AS1 in non-small cell lung cancer and the results showed that the expression level of OIP5-AS in tumor tissues was significantly reduced compared with those of non-tumor patients. These studies suggest that RASSF3 and OIP5-AS may be potential tumor-critical target genes for SCLC.

Conclusion

In this study, the exosome RNA related to the occurrence and development of SCLC was successfully identified, and the differentially expressed mRNA, lncRNA, and circRNA genes were screened out. Meanwhile, KEGG enrichment analysis was performed to construct the corresponding ceRNA network and identify the genes RASSF3 and OIP5-AS that are key to the occurrence and development of SCLC, so as to provide an exact target for future research on the occurrence and development of SCLC.

However, there are still the following limitations: The sample size of exosomes is small, which requires further clinical large-sample test verification; Lack of joint analysis with other databases; Lack of further basic research. Therefore, further experimental studies are needed to verify and explore the specific mechanism in the future.

Declarations

Author contributions

KLZ and JND wrote the main manuscript text, ZHC and JDX prepared figures 1-5, KLZ prepared table 1, JLC and LW edited manuscript.All authors reviewed the manuscript.

Funding

Jiangsu college students' innovation and entrepreneurship training program (No. 202113993016y)

Availability of data and materials

The data that support the findings of this study are publicly available in the exoRbase repository at http://www.exorbase.org/.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015 Mar 1,136(5):E359-86. doi: 10.1002/ijc.29210. Epub 2014 Oct 9. PMID: 25220842.
2. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin. 2015 Mar,65(2):87-108. doi: 10.3322/caac.21262. Epub 2015 Feb 4. PMID: 25651787.
3. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018 Nov,68(6):394-424. doi: 10.3322/caac.21492. Epub 2018 Sep 12. Erratum in: CA Cancer J Clin. 2020 Jul,70(4):313. PMID: 30207593.
4. Alvarado-Luna G, Morales-Espinosa D. Treatment for small cell lung cancer, where are we now?-a review. Transl Lung Cancer Res. 2016 Feb,5(1):26-38. doi: 10.3978/j.issn.2218-6751.2016.01.13. PMID: 26958491, PMCID: PMC4758961.
5. Farago AF, Keane FK. Current standards for clinical management of small cell lung cancer. Transl Lung Cancer Res. 2018 Feb,7(1):69-79. doi: 10.21037/tlcr.2018.01.16. PMID: 29535913, PMCID: PMC5835595.

6. Bi N, Cao J, Song Y, Shen J, Liu W, Fan J, He J, Shi Y, Zhang X, Lu N, Zhan Q, Wang L. A microRNA signature predicts survival in early stage small-cell lung cancer treated with surgery and adjuvant chemotherapy. PLoS One. 2014 Mar 17,9(3):e91388. doi: 10.1371/journal.pone.0091388. PMID: 24637927, PMCID: PMC3956664.
7. Rak J. Extracellular vesicles - biomarkers and effectors of the cellular interactome in cancer. Front Pharmacol. 2013 Mar 6,4:21. doi: 10.3389/fphar.2013.00021. PMID: 23508692, PMCID: PMC3589665.
8. Lässer C, Alikhani VS, Ekström K, Eldh M, Paredes PT, Bossios A, Sjöstrand M, Gabrielsson S, Lötvall J, Valadi H. Human saliva, plasma and breast milk exosomes contain RNA: uptake by macrophages. J Transl Med. 2011 Jan 14,9:9. doi: 10.1186/1479-5876-9-9. PMID: 21235781, PMCID: PMC3033821.
9. Zheng Yujun, Jiang Wei, Chen Dongyan, Wang Lei, Li Yanjun, Dai Lulu, Huang Lei, Wang Mingji. Research progress of exosome in malignant tumor [J]. Chinese Journal of Lung Cancer, 2020,23(08):689-694.
10. Salmena L, Poliseno L, Tay Y, Kats L, Pandolfi PP. A ceRNA hypothesis: the Rosetta Stone of a hidden RNA language? Cell. 2011 Aug 5,146(3):353-8. doi: 10.1016/j.cell.2011.07.014. Epub 2011 Jul 28. PMID: 21802130, PMCID: PMC3235919.
11. Chen Mengqing, Wang Wenjun. Research progress of ceRNA network and related research in respiratory diseases [J]. Modern Medicine and Health, 2017,33(03):399-401.
12. Leonardi GC, Gainor JF, Altan M, et al. Safety of Programmed Death-1 Pathway Inhibitors Among Patients With Non-Small-Cell Lung Cancer and Preexisting Autoimmune Disorders. J Clin Oncol. 2018,36(19):1905-1912. doi:10.1200/JCO.2017.77.0305
13. Chen F, Chen J, Yang L, et al. Extracellular vesicle-packaged HIF-1α-stabilizing lncRNA from tumour-associated macrophages regulates aerobic glycolysis of breast cancer cells. Nat Cell Biol. 2019,21(4):498-510. doi:10.1038/s41556-019-0299-0
14. Poliseno L, Salmena L, Zhang J, Carver B, Haveman WJ, Pandolfi PP. A coding-independent function of gene and pseudogene mRNAs regulates tumour biology. Nature. 2010,465(7301):1033-1038. doi:10.1038/nature09144
15. Poliseno L, Salmena L, Zhang J, Carver B, Haveman WJ, Pandolfi PP. A coding-independent function of gene and pseudogene mRNAs regulates tumour biology. Nature. 2010,465(7301):1033-1038. doi:10.1038/nature09144
16. Xia T, Liao Q, Jiang X, et al. Long noncoding RNA associated-competing endogenous RNAs in gastric cancer. Sci Rep. 2014,4:6088. Published 2014 Aug 15. doi:10.1038/srep06088
17. Zhang R, Guo Y, Ma Z, et al. Long non-coding RNA PTENP1 functions as a ceRNA to modulate PTEN level by decoying miR-106b and miR-93 in gastric cancer. Oncotarget. 2017,8(16):26079-26089. doi:10.18632/oncotarget.15317
18. Liu XH, Sun M, Nie FQ, et al. Lnc RNA HOTAIR functions as a competing endogenous RNA to regulate HER2 expression by sponging miR-331-3p in gastric cancer. Mol Cancer. 2014,13:92. Published 2014

