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Original Article

Exploring genes of rectal cancer based on protein interaction network

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Abstract: Objective: We have developed a protein-protein interaction network of rectal cancer which is based on genetic genes, and then predicted biological pathways underlying the molecular complexes in the network. The aim of this study is to analyze and summarize the genetic markers related to rectal cancer. Methods: The gene expression profile was downloaded from OMIM (Online Mendelian Inheritance in Man) database; The protein-protein interaction network of rectal cancer was established by Cytoscape 3.2; The molecular complexes in the network were detected by Clusterviz plugin and the pathways enrichment of molecular complexes were performed by DAVID online and Bingo plugin (The Biological Networks Gene Ontology tool). Results: a total of 127 rectal cancer-related genes were identified to express differentially in OMIM Database. The protein-protein interaction network of rectal cancer contained 966 nodes (proteins), 3377 edges (interactive relationships) and 7 molecular complexes (score >7.0). Regulatory effects of genes and proteins were focused on cell cycle, transcription regulation and cellular protein metabolic process. Genes such as *DDK1, sparcl1, wisp2, cux1, pabpc1, ptk2* and *htra1* were key nodes in PPI network. The discovery of rectal cancer-related genes has a great significance on exploring mechanism, distinguishing cancer tissues and exploring new treatments for rectal cancer.

Keywords: Protein-protein interaction networks, rectal cancer, molecular complexes, pathway, genes

Introduction

Rectal cancer is one of the common fatal malignant tumors in the world, which is secondly lethal cancer in United States as well as thirdly in Europe. Despite advances in detection and care, morbidity and mortality from rectal cancer continues to be at high level [1]. Early detection and diagnosis would be of great significance to reduce mortality and improve prognosis, as well as, identifying those who were at the highest risk and improving triage would have the vital impact on rectal cancer. A few studies have shown that rectal cancer is a prime paradigm for cancer genetics which can be prevented by early detection of the pre-disease (neoplastic) state. Therefore, the roles of genetics in rectal cancer have been critical to the missions of disease prevention, early detection and effective treatment.

As report goes, approximately 10% of well defined hereditary rectal cancer has special syndromes [2], such as slow growth, low potential risk of carcinomas and empowerment to reduce the disease burden. It is well known that there are discrepancies in the diagnosis of gastrointestinal neoplasia between Western and Japanese pathologists [3]. So comparing with other malignant tumor, there will be more significant to discover the process of rectal cancer [4]. Up to now, genetic markers of rectal cancer can be summarized by the following six aspects: Genomic instability, CpG island methylator phenotype, specific microthe related genes (specific related genes), proteins and pathways for hereditary rectal cancer.

A large number of mutations, mismatch, inactivation of tumor suppressor genes and activations of oncogenes are involved in RNAs, his-

Table 1. The genes related to rectal cancers

Symbol	Aliases	Exon_count
KRAS	C-K-RAS, CFC2, K-RAS2A, K-RAS2B, K-RAS4A, K-RAS4B, KI-RAS1, KRAS2, NS, NS3, RASK2, KRAS	6
HIF1A	HIF-1A, HIF-1alpha, HIF1, HIF1-ALPHA, MOP1, PASD8, bHLHe78	16
TP53	BCC7, LFS1, P53, TRP53	12
TYMS	HST422, TMS, TS	7
EGFR	ERBB, ERBB1, HER1, NISBD2, PIG61, mENA	30
VEGFA	MVCD1, VEGF, VPF	9
CXCL12	IRH, PBSF, SCYB12, SDF1, TLSF, TPAR1	6
SLC2A1	CSE, DYT17, DYT18, DYT9, EIG12, GLUT, GLUT-1, GLUT1, GLUT1DS, HTLVR, PED	10
PROM1	AC133, CD133, CORD12, MCDR2, MSTP061, PROML1, RP41, STGD4	39
ALDH1A1	ALDC, ALDH-E1, ALDH1, ALDH11, HEL-9, HEL-S-53e, HEL12, PUMB1, RALDH1	13
MTHFR		14
ERBB2	CD340, HER-2, HER-2/neu, HER2, MLN 19, NEU, NGL, TKR1	32
CD44	CDW44, CSPG8, ECMR-III, HCELL, HUTCH-I, IN, LHR, MC56, MDU2, MDU3, MIC4, Pgp1	21
EZR	CVIL, CVL, HEL-S-105, VIL2	14
MMP7	MMP-7, MPSL1, PUMP-1	6
CEACAM7	CGM2	5
PEBP4	CORK-1, CORK1, GWTM1933, HEL-S-300, PEBP-4, PRO4408, hPEBP4	9
PPARG	CIMT1, GLM1, NR1C31, PPARG2, PPARgamma, PPARG	11
CTNNB1	CTNNB, MRD19, armadillo	17
SERPINE1	PAI, PAI-1, PAI1, PLANH1	9
BIRC5	API4, EPR-1	6
XRCC1	RCC	17
PIK3CA	CLOVE, CWS5, MCAP, MCM, MCMTC, PI3K, p110-alpha	23
HRAS	C-BAS/HAS, C-H-RAS, C-HA-RAS1, CTLO, H-RASIDX, HAMSV1, RASH1, p21ras, HRAS	7
CYP2E1	CPE1, CYP2E, P450-J, P450C2E	9
EZH2	ENX-1, ENX1, EZH1b, KMT6, KMT6A, WVS, WVS2, EZH2	25
MKI67	KIA, MIB-, MIB-1, PPP1R105	16
CA9	CAIX, MN	12
CEACAM1	BGP, BGP1, BGPI	10
DPYD	DHP, DHPDHASE, DPD	25
TGFA	TFGA	7
CEACAM5	CD66e, CEA	10
PDPK1	PDK1, PDPK2, PDPK2P, PRO0461	18
LGR5	FEX, GPR49, GPR67, GRP49, HG38	21
ETV4	E1A-F, E1AF, PEA3, PEAS3	14
APOE	AD2, APO-E, LDLCQ5, LPG	6
IL6	BSF2, HGF, HSF, IFNB2, IL-6	6
TGFB1	CED, DPD1, LAP, TGFB, TGFbeta	7
PTGS2	COX-2, COX2, GRIPGHS, PGG/HS, PGHS-2, PHS-2, hCox-2	10
CRP	PTX1	3
IL1B	IL-1, IL1-BETA, IL1F2	7
AKT1	AKT, CWS6, PKB, PKB-ALPHA, PRKBA, RAC, RAC-ALPHA	17
VDR	NR1I1, PPP1R163	11
TLR4	ARMD10, CD284, TLR-4, TOLL	4
GSTM1	GST1-1, GSTM1a-1a, GSTM1b-1b, GTH4, GTM1, H-B, MU, MU-1, GSTM1	8
PTEN	10q23del, BZS, CWS1, DEC, GLM2, MHAM, MMAC11, TEP1, PTEN	16
CDH1	Arc-1, CD324, CDHE, ECAD, LCAM, UVO	18
TERT	CMM9, DKCA2, DKCB4, EST2, PFBMFT1, TCS1, TP2, TRT, hEST2, hTRT	18
BCL2	Bcl-2, PPP1R50	6
CXCR4	CD184, D2S201E, FB22, HM89, HSY3RR, LAP-3, LAP3, LCR1, LESTR, NPY3R, NPYR, NPYRL, NPYY3R, WHIM, WHIMS	2
CCND1	BCL1, D11S287E, PRAD1, U21B31	6
HLA-DQB1	CELIAC1, HLA-DQB, IDDM1	6
RELA	NFKB3, p65	11
CASP3	CPP32, CPP32B, SCA-1	8

HLA-G	MHC-G	8
MAPK3	ERK-1, ERK1, ERT2, HS44KDAP, HUMKER1A, P44ERK1, P44MAPK, PRKM3, p44-ERK1, p44-MAPK	10
MMP1	CLG, CLGN	10
APC	BTPS2, DP2, DP2.5, DP3, GS, PPP1R46	18
CYP19A1	ARO, ARO1, CPV1, CYAR, CYP19, CYPXIX, P-450AROM	13
ERCC2	COFS2, EM9, TFIIH, TTD, TTD1, XPD	24
TCF7L2	TCF-4, TCF4	21
F3	CD142, TF, TFA	6
TP73	P73	17
LCN2	24p3, MSFI, NGAL	7
RUNX1	AML1, AML1-EVI-1, AMLCR1, CBF2alpha, CBFA2, EVI-1, PEBP2aB, PEBP2alpha	13
FGFR2	BBDS, BEK, BFR-1, CD332, CEK3, CFD1, ECT1, JWS, K-SAM, KGFR, TK14, TK25	23
CHEK2	CDS1, CHK2, HuCds1, LFS2, PP1425, RAD53, hCds1	22
PLAU	ATF, BDPLT5, QPD, UPA, URK, u-PA	12
TIMP1	CLGI, EPA, EPO, HCI, TIMP	6
RAD51	BRCC5, FANCR, HRAD51, HsRad51, HsT16930, MRMV2A, RECA, RAD51	13
PLK1	PLK, STPK13	10
POU5F1	OCT3, OCT4, OTF-3, OTF3, OTF4, Oct-3, Oct-4	6
XRCC3	CMM6	10
SOX2	ANOP3, MCOPS3	1
PDGFRB	CD140B, IBGC4, IMF1, JTK12, PDGFR, PDGFR-1, PDGFR1	26
STK11	LKB1, PJS, hLKB1	13
DKK1	DKK-1, SK	4
EPAS1	ECYT4, HIF2A, HLF, MOP2, PASD2, bHLHe73	17
CFLAR	CASH, CASP8AP1, CLARP, Casper, FLAME, FLAME-1, FLAME1, FLIP, I-FLICE, MRIT, c-FLIP, c-FLIPL, c-FLIPR, c-FLIPS	14
FOS	AP-1, C-FOS, p55	4
SKP2	FBL1, FBXL1, FLB1, p45	12
NRAS	ALPS4, CMNS, N-ras, NCMS1, NS6, NRAS	7
CCNE1	CCNE, pCCNE1	12
IL23R		14
PPARD	FAAR, NR1C2, NUC1, NUCI, NUCII, PPARB	11
RPS6KB1	PS6K, S6K, S6K-beta-1, S6K1, STK14A, p70 S6KA, p70(S6K)-alpha, p70-S6K, p70-alpha	19
ANXA1	ANX1, LPC1	15
PTGS1	COX1, COX3, PCOX1, PES-1, PGG/HS, PGHS-1, PGHS1, PHS1, PTGHS	13
BLM	BS, RECQ2, RECQL2, RECQL3	25
CD163	M130, MM130	17
SPINK1	PCTT, PSTI, Spink3, TATI, TCP	5
CLDN1	CLD1, ILVASC, SEMP1	4
PDCD4	H731	13
IFNGR1	CD119, IFNGR, IMD27A, IMD27B	9
IL24	C49A, FISP, IL10B, MDA7, MOB5, ST16	7
ABCC4	MOAT-B, MOATB, MRP4	35
ALOX12	12-LOX, 12S-LOX, LOG12	14
BIRC7	KIAP, LIVIN, ML-IAP, MLIAP, RNF50	7
SATB1		16
TFF3	ITF, P1B, TFI	3
CSF3R	CD114, GCSFR	18
RBL2	P130, Rb2	25
RPS6KA1	HU-1, MAPKAPK1A, RSK, RSK1, p90Rsk	26
FIGF	VEGF-D, VEGFD	7
TPSAB1	TPS1, TPS2, TPSB1	6
GSK3A		11
ABCC3	ABC31, EST90757, MLP2, MOAT-D, MRP3, cMOAT2	32
MIR137	MIRN137, miR-137	1
TAZ	BTHS, CMD3A, EFE, EFE2, G4.5, LVNCX, Taz1	11
UGT2B15	HLUG4, UDPGT 2B8, UDPGT2B15, UDPGTH3, UGT2B8	6
PPP1R13L	IASPP, NKIP1, RAI, RAI4	14