Apr 28. doi:10.1186/1476-4598-13-92

19. Wang Lianjing, Liu Lihong. Research progress of RASSF gene family in tumor [J]. Modern Oncology Medicine, 2016,v.24, No.190(04):660-664.
20. Fukatsu A, Ishiguro F, Tanaka I, Kudo T, Nakagawa K, Shinjo K, Kondo Y, Fujii M, Hasegawa Y, Tomizawa K, Mitsudomi T, Osada H, Hata Y, Sekido Y. RASSF3 downregulation increases malignant phenotypes of non-small cell lung cancer. Lung Cancer. 2014 Jan,83(1):23-9. doi: 10.1016/j.lungcan.2013.10.014. Epub 2013 Oct 31. PMID: 24246507.
21. Kudo T, Ikeda M, Nishikawa M, Yang Z, Ohno K, Nakagawa K, Hata Y. The RASSF3 candidate tumor suppressor induces apoptosis and G1-S cell-cycle arrest via p53. Cancer Res. 2012 Jun 1,72(11):2901-11. doi: 10.1158/0008-5472.CAN-12-0572. Epub 2012 May 16. PMID: 22593196.
22. Zhao Yuqiao, Wang Weina, Hu Zengtao, Guan Canghai, Jiang Xingming. Research progress of expression and regulation effect of OIP5-AS1 in tumor [J]. Modern Medicine, 2020,48(07):911-915.
23. Wang M, Sun X, Yang Y, Jiao W. Long non-coding RNA OIP5-AS1 promotes proliferation of lung cancer cells and leads to poor prognosis by targeting miR-378a-3p. Thorac Cancer. 2018 Aug,9(8):939-949. doi: 10.1111/1759-7714.12767. Epub 2018 Jun 13. PMID: 29897167, PMCID: PMC6068457.
24. Zhang Yaosen, Lu Guojie, Zhong Huiling, Gao Jianwei, Chen Yayong, Hu Ruijuan. Effect of LncRNA OIP5-AS1 targeting miR-511-3p on inhibiting proliferation, migration and invasion of lung cancer cells [J]. Journal of Molecular Diagnosis and Therapy, 2021,13(02):229-233.
25. Esfandi F, Kholghi Oskooei V, Taheri F, Kiani A, Taheri M, Ghafouri-Fard S. Expression Analysis of OIP5-AS1 in Non-Small Cell Lung Cancer. Klin Onkol. 2018 Summer,31(4):260-263. English. doi: 10.14735/amko2018260. PMID: 30541307.

Figures

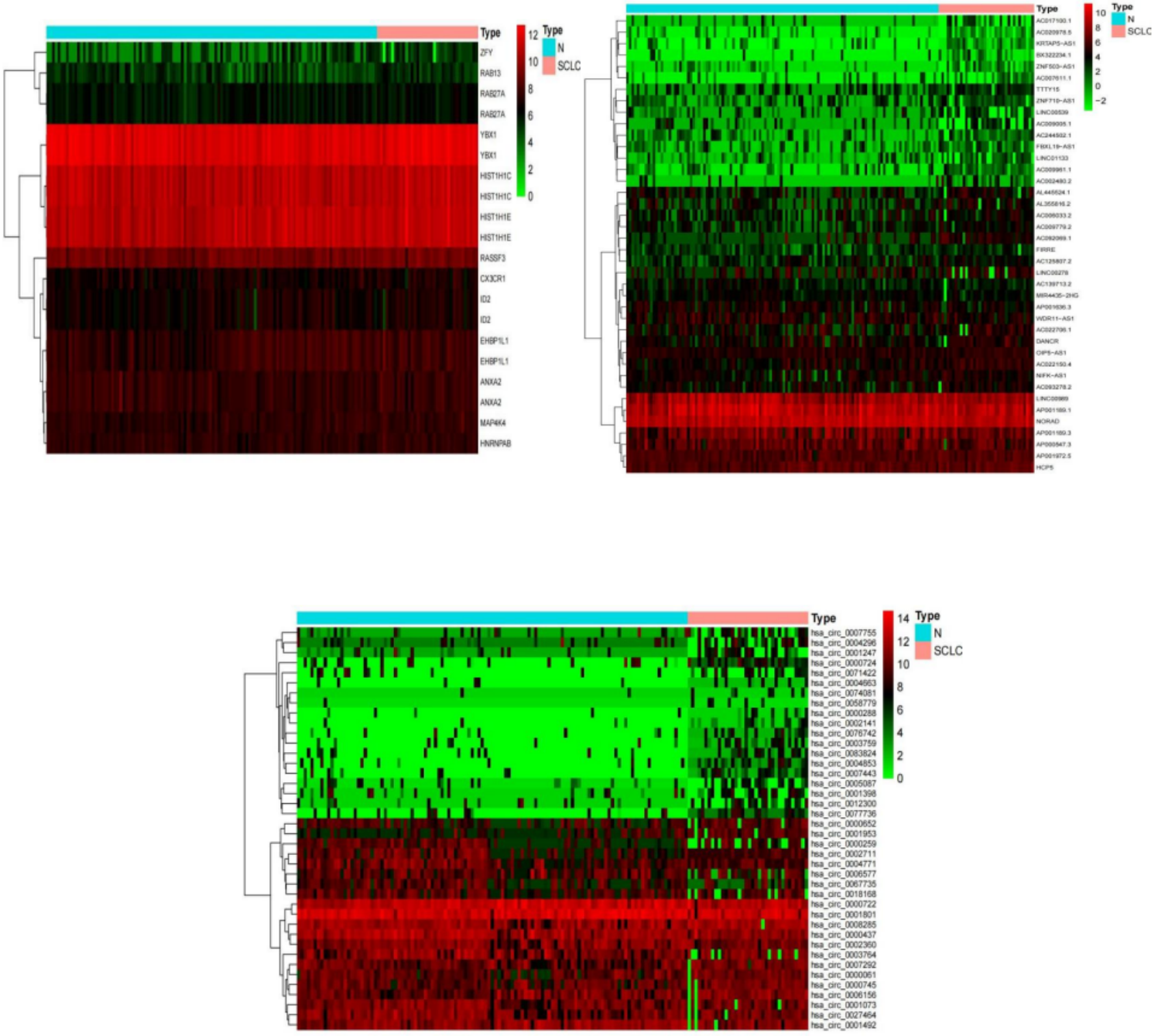

Figure 1

(A) heatmap of differential mRNA expression, (B) heatmap of differential circRNA expression, (C) heatmap of differential lncRNA expression