REG4	GISP, REG-IV, RELP	7
WISP1	CCN4c, WISP1i, WISP1tc, WISP1	6
ASNS	ASNSD, TS11	15
UMPS	OPRT	7
F2RL2	PAR-3, PAR3	2
LIMS1	PINCH, PINCH-1, PINCH1	16
MUC6	MUC-6	33
RSF1	HBXAP, RSF-1, XAP8, p325	16
MYCL	L-Myc, LMYC1, bHLHe38, MYCL	2
RPS6KB2	KLS, P70-beta, P70-beta-1, P70-beta-2, S6K-beta2, S6K2, SRK, STK14B, p70(S6K)-beta, p70S6Kb	16
RNF7	CKBBP1, ROC2, SAG	4
RPS6KA2	HU-2, MAPKAPK1C, RSK, RSK3, S6K-alpha, S6K-alpha2, p90-RSK3, pp90RSK3	26
SPARCL1	MAST 9, MAST9, PIG33, SC1	14
SPEN	HIAA0929, MINT, RBM15C, SHARP	15
SEMA4C	M-SEMA-F, SEMACL1, SEMAF, SEMAI	19
DNAJC12	JDP1	6

tone modification, gene mutation and protein biomarkers. The protein-protein interaction network, which is a model of biological molecular interactions, can more clearly show the genes, proteins and pathogenesis in the development process of the disease [5]. These genetic traits may partially explain the geographical variance in rectal cancer incidence and mortality as well as the differences between hereditary and sporadic rectal cancer [6].

Materials and methods

Methods

OMIM (Online Mendelian Inheritance in Man) is a comprehensive, authoritative, daily updated human phenotype database, containing more than 12000 genes of all human genetic diseases, and mainly focusing on hereditary diseases. In addition, text messages, related reference information, sequence records, maps, and related databases are available for each gene [7, 8]. This study started from August 22 (2015), searched "rectal cancer" in the OMIM database and obtained human genes associated with rectal cancer information. The construction of gene/protein interaction networks: Rectal cancer associated genes were submitted to Cytoscape 3.2.1 plugin Agilent Literature Search 2.8 (USA Agilent Technologies company) and Pubmed [9]. False positive interaction information was removed from retrieval results. Then, gene/protein interaction relations were read in Cytoscape 3.2.1 and visualized [10].

MODE algorithm in Cytoscape 3.2.1 web analytics plugin Clusterviz of 1.2 was administrated to make the correlation analysis for the area of the construction of biological networks [11, 12]. By analyzing the network structure, proteins were grouped to form molecular compounds in the entire network and shown in Cytoscape according to the correlation integral value. The areas with integral values higher than 3 were regarded as molecular compounds. The gene/protein names contained in the molecular compounds were submitted to The Database for Annotation, Visualization and Integrated Discovery [13, 14]. By retrieving Kyoko Encyclopedia of Genes and Genomes (KEGG) Database, biological pathways involved in chronic myelogenous leukaemia heredity were identified. Then the Biological pathways data were submitted to Bingo (in Networks Gene Ontology tool) for enrichment analysis.

Protein networks were constructed based on the rectal cancer-related genes, nodes (proteins) and edges (interaction between), molecular complexes in the network and its associated interaction points and nodes (protein) and the edge (interaction between), analyze the biological pathways has involved in the molecular complexes.

Results

Rectal cancer related genes in OMIM

According the OMIM database retrieval, it can found that 127 genes were reported to be associated with rectal cancer. After screening and deleting duplicate genes, 127 related genes were identified, which were shown in **Table 1**.

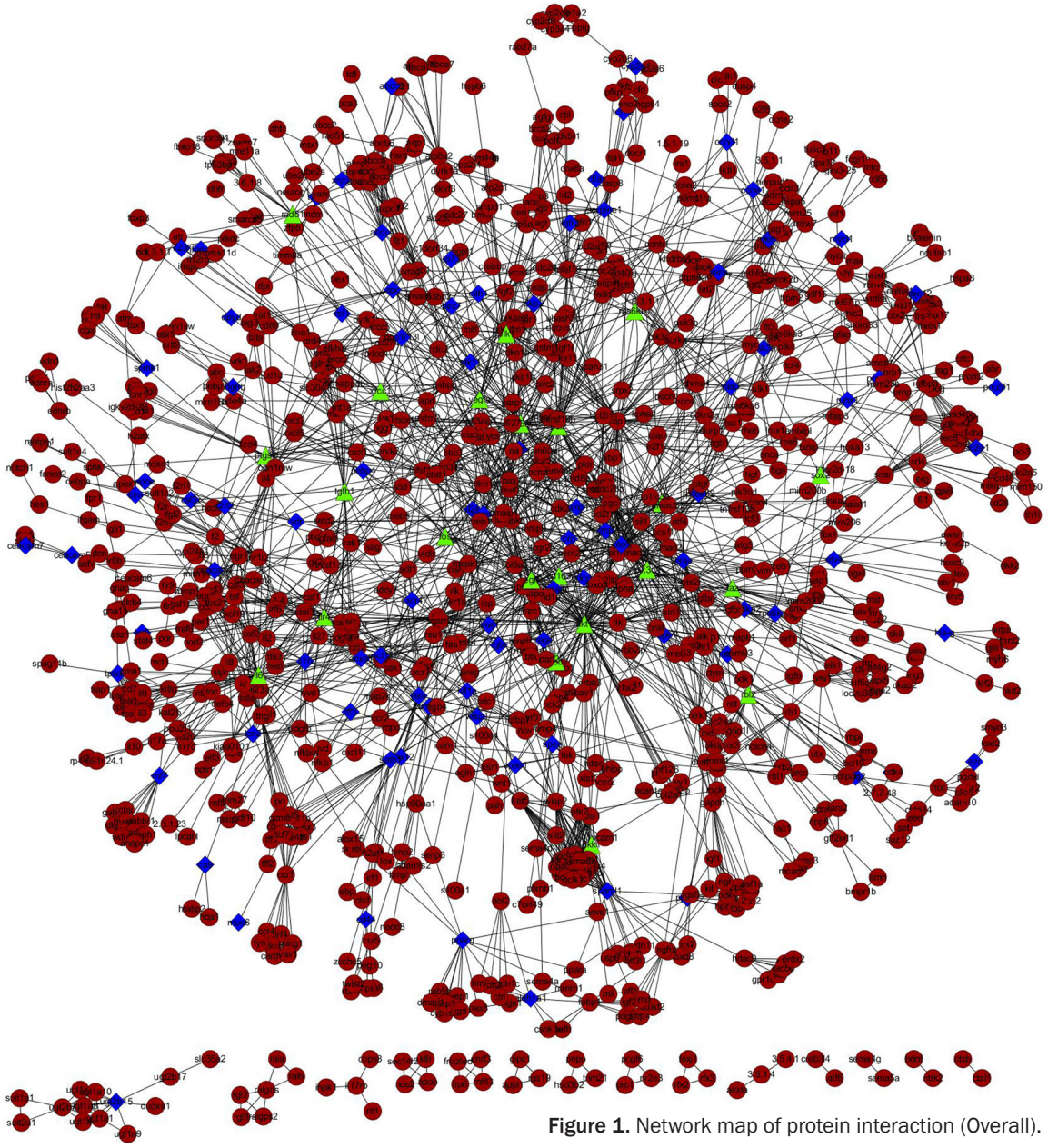


Figure 1. Network map of protein interaction (Overall).

Through text mining, 127 genetic-related genes shown that there was a network diagram with 996 nodes (proteins), 3377 edges (interactions). As shown in **Figures 1-3**, the diamond is represented OMIM genetic disease related proteins, while the round represented the proteins obtained from text mining. As shown in **Figure 1**, the protein-protein interaction network of rectal cancer is extremely complex. The edges intersect with each other and several clusters emerge in the figure. The more edges among the genes, the correlation of the genes is more tightening. So the genes formed the round network at the top of **Figure 1** connected with each other more tightly than the genes in the bottom.

After removing the protein molecule in the network, the relationship between proteins in network became more clear, in the centre part of protein-protein network, the relationship between protein complexes emerged closer, however, at the farther edge of the network, the relationship of them became looser, as shown in **Figure 2**. As shown in **Figure 3**, some common genes and pathways such as jak2-stat1, Kras, P53, etc as well as the genes associated with them were found.