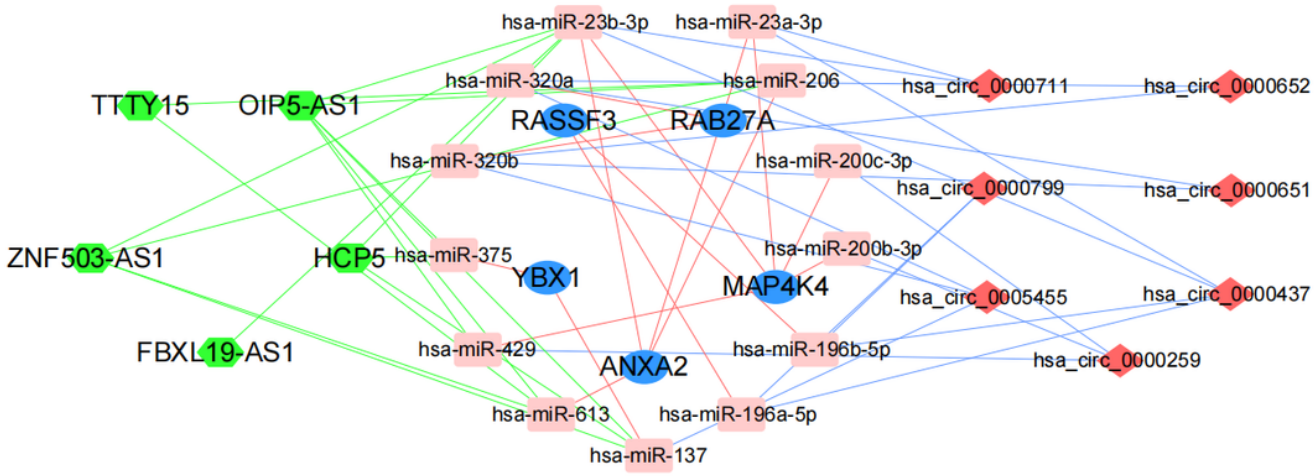

Figure 2

ceRNA network of differentially expressed genes

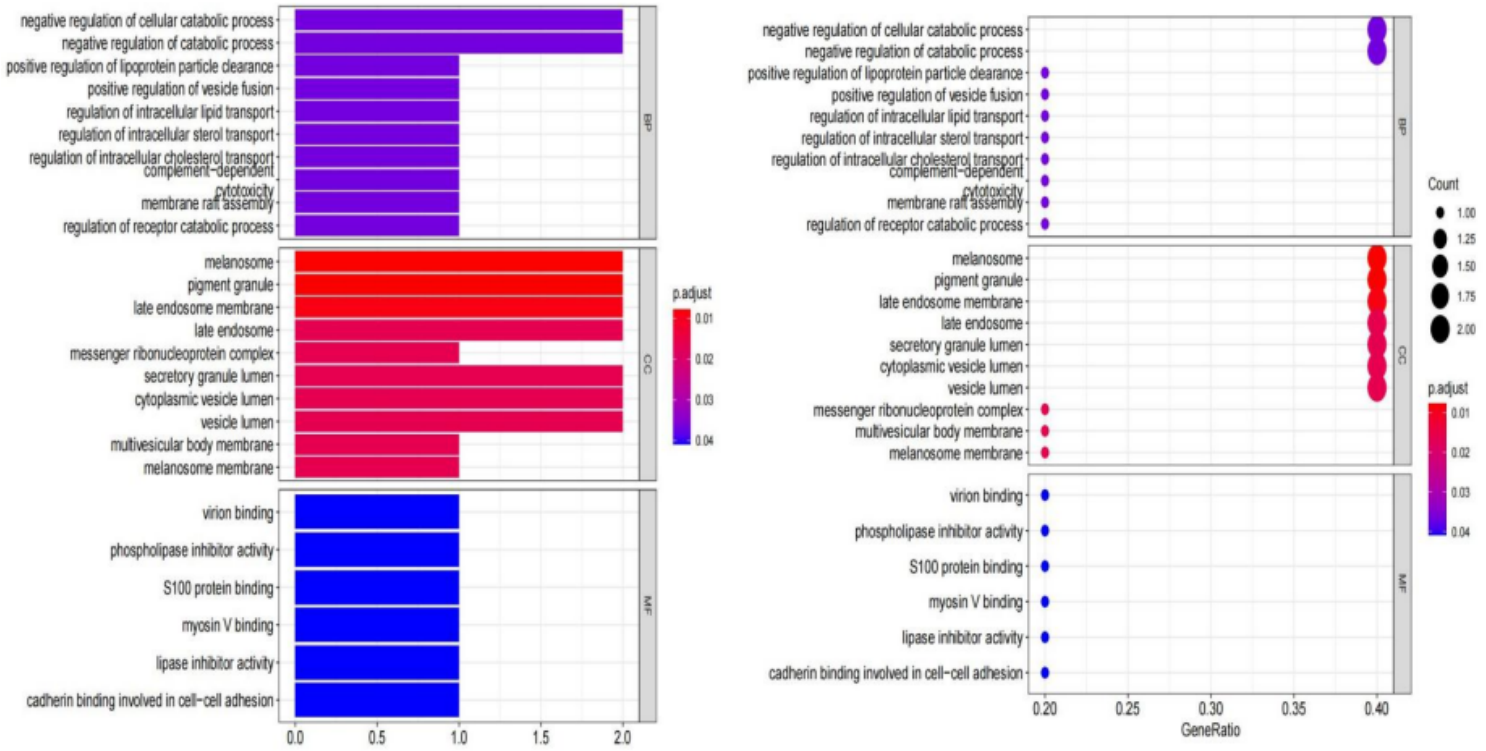

Figure 3

GO enrichment analysis of differential mRNA

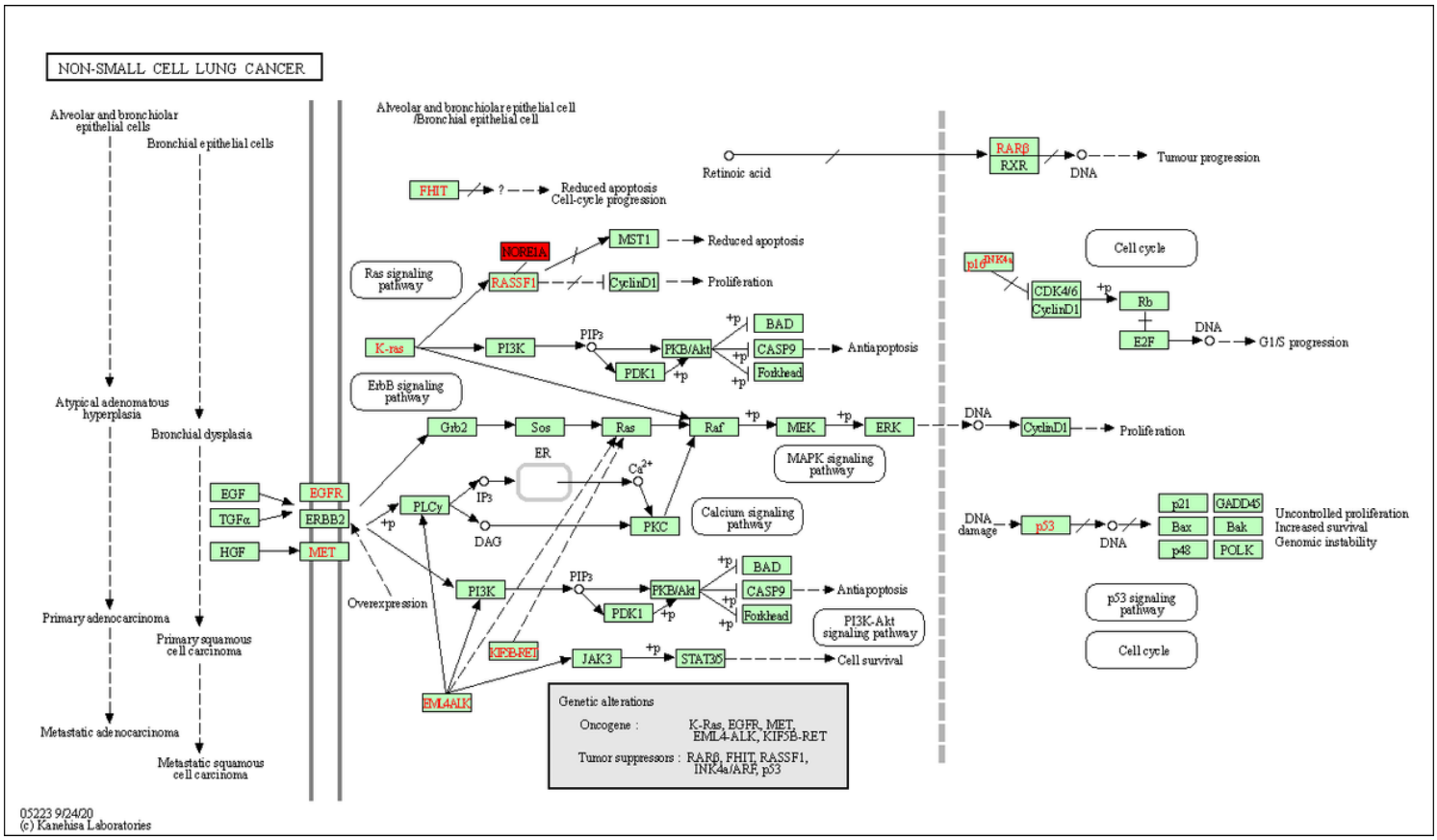

Figure 4