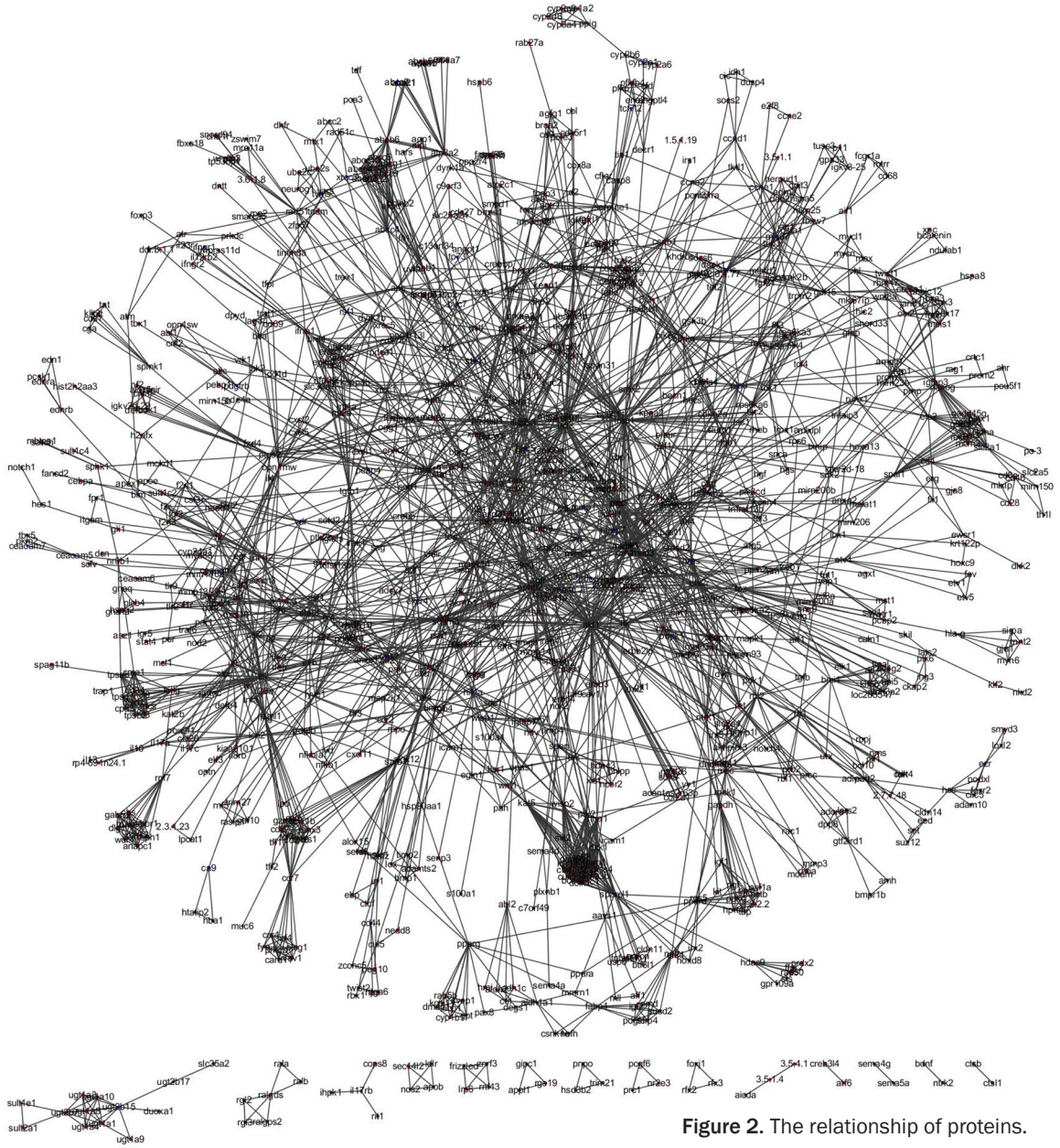
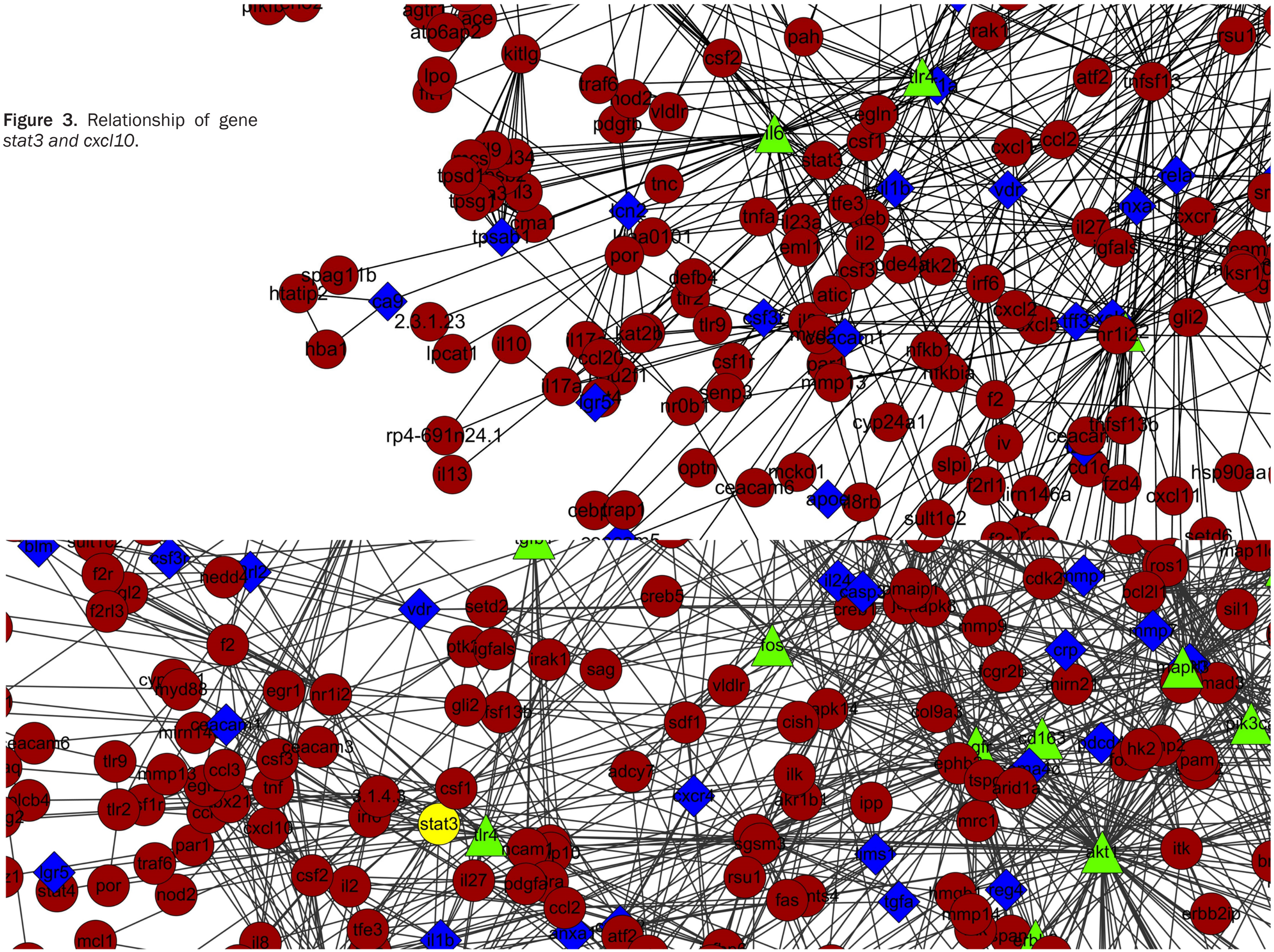


Figure 2. The relationship of proteins.

Network topology attribute analysis

Network topology attribute analysis has shown that the connectivity of nodes in the network (the number of nodes in the network) obeys descending distribution, i.e. with the increase of edges connected to the node, correspondingly the number of nodes decrease, so it can be seen that the gene-protein interaction networks are scale-free networks [15]. We found that the connectivity of nodes in the network greater than or equal to 25 corresponds to a sharp reduction in the number of nodes **Figure 4**. Therefore, we regarded the nodes which the connectivity is greater than/equal to 20 as the key nodes (hub). Key nodes (connectivity score) included: Hif1a (25), cdkn1b (25), rb1 (26), plau (26), brca1 (27), asns (28), pcna (28), Vegfa (29), stat1 (29), cdkn2a (29), egfr (30), tp53 (71). (The horizontal axis represents between nodes, and the ordinate represents the connectivity degree of protein interaction network. And the graphic in the table represents each node in the network). It can be seen that the connectivity (the number of nodes in the network) of nodes in the network obeys descend-

Figure 3. Relationship of gene *stat3 and cxcl10*.



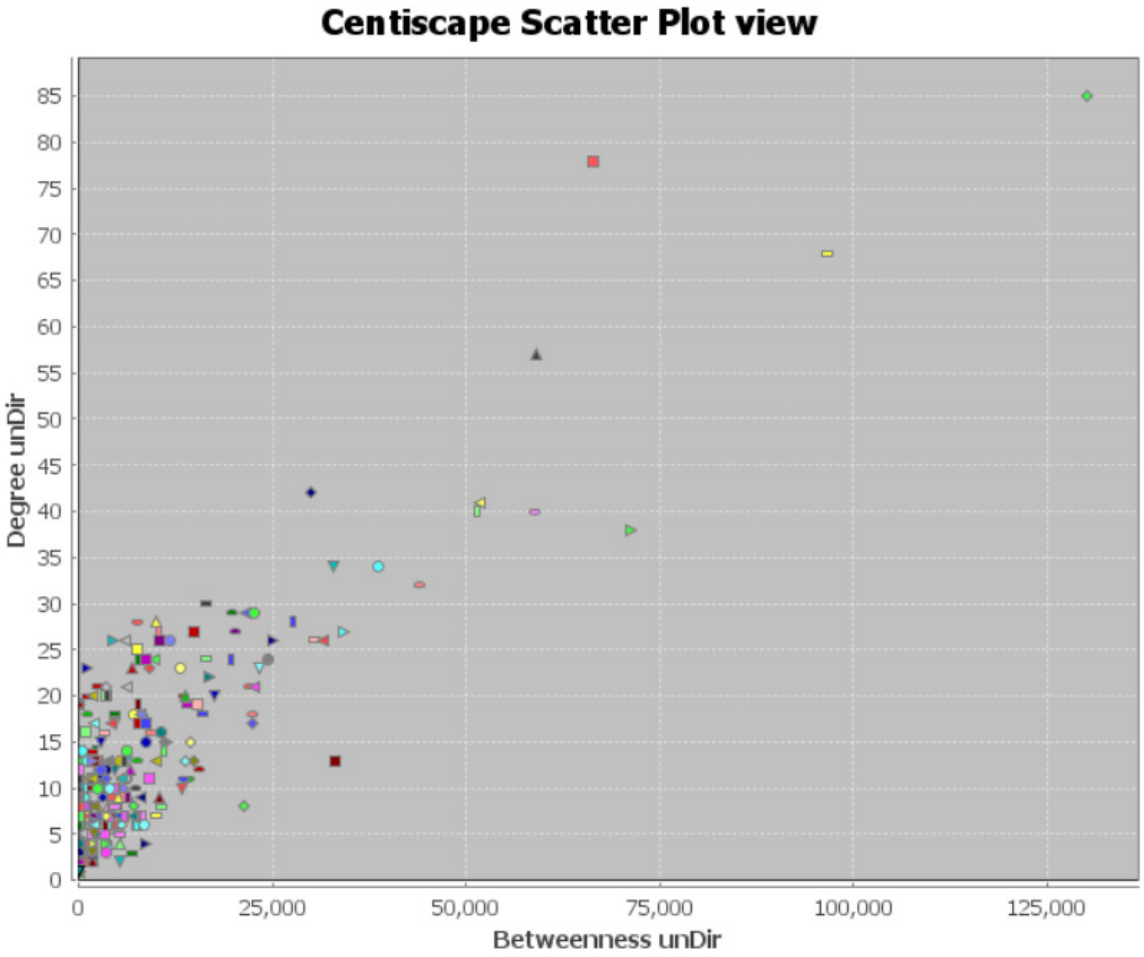


Figure 4. Connectivity degree of each node and betweenness comparison.

ing distribution, while the connectivity is greater than/equal to 25, the number of nodes corresponding to a sharp decrease.

The detection of molecular complexes

According MCOMD algorithm analysis, analyze the correlation between genes in network and calculate the score, the number of nodes, the number of edges. There is a total of 74 molecular complexes and 7 of them showed correlation integral values higher than 7.0 (**Figure 5**).

The details of the relationship of proteins in molecular complexes 7 were shown in **Figure 6**. The whole network has a total of six parts, including mitogen-activated protein kinase, Specific microRNAs, SRY-related HMG-box, matrix metalloproteinases, cyclin D.

Molecular complex pathway enrichment

Submit the genes of the protein complexes online to obtain the relevant pathways, and the result was shown in **Table 2**. We can see that the biological pathways of protein complexes 1 didn't exist, and other complexes contained different pathways. Regulatory effects of genes and proteins mainly focused on cell cycle, transcription regulation, and cellular protein metabolic process.

Bingo results have shown the gene oncology hierarchical network to the biological processes (**Figure 7**). The size of the node represents the number of the genes, the depth of the node color represents the *P* values. Diagrams have presented the main biological processes of cluster1, 4, 6, 7 containing metabolic regulation, transcriptional regulation, biosynthesis, cell differentiation and gene expression regulation and signal transduction, etc.

Discussions

Based on a large number of research references, the progression of rectal cancer is a multi-

Rank 1	Score 20	Node 20	Edges 190
Rank 2	Score 20	Node 20	Edges 190
Rank 3	Score 14	Node 14	Edges 91
Rank 4	Score 11.662	Node 78	Edges 449
Rank 5	Score 3.143	Node 21	Edges 66
Rank 6	Score 9	Node 9	Edges 36
Rank 7	Score 7.673	Node 56	Edges 221

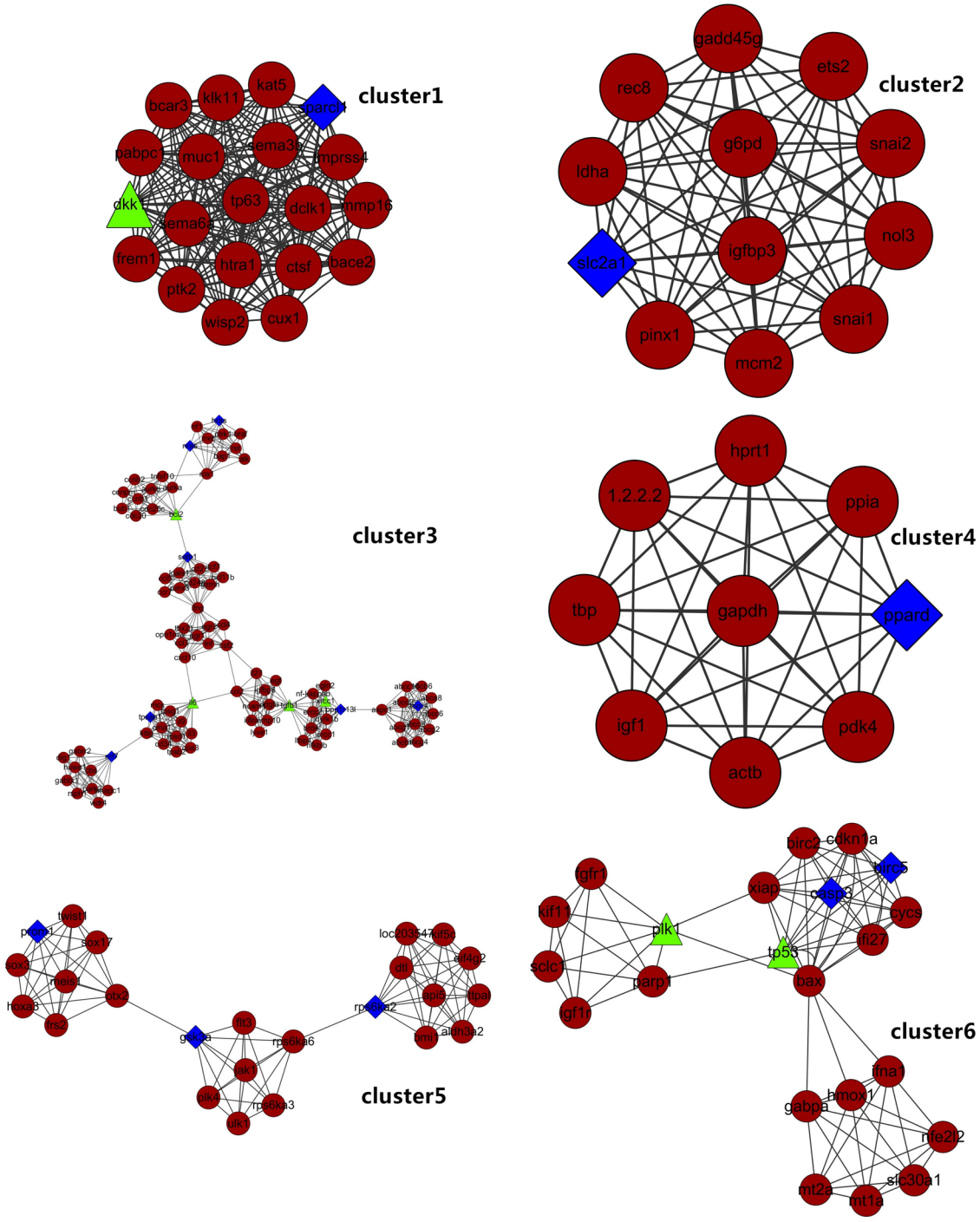


Figure 5. Molecular complexes obtained by MCOMD algorithm analysis.

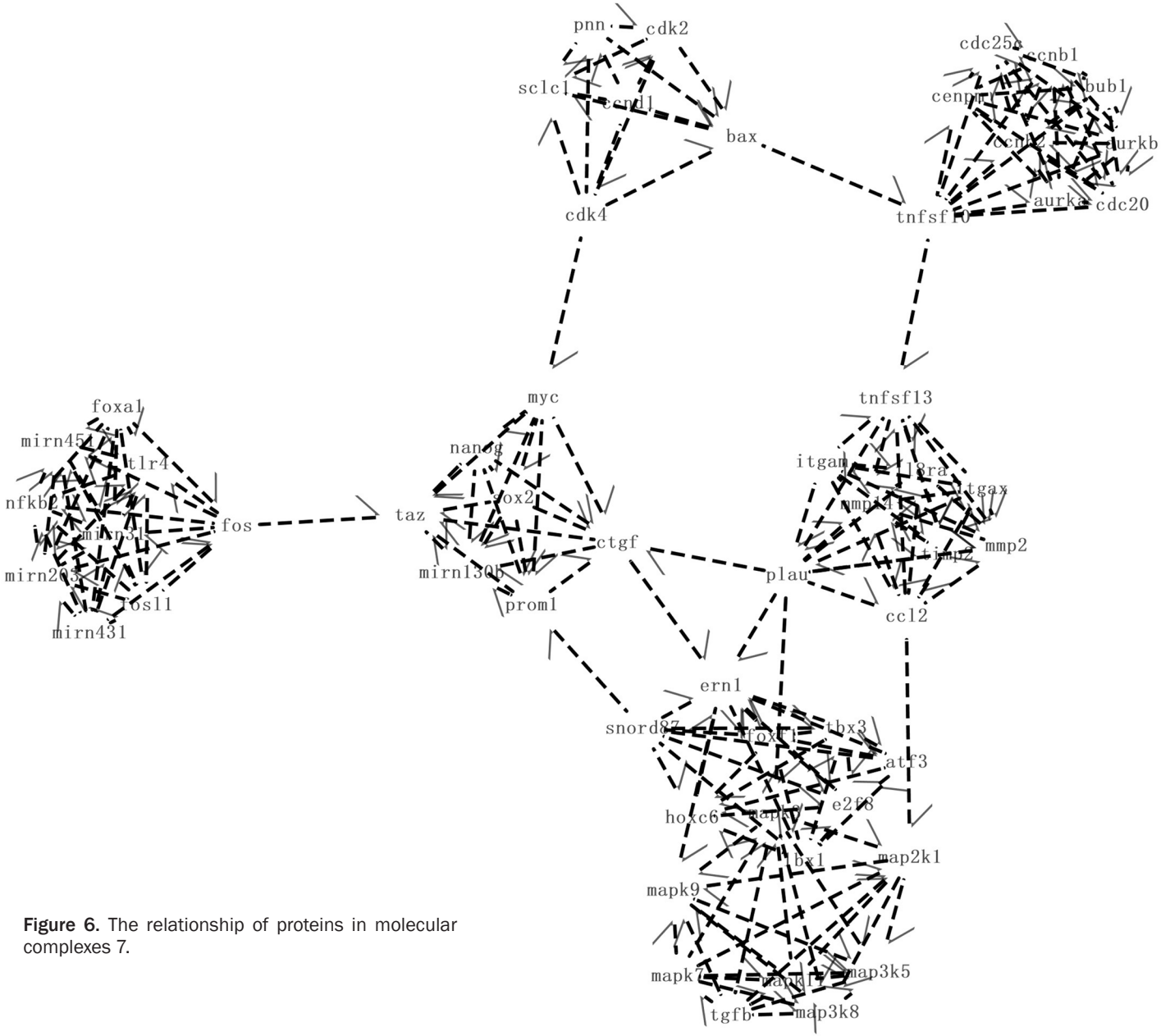


Figure 6. The relationship of proteins in molecular complexes 7.