Non-small cell lung cancer signaling pathway mechanism diagram

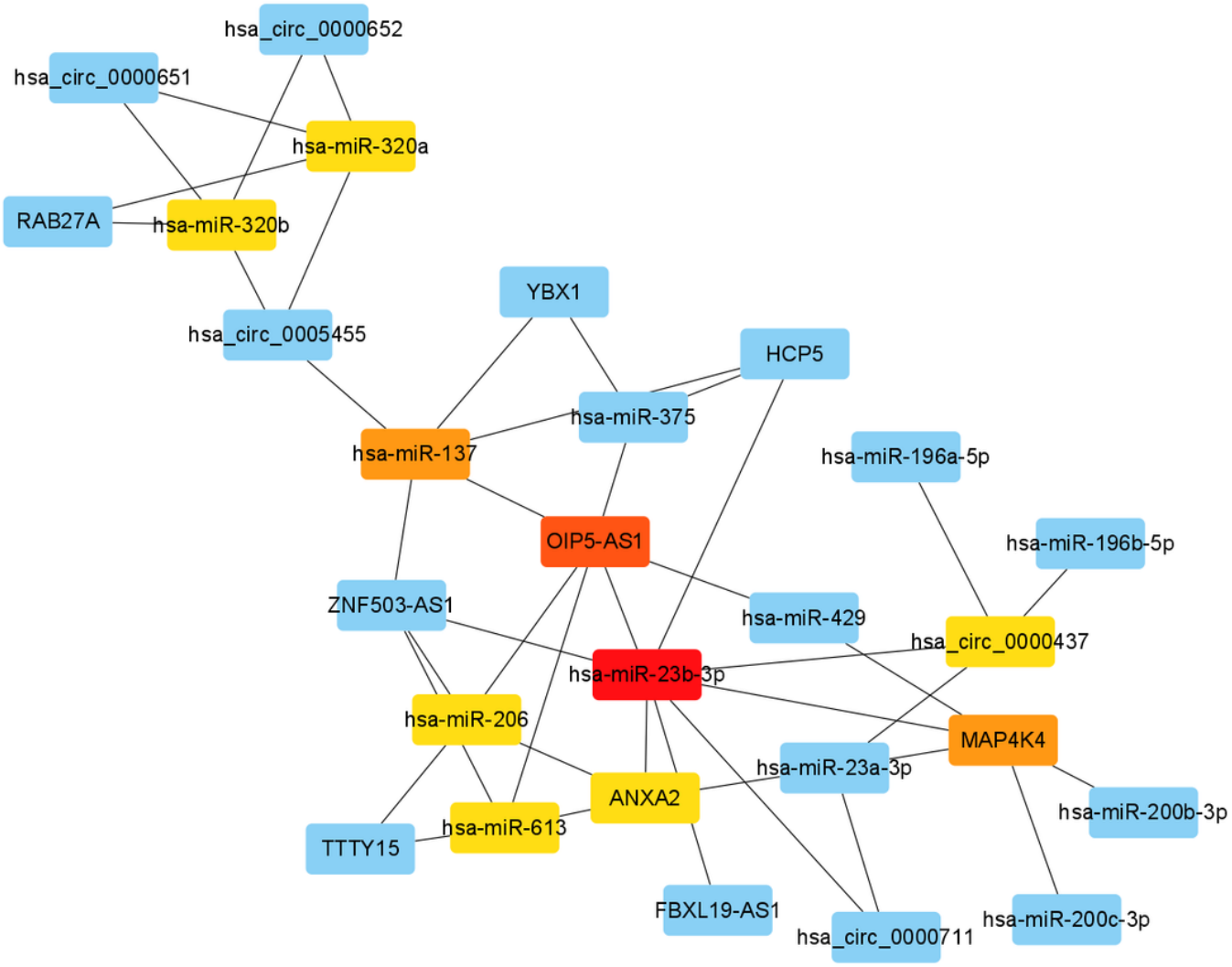

Figure 5

Hub gene network diagram