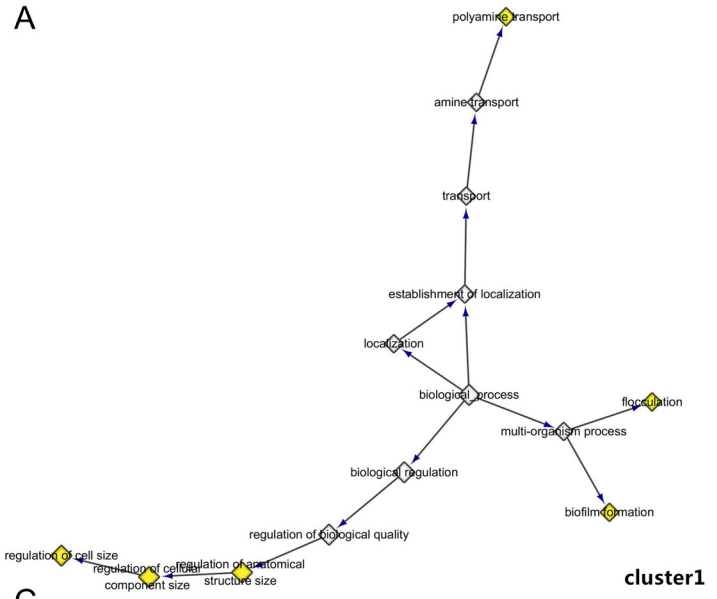
Table 2. Enrichment of pathways related to molecular complexes

Category	Term	*P* Value	Genes	FDR
Cluster1				
KEGG_PATHWAY	hsa04360: Axon guidance	0.006073822	SEMA6A, PTK2, SEMA3B	3.843791544
EC_NUMBER	3.4.21.-	0.009036531	HTRA1, KLK11, TMPRSS4	4.848129606
PANTHER_PATHWAY	P00004: Alzheimer disease-presenilin pathway	0.019326937	BACE2, MMP16, KAT5	11.44756514
Cluster2				
KEGG_PATHWAY	hsa04630: Jak-STAT signaling pathway	3.32E-22	IL23R, IL6ST, SOCS1, STAT1, TYK2, IL12RB2, STAT4, IL23A, IL12RB1, IFNG, IL12A, JAK2, IL12B, IFNGR2, IFNGR1	2.53E-19
BIOCARTA	h_no2il12Pathway: NO2-dependent IL 12 Pathway in NK cells	1.28E-10	IL12RB2, TYK2, STAT4, IL12RB1, IFNG, IL12A, JAK2	1.10E-07
BIOCARTA	h_th1th2Pathway: Th1/Th2 Differentiation	2.81E-09	IL12RB2, IL12RB1, IFNG, IL12A, IL12B, IFNGR2, IFNGR1	2.42E-06
BIOCARTA	h_IL12Pathway: IL12 and Stat4 Dependent Signaling Pathway in Th1 Development	2.81E-09	IL12RB2, TYK2, STAT4, IL12RB1, IFNG, IL12A, JAK2	2.42E-06
KEGG_PATHWAY	hsa04060: Cytokine-cytokine receptor interaction	3.57E-09	IL12RB2, IL23A, IL12RB1, IL23R, IL6ST, IFNG, IL12A, IL12B, IFNGR2, IFNGR1	2.72E-06
BIOCARTA	h_ifngPathway: IFN gamma signaling pathway	4.16E-08	IFNG, JAK2, STAT1, IFNGR2, IFNGR1	3.57E-05
BIOCARTA	h_nktPathway: Selective expression of chemokine receptors during T-cell polarization	7.64E-07	IL12RB2, IL12RB1, IFNG, IL12A, IFNGR2, IFNGR1	6.57E-04
PANTHER_PATHWAY	P00035: Interferon-gamma signaling pathway	6.85E-06	IFNG, JAK2, STAT1, IFNGR2, IFNGR1	0.004406679
PANTHER_PATHWAY	P00038: JAK/STAT signaling pathway	8.34E-05	STAT4, SOCS1, JAK2, STAT1	0.053656257
BBID	12.IL-6_type_cytok-signal-transduct	8.71E-05	TYK2, IL6ST, SOCS1, JAK2, STAT1	0.07288153
PANTHER_PATHWAY	P00036: Interleukin signaling pathway	9.85E-05	IL12RB2, STAT4, IL23A, IL12RB1, IL6ST, IL12A, STAT1	0.063347144
BIOCARTA	h_tidPathway: Chaperones modulate interferon Signaling Pathway	2.84E-04	IFNG, JAK2, IFNGR2, IFNGR1	0.243475935
BBID	48.mice_minus_JAKs_and_STATs	7.11E-04	TYK2, STAT4, JAK2, STAT1	0.593475439
PANTHER_PATHWAY	P00031: Inflammation mediated by chemokine and cytokine signaling pathway	7.32E-04	TYK2, STAT4, IFNG, JAK2, STAT1, IFNGR2, IFNGR1	0.470260756
BBID	75.Stats_activators_of_Apoptosis	0.00193497	IFNG, JAK2, STAT1	1.607237902
KEGG_PATHWAY	hsa05330: Allograft rejection	0.004204138	IFNG, IL12A, IL12B	3.155617774
KEGG_PATHWAY	hsa04940: Type I diabetes mellitus	0.005691714	IFNG, IL12A, IL12B	4.251279397
EC_NUMBER	2.7.10.2	0.009766127	TYK2, JAK2	0.976612696
Cluster3				
REACTOME_PATHWAY	REACT_15518: Transmembrane transport of small molecules	1.40E-04	SLC38A2, SLC7A1, SLC7A5, SLC7A11	0.07222524
REACTOME_PATHWAY	REACT_13: Metabolism of amino acids	5.32E-04	SLC38A2, SLC7A1, ASNS, SLC7A5, SLC7A11	0.274131661
Cluster4				
KEGG_PATHWAY	hsa05200: Pathways in cancer	8.49E-14	EGFR, CEBPA, IL6, EPAS1, STAT5A, MET, TP53, KITLG, CDH1, BIRC5, NFKB1, RB1, TGFB1, AKT1, MAPK1, NRAS, LAMB4, CDKN2A, HIF1A, KRAS, VEGFA, PIK3CA	9.07E-11
KEGG_PATHWAY	hsa05219: Bladder cancer	6.35E-11	EGFR, NRAS, MAPK1, CDKN2A, KRAS, VEGFA, TP53, CDH1, RB1, THBS1	6.79E-08
KEGG_PATHWAY	hsa05218: Melanoma	4.01E-10	EGFR, AKT1, NRAS, MAPK1, CDKN2A, KRAS, MET, TP53, PIK3CA, CDH1, RB1	4.29E-07
KEGG_PATHWAY	hsa05212: Pancreatic cancer	4.63E-10	EGFR, AKT1, MAPK1, CDKN2A, KRAS, VEGFA, TP53, PIK3CA, NFKB1, RB1, TGFB1	4.94E-07
KEGG_PATHWAY	hsa05220: Chronic myeloid leukemia	7.02E-10	AKT1, NRAS, MAPK1, CDKN2A, KRAS, STAT5A, TP53, PIK3CA, NFKB1, RB1, TGFB1	7.50E-07
KEGG_PATHWAY	hsa05211: Renal cell carcinoma	7.70E-09	AKT1, NRAS, MAPK1, HIF1A, KRAS, EPAS1, MET, VEGFA, PIK3CA, TGFB1	8.23E-06
KEGG_PATHWAY	hsa05223: Non-small cell lung cancer	1.81E-08	EGFR, AKT1, NRAS, MAPK1, CDKN2A, KRAS, TP53, PIK3CA, RB1	1.93E-05

KEGG_PATHWAY	hsa05214: Glioma	6.34E-08	EGFR, AKT1, NRAS, MAPK1, CDKN2A, KRAS, TP53, PIK3CA, RB1	6.78E-05
PANTHER_PATHWAY	P04398: p53 pathway feedback loops 2	2.17E-07	AKT1, NRAS, CDKN2A, KRAS, MAPK14, TP53, PIK3CA, RB1, TP73	1.98E-04
KEGG_PATHWAY	hsa05213: Endometrial cancer	3.04E-07	EGFR, AKT1, NRAS, MAPK1, KRAS, TP53, PIK3CA, CDH1	3.25E-04
KEGG_PATHWAY	hsa05210: Colorectal cancer	6.20E-07	EGFR, AKT1, MAPK1, KRAS, MET, TP53, PIK3CA, BIRC5, TGFB1	6.62E-04
KEGG_PATHWAY	hsa05221: Acute myeloid leukemia	6.57E-07	CEBPA, AKT1, NRAS, MAPK1, KRAS, STAT5A, PIK3CA, NFKB1	7.01E-04
KEGG_PATHWAY	hsa05215: Prostate cancer	9.71E-07	EGFR, AKT1, NRAS, MAPK1, KRAS, TP53, PIK3CA, NFKB1, RB1	0.001037757
KEGG_PATHWAY	hsa04722: Neurotrophin signaling pathway	1.17E-06	AKT1, NRAS, MAPK1, BDNF, KRAS, MAPK14, TP53, PIK3CA, NFKB1, TP73	0.00125362
KEGG_PATHWAY	hsa04010: MAPK signaling pathway	2.69E-06	EGFR, AKT1, MAPK1, NRAS, BDNF, KRAS, ARRB2, MAPK14, GADD45G, TP53, NFKB1, TGFB1, RASA1	0.002871532
BIOCARTA	h_erythPathway: Erythrocyte Differentiation Pathway	3.22E-06	IL3, IL6, IL9, KITLG, TGFB1, EPO	0.003887971
REACTOME_PATHWAY	REACT_16888: Signaling by PDGF	9.59E-06	NRAS, MAPK1, KRAS, STAT5A, PIK3CA, THBS1, RASA1	0.007693883
PANTHER_PATHWAY	P00056: VEGF signaling pathway	1.68E-05	AKT1, NRAS, MAPK1, HIF1A, KRAS, MAPK14, VEGFA, PIK3CA	0.015328038
EC_NUMBER	3.4.21.59	4.75E-05	TPSAB1, TPSB2, TPSD1, TPSG1	0.030526793
KEGG_PATHWAY	hsa04370: VEGF signaling pathway	4.94E-05	AKT1, NRAS, MAPK1, KRAS, MAPK14, VEGFA, PIK3CA	0.052708911
REACTOME_PATHWAY	REACT_11061: Signalling by NGF	5.63E-05	AKT1, MAG, NRAS, MAPK1, KRAS, MAPK14, PIK3CA, NFKB1, SORCS3	0.045131702
KEGG_PATHWAY	hsa04664: Fc epsilon RI signaling pathway	6.17E-05	AKT1, NRAS, MAPK1, IL3, KRAS, MAPK14, PIK3CA	0.065876411
KEGG_PATHWAY	hsa04150: mTOR signaling pathway	9.18E-05	AKT1, MAPK1, HIF1A, STK11, VEGFA, PIK3CA	0.097993218
PANTHER_PATHWAY	P00005: Angiogenesis	9.21E-05	AKT1, NRAS, MAPK1, NOTCH1, HIF1A, KRAS, MAPK14, VEGFA, PIK3CA, BIRC5, RASA1	0.084242254
PANTHER_PATHWAY	P00018: EGF receptor signaling pathway	1.11E-04	EGFR, AKT1, NRAS, MAPK1, KRAS, MAPK14, STAT5A, PIK3CA, RASA1	0.101309728
KEGG_PATHWAY	hsa04012: ErbB signaling pathway	1.14E-04	EGFR, AKT1, NRAS, MAPK1, KRAS, STAT5A, PIK3CA	0.121813791
KEGG_PATHWAY	hsa05216: Thyroid cancer	1.18E-04	NRAS, MAPK1, KRAS, TP53, CDH1	0.126019896
BIOCARTA	h_hcmvPathway: Human Cytomegalovirus and Map Kinase Pathways	1.34E-04	AKT1, MAPK1, MAPK14, NFKB1, RB1	0.161807042
KEGG_PATHWAY	hsa04115: p53 signaling pathway	3.30E-04	CDKN2A, GADD45G, RPRM, TP53, THBS1, TP73	0.352478227
KEGG_PATHWAY	hsa04660: T cell receptor signaling pathway	3.75E-04	AKT1, NRAS, MAPK1, KRAS, MAPK14, PIK3CA, NFKB1	0.399792892
BIOCARTA	h_telPathway: Telomeres, Telomerase, Cellular Aging, and Immortality	3.86E-04	EGFR, AKT1, KRAS, TP53, RB1	0.465899729
PANTHER_PATHWAY	P04393: Ras Pathway	3.87E-04	AKT1, NRAS, MAPK1, CDKN2A, KRAS, MAPK14, PIK3CA	0.353518988
REACTOME_PATHWAY	REACT_9417: Signaling by EGFR	5.16E-04	EGFR, NRAS, MAPK1, KRAS, PIK3CA	0.413199584
KEGG_PATHWAY	hsa04662: B cell receptor signaling pathway	5.22E-04	AKT1, NRAS, MAPK1, KRAS, PIK3CA, NFKB1	0.556225736
KEGG_PATHWAY	hsa05222: Small cell lung cancer	8.79E-04	AKT1, LAMB4, TP53, PIK3CA, NFKB1, RB1	0.934847379
BIOCARTA	h_RacCycDPathway: Influence of Ras and Rho proteins on G1 to S Transition	0.001228749	AKT1, MAPK1, PIK3CA, NFKB1, RB1	1.475202636
KEGG_PATHWAY	hsa04320: Dorso-ventral axis formation	0.001386389	EGFR, MAPK1, NOTCH1, KRAS	1.471198696
REACTOME_PATHWAY	REACT_6900: Signaling in Immune system	0.001592713	MAG, NRAS, MAPK1, KRAS, CD34, PECAM1, PIK3CA, NFKB1, CDH1	1.270531117
PANTHER_PATHWAY	P00059: p53 pathway	0.001789034	AKT1, CDKN2A, GADD45G, TP53, PIK3CA, THBS1, TP73	1.624912242
KEGG_PATHWAY	hsa04510: Focal adhesion	0.001957264	EGFR, AKT1, MAPK1, LAMB4, MET, VEGFA, PIK3CA, THBS1	2.071273278
KEGG_PATHWAY	hsa04620: Toll-like receptor signaling pathway	0.002011203	AKT1, MAPK1, IL6, MAPK14, PIK3CA, NFKB1	2.127799484
KEGG_PATHWAY	hsa04060: Cytokine-cytokine receptor interaction	0.002108909	EGFR, IL3, IL6, MET, VEGFA, IL9, KITLG, TGFB1, EPO	2.230116541
PANTHER_PATHWAY	P00010: B cell activation	0.002214285	NRAS, MAPK1, KRAS, MAPK14, PIK3CA, NFKB1	2.007674836
REACTOME_PATHWAY	REACT_604: Hemostasis	0.002330368	MAG, NRAS, KRAS, VEGFA, PECAM1, PIK3CA, THBS1, TGFB1	1.854165541

KEGG_PATHWAY	hsa04630: Jak-STAT signaling pathway	0.002487246	AKT1, IL3, IL6, STAT5A, IL9, PIK3CA, EPO	2.62539532
PANTHER_PATHWAY	P00021: FGF signaling pathway	0.003144809	AKT1, NRAS, MAPK1, KRAS, MAPK14, PIK3CA, RASA1	2.840604013
BIOCARTA	h_il17Pathway: IL 17 Signaling Pathway	0.003157025	IL3, IL6, CD34, KITLG	3.750040719
BIOCARTA	h_stemPathway: Regulation of hematopoiesis by cytokines	0.003157025	IL3, IL6, IL9, EPO	3.750040719
PANTHER_PATHWAY	P04397: p53 pathway by glucose deprivation	0.003458487	AKT1, STK11, TP53, TP73	3.119958155
REACTOME_PATHWAY	REACT_498: Signaling by Insulin receptor	0.003756119	NRAS, MAPK1, KRAS, PIK3CA	2.973670175
KEGG_PATHWAY	hsa04110: Cell cycle	0.005068716	CDKN2A, GADD45G, PCNA, TP53, RB1, TGFB1	5.284031958
BIOCARTA	h_badPathway: Regulation of BAD phosphorylation	0.005426648	AKT1, MAPK1, IL3, KITLG	6.365799458
BIOCARTA	h_crebPathway: Transcription factor CREB and its extracellular signals	0.005426648	AKT1, MAPK1, MAPK14, PIK3CA	6.365799458
KEGG_PATHWAY	hsa04062: Chemokine signaling pathway	0.006278908	AKT1, NRAS, MAPK1, KRAS, ARRB2, PIK3CA, NFKB1	6.507599178
BIOCARTA	h_keratinocytePathway: Keratinocyte Differentiation	0.006958557	EGFR, CEBPA, MAPK1, MAPK14, NFKB1	8.094303481
KEGG_PATHWAY	hsa04914: Progesterone-mediated oocyte maturation	0.007248802	AKT1, MAPK1, KRAS, MAPK14, PIK3CA	7.477850945
KEGG_PATHWAY	hsa04640: Hematopoietic cell lineage	0.007248802	IL3, IL6, CD34, KITLG, EPO	7.477850945
KEGG_PATHWAY	hsa04210: Apoptosis	0.007548465	AKT1, IL3, TP53, PIK3CA, NFKB1	7.7757735
PANTHER_PATHWAY	P00036: Interleukin signaling pathway	0.007614161	AKT1, NRAS, MAPK1, IL6, KRAS, STAT5A, PIK3CA, RASA1	6.753977015
REACTOME_PATHWAY	REACT_216: DNA Repair	0.009001	MGMT, PCNA, XRCC1, ERCC1, ERCC2	6.996374809
PANTHER_PATHWAY	P00053: T cell activation	0.009738791	AKT1, NRAS, MAPK1, KRAS, PIK3CA, NFKB1	8.564577054
Cluster5				
KEGG_PATHWAY	hsa04120: Ubiquitin mediated proteolysis	6.19E-04	ANAPC1, RNF7, HUWE1, PARK2	0.370875716
EC_NUMBER	6.3.2.-	0.069187942	HUWE1, PARK2	14.94398228
Cluster6				
REACTOME_PATHWAY	REACT_1698: Metablism of nucleotides	5.07E-04	UMPS, ATIC, HPRT1	NaN
KEGG_PATHWAY	hsa00983: Drug metabolism	0.001025542	ITPA, UMPS, HPRT1	0.657964401
BIOCARTA	h_mapkPathway: MAPKinase Signaling Pathway	0.00306271	MAP3K9, MAP2K4, MAP3K10	2.110065352
PANTHER_PATHWAY	P05918: p38 MAPK pathway	0.005195037	MAP3K9, MAP2K4, MAP3K10	3.701051163
KEGG_PATHWAY	hsa00230: Purine metabolism	0.012459659	ITPA, ATIC, HPRT1	7.749728301
EC_NUMBER	2.7.11.25	0.030208436	MAP3K9, MAP3K10	16.18260742
KEGG_PATHWAY	hsa00860: Porphyrin and chlorophyll metabolism	0.038330298	COX10, COX15	22.23317069
PANTHER_PATHWAY	P00029: Huntington disease	0.04121774	MAP3K9, MAP2K4, MAP3K10	26.27015356
BIOCARTA	h_p38mapkPathway: p38 MAPK Signaling Pathway	0.045417275	MAP3K9, MAP2K4	27.61443797
BBID	100.MAPK_signaling_cascades	0.058659218	MAP2K4, MAP3K10	17.32821753
Cluster7				
KEGG_PATHWAY	hsa04914: Progesterone-mediated oocyte maturation	2.08E-08	CCNB1, CCNB2, MAP2K1, MAPK3, BUB1, MAPK9, MAPK11, CDC25C, CDK2	2.13E-05
KEGG_PATHWAY	hsa04114: Oocyte meiosis	1.46E-07	CCNB1, CCNB2, MAP2K1, MAPK3, BUB1, CDC20, AURKA, CDC25C, CDK2	1.50E-04
KEGG_PATHWAY	hsa04110: Cell cycle	3.96E-07	CCNB1, CCND1, CCNB2, BUB1, CDC20, CDK4, CDC25C, MYC, CDK2	4.05E-04
KEGG_PATHWAY	hsa05219: Bladder cancer	3.68E-06	CCND1, MAP2K1, MAPK3, CDK4, MYC, MMP2	0.00376453
KEGG_PATHWAY	hsa05210: Colorectal cancer	7.34E-06	FOS, CCND1, MAP2K1, BAX, MAPK3, MAPK9, MYC	0.007502731
KEGG_PATHWAY	hsa05200: Pathways in cancer	1.02E-05	FOS, CCND1, MAP2K1, BAX, MAPK3, MAPK9, NFKB2, CDK4, MYC, MMP2, CDK2	0.010452597
KEGG_PATHWAY	hsa04010: MAPK signaling pathway	1.43E-05	FOS, MAP3K5, MAP2K1, MAPK3, MAP3K8, MAPK9, MAPK11, NFKB2, MAPK7, MYC	0.014636534

REACTOME_PATHWAY	REACT_152: Cell Cycle, Mitotic	1.79E-05	CCNB1, CENPM, CCND1, CCNB2, BUB1, CDC20, AURKA, AURKB, CDK4, CDC25C, CDK2	0.012929573
KEGG_PATHWAY	hsa04912: GnRH signaling pathway	1.79E-05	MAP2K1, MAPK3, MAPK9, MAPK11, MAPK7, MMP14, MMP2	0.018347497
EC_NUMBER	2.7.11.24	2.02E-05	MAPK3, MAPK9, MAPK11, MAPK7	0.012135676
KEGG_PATHWAY	hsa04620: Toll-like receptor signaling pathway	2.13E-05	FOS, MAP2K1, MAPK3, MAP3K8, MAPK9, MAPK11, TLR4	0.02182043
PANTHER_PATHWAY	P00006: Apoptosis signaling pathway	2.68E-05	FOS, TNFSF10, MAP3K5, ATF3, BAX, MAPK3, MAPK9, NFKB2, MAPK7	0.02355655
KEGG_PATHWAY	hsa04660: T cell receptor signaling pathway	3.13E-05	FOS, MAP2K1, MAPK3, MAP3K8, MAPK9, MAPK11, CDK4	0.032014891
PANTHER_PATHWAY	P00054: Toll receptor signaling pathway	3.16E-05	MAP2K1, MAPK3, MAP3K8, MAPK9, MAPK11, TLR4, NFKB2	0.02781923
KEGG_PATHWAY	hsa04115: p53 signaling pathway	4.05E-05	CCNB1, CCND1, CCNB2, BAX, CDK4, CDK2	0.041438576
KEGG_PATHWAY	hsa04722: Neurotrophin signaling pathway	6.84E-05	MAP3K5, MAP2K1, BAX, MAPK3, MAPK9, MAPK11, MAPK7	0.069959614
BIOCARTA	h_mapkPathway: MAPKinase Signaling Pathway	3.55E-04	FOS, MAP3K5, MAP2K1, MAPK3, MAP3K8, MAPK9, MAPK11, MAPK7	0.400316292
KEGG_PATHWAY	hsa05216: Thyroid cancer	6.11E-04	CCND1, MAP2K1, MAPK3, MYC	0.622621821
PANTHER_PATHWAY	P00052: TGF-beta signaling pathway	6.33E-04	FOS, FOXF1, FOXA1, MAPK3, MAPK9, MAPK11, MAPK7, FOSL1	0.555596842
KEGG_PATHWAY	hsa05212: Pancreatic cancer	7.67E-04	CCND1, MAP2K1, MAPK3, MAPK9, CDK4	0.781138732
KEGG_PATHWAY	hsa05220: Chronic myeloid leukemia	8.95E-04	CCND1, MAP2K1, MAPK3, CDK4, MYC	0.91105286
PANTHER_PATHWAY	P00010: B cell activation	0.001400729	FOS, MAP2K1, MAPK3, MAPK9, MAPK11, NFKB2	1.225108429
BIOCARTA	h_p53Pathway: p53 Signaling Pathway	0.003024948	CCND1, BAX, CDK4, CDK2	3.364924295
KEGG_PATHWAY	hsa05213: Endometrial cancer	0.003370738	CCND1, MAP2K1, MAPK3, MYC	3.393288113
KEGG_PATHWAY	hsa05223: Non-small cell lung cancer	0.003753245	CCND1, MAP2K1, MAPK3, CDK4	3.77171584
PANTHER_PATHWAY	P00035: Interferon-gamma signaling pathway	0.004182552	MAPK3, MAPK9, MAPK11, MAPK7	3.618778393
KEGG_PATHWAY	hsa05221: Acute myeloid leukemia	0.004595499	CCND1, MAP2K1, MAPK3, MYC	4.600275355
PANTHER_PATHWAY	P00034: Integrin signalling pathway	0.005122253	MAP3K5, MAP2K1, ITGAX, MAPK3, MAPK9, MAPK11, MAPK7, ITGAM	4.415663351
KEGG_PATHWAY	hsa04621: NOD-like receptor signaling pathway	0.005544037	CCL2, MAPK3, MAPK9, MAPK11	5.525680097
KEGG_PATHWAY	hsa05214: Glioma	0.005798209	CCND1, MAP2K1, MAPK3, CDK4	5.772273682
REACTOME_PATHWAY	REACT_1538: Cell Cycle Checkpoints	0.007137442	CCNB1, CCNB2, CDC20, CDC25C, CDK2	5.054206969
KEGG_PATHWAY	hsa05218: Melanoma	0.008084875	CCND1, MAP2K1, MAPK3, CDK4	7.964786431
BIOCARTA	h_RacCycDPathway: Influence of Ras and Rho proteins on G1 to S Transition	0.008275776	CCND1, MAPK3, CDK4, CDK2	8.961786045
BIOCARTA	h_cellcyclePathway: Cyclins and Cell Cycle Regulation	0.009291865	CCNB1, CCND1, CDK4, CDK2	10.010086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amine transport
transport
establishment of localization
localization
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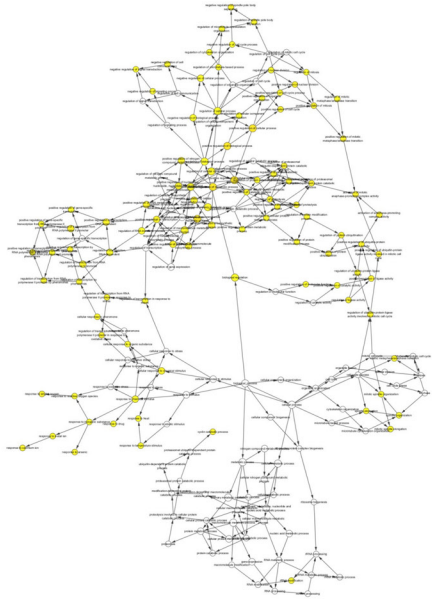
regulation of cellular component size
regulation of anatomical structure size
cluster1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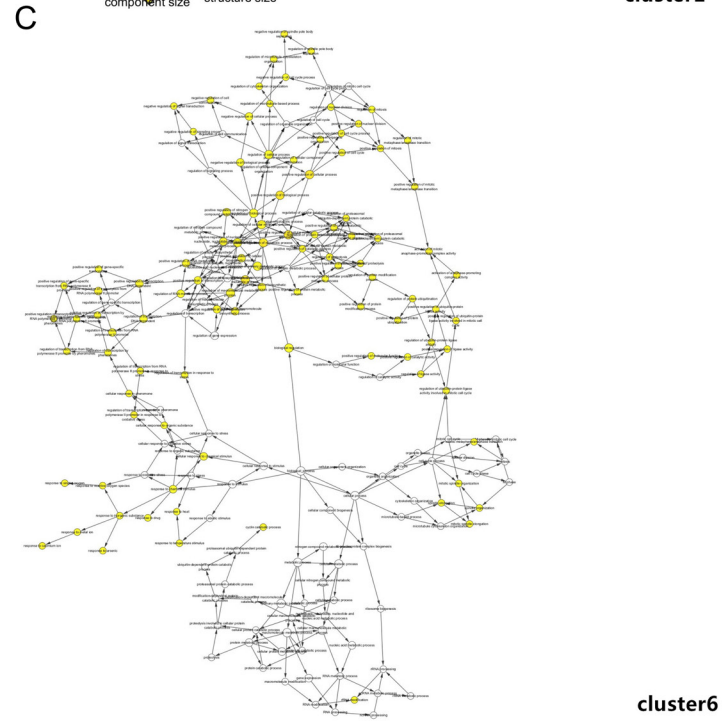
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cluster6

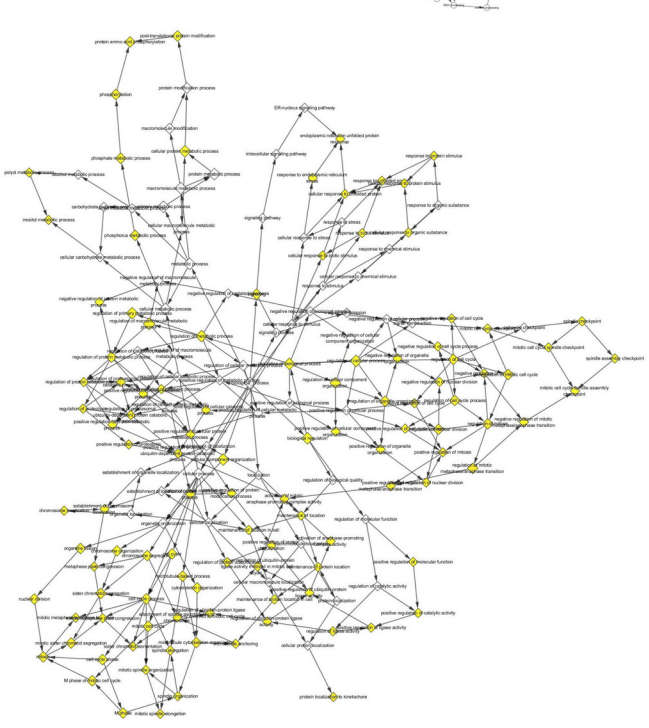
D
cluster7

Figure 7. A. Bingo results show that the basic structure of the biological cluster1; B. Bingo results show that the basic structure of the biological cluster4; C. Bingo results show that the basic structure of the biological cluster6; D. Bingo results show that the basic structure of the biological cluster7.

step process, containing overcome apoptosis, inhibiting senescence (infinite proliferation), secretion proliferation signal itself, not sensitive to growth signals, angiogenesis and invasion, which requires a large number of genes and proteins in action [16]. Genetic markers of rectal cancer can be summarized from the following six aspects: He first part is genomic instability, close to 12-17% of sporadic rectal cancer cases exist with microsatellite instability (MSI). At present, microsatellite instability-high-H (MSI) has become a positive prognosis of rectal cancer patients' overall survival [17]. 50-85% of Rectal cancer patients has chromosome aberration frequency, chromosome instability (CIN+) usually be associated with colorectal cancer patients' overall survival, progression-free survival (PFS) and poor prognosis after 5-fluorouracil therapy; The second part is CpG island methylator phenotype. Nearly 29.6% of the rectal cancer patients shown CpG island methylation phenotype-high (CIMP-H) [18], however, its value is still in research. Specific microRNAs and histone modification are another two aspects, which mainly associate with colorectal cancer patients' overall survival and progression-free serial, tumor metastasis, local invasion, tumor volume, tumor staging, treatment results, relapse and drug resistance.

What is more, gene mutations and protein biomarkers have brought a special significance. The APC gene mutant p.D1822V containing homozygous V/V would reduce the risk of rectal cancer [19]. According to the APC (rs565453 y rs1816769) and CTNNB1 (rs229303) gene polymorphisms, the death risk stratification in patients with rectal cancer can be analyzed. The APC gene mutant p.I1307K as risk factors of the rectal cancer among Ashkenazi Jewishes has been found [20]. The loss of PTEN gene in 22% of rectal cancer patients has caused no response to the EGFR inhibitors and higher risk of death [21]. And the clinical application of protein molecular markers colorectal cancer mainly included: early diagnosis (hnRNP A1, kininogen-1, adipophilin, Apo AI and C9, OLFM4), Prognosis (SM3, desmin, surviving, hTERT and NM23), Potential therapeutic targets (EB1) [22, 23]. Therefore, exploring the protein interaction network of tumors, analyzing the characteristics of the protein molecular interaction network, and excavating a variety of signaling pathway and the genes will provide a biological basis for the study of the molecular mechanism of tumor and the further treatment as well.

Bio-molecular network analysis is an important direction of systematic biology research. Large-scale human protein-protein network can provide new insights into protein functions, pathways, molecular machines and functional protein modules [24]. The function of bio-molecular often depends on modularization, the network module is made by a number of nodes in the conjunction of each other and has a stable structure which can often reflect a similar nature between the nodes [25, 26]. Analyzing the function module is the one of the most common method to analyze biological molecular network. According to 127 genes provided by OMIM, our research has built up protein interaction network of rectal cancer, which contains 996 nodes (proteins), 3377 edges (interactions). Due to the network is very large, the experimental introduced MCOMD algorithm to evaluate the network's regional integration through the correlation integral. Correlation integral described the proteins associated with the degree in the region. Proteins of the same molecular complex generally have the same biological function, and therefore we discovered the unknown gene functions or new molecular functional groups, such as cluster1.

Genes such as *DDK1, sparcl1, wisp2, cux1, pabpc1, ptk2* and *htra1* as the composition members of the cluster1 (score 20) in the centre have closely relationships with each other as well as other genes. It has reported that the secreted protein acidic and rich in cysteine-like 1 (*sparcl1*) is expressed in various normal tissues and many types of cancers. Another study has shown that marker *sparcl1* was significantly related to the prognosis and clinical pathological features of the CRC patients [27]. S*parcl1* expression increased with RT and is related to a better prognosis in rectal cancer patients with RT but not in patients without RT.

This result may help us to select the patients to the best suited preoperative RT. In the process of rectal cancer, gene WISP2 knockout significantly increased Caco-2 cell invasion and motility. Up-regulation of MMP2, -7 and -9 may indicate that WISP2 regulates invasion and motility through MMPs. Regulation of invasion by WISP2 may involve the WNT signalling pathway [28]. Thus, some studies have identified CUX1 as a pan-driver of tumorigenesis and uncover a potential strategy for treating CUX1-mutant tumors. So from cluster1 we predicted the effect of gene Cut1 to rectal cancer may be that CUX1 deficiency activates phosphoinositide 3-kinase (PI3K) signaling through directing transcriptional downregulation of the PI3K inhibitor PIK3IP1 (phosphoinositide-3-kinase interacting protein 1), leading to increased tumor growth and susceptibility to PI3K-AKT inhibition. And we also forecasted a few clones existing in colorectal cancer, containing gene mutation of ptk2, htra1 and PABPC1.

Rectal cancer is not demonstrated simply controlled by one particular gene or one signaling pathway, but by the complex gen network system which consist a variety of signaling pathways and multiple genes. In the signaling network, it is likely there is some “key regulatory point”. At last, a best understanding of chemotherapy molecular targets allowed the identification of genetic markers that can predict the response and/or the toxicity of anti-cancer drugs used in rectal cancers, which could be helpful in the future to propose for each patient a personalized treatment [29-31]. Mutations that can predict the response of new target therapies such as the inhibitors of the JAK kinase inhibitor AG4 90 in colorectal cancer have also been found and will allow the selection of patients who can have benefit from these new therapeutic drugs. The experiment dig out a variety of signaling pathways and genes which can provide reliable directions for molecular mechanism research of treatment, and it needs to be further verified.

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Disclosure of conflict of interest

None.

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References

[1] Spreadborough P and Doran C. The current thinking on colorectal cancer. J R Nav Med Serv 2015; 101: 47-54.

[2] Stoffel EM and Boland CR. Genetics and genetic testing in hereditary colorectal cancer. Gastroenterology 2015; 149: 1191-1203.

[3] Schlemper RJ, Dawsey SM, Itabashi M, Iwashita A, Kato Y, Koike M, Lewin KJ, Riddell RH, Shimoda T, Sipponen P, Stolte M and Watanabe H. Differences in diagnostic criteria for esophageal squamous cell carcinoma between Japanese and Western pathologists. Cancer 2000; 88: 996-1006.

[4] Schlussel AT, Gagliano RA Jr, Seto-Donlon S, Eggerding F, Donlon T, Berenberg J, Lynch HT. The evolution of colorectal cancer geneti cs-Part 1: From discovery to practice. J Gastrointest Oncol 2014; 5: 326-335.

[5] Zhou C, Teng WJ, Yang J, Hu ZB, Wang CC, Qin BN, Lv QL, Liu ZW and Sun CG. Construction of a protein-protein interaction network for chronic myelocytic leukemia and pathway prediction of molecular complexes. Asian Pac J Cancer Prev 2014; 15: 5325-5330.

[6] Macaron C, Heald B and Burke CA. Using genetics to identify hereditary colorectal polyposis and cancer syndromes in your patient. Curr Gastroenterol Rep 2015; 17: 463.

[7] Hamosh A, Scott AF, Amberger JS, Bocchini CA and McKusick VA. Online Mendelian Inheritance in Man (OMIM), a knowledgebase of human genes and genetic disorders. Nucleic Acids Res 2005; 33: D514-D517.

[8] Amberger J, Bocchini CA, Scott AF and Hamosh A. McKusick’s online Mendelian inheritance in man (OMIM). Nucleic Acids Res 2009; 37: D793-D796.

[9] Vailaya A, Bluvas P, Kincaid R, Kuchinsky A, Creech M and Adler A. An architecture for biological information extraction and representation. Bioinformatics 2005; 21: 430-438.

[10] Shannon P, Markiel A, Ozier O, Baliga NS, Wang JT, Ramage D, Amin N, Schwikowski B and Ideker T. Cytoscape: a software environment for integrated models of biomolecular interaction networks. Genome Res 2003; 13: 2498-2504.
[11] Chen L, Wang H, Zhang L, Li W, Wang Q, Shang Y, He Y, He W, Li X, Tai J and Li X. Uncovering packaging features of co-regulated modules based on human protein interaction and transcriptional regulatory networks. BMC Bioinformatics 2010; 11: 392.
[12] Wu BL, Zou HY, Lv GQ, Du ZP, Wu JY, Zhang PX, Xu LY and Li EM. Protein-protein interaction network analyses for elucidating the roles of LOXL2-delta72 in esophageal squamous cell carcinoma. Asian Pac J Cancer Prev 2014; 15: 2345-51.
[13] Dennis G Jr, Sherman BT, Hosack DA, Yang J, Gao W, Lane HC and Lempicki RA. DAVID: database for annotation, visualization, and integrated discovery. Genome Biol 2003; 4: P3.
[14] Huang da W, Sherman BT and Lempicki RA. Systematic and integrative analysis of large gene lists using DAVID bioinformatics resources. Nat Protoc 2009; 4: 44-57.
[15] Burkard TR, Rix U, Breitwieser FP, Superti-Furga G and Colinge J. A computational approach to analyze the mechanism of action of the kinase inhibitor bafetinib. PLoS Comput Biol 2010; 6: e1001001.
[16] Smolle MA, Pichler M, Haybaeck J and Gerger A. Genetic markers of recurrence in colorectal cancer. Pharmacogenomics 2015; 12: 1-14.
[17] Bacher JW, Sievers CK, Albrecht DM, Grimes IC, Weiss JM, Matkowskyj KA, Agni RM, Vyazunova I, Clipson L, Storts DR, Thliveris AT and Halberg RB. Improved detection of microsatellite instability in early colorectal lesions. PLoS One 2015; 7: e0132727.
[18] Lee DW, Han SW, Cha Y, Rhee YY, Bae JM, Cho NY, Lee KH, Kim TY, Oh DY, Im SA, Bang YJ, Jeong SY, Park KJ, Kang GH and Kim TY. Different prognostic effect of CpG island methylation according to sex in colorectal cancer patients treated with adjuvant FOLFOX. Clin Epigenetics 2015; 7: 63.
[19] Guerreiro CS, Cravo ML, Brito M, Vidal PM, Fidalgo PO and Leitão CN. The D1822V APC polymorphism interacts with fat, calcium, and fiber intakes in modulating the risk of colorectal cancer in Portuguese persons. Am J Clin Nutr 2007; 85: 1592-1597.
[20] Stern HS, Viertelhausen S, Hunter AG, O'Rourke K, Cappelli M, Perras H, Serfas K, Blumenthall A, Dewar D, Baumann E and Lagarde AE. APC I1307K increases risk of transition from polyp to colorectal carcinoma in Ashkenazi Jews. Gastroenterology 2001; 120: 392-400.
[21] Mao C, Zhou J, Yang Z, Huang Y, Wu X, Shen H, Tang J and Chen Q. KRAS, BRAF and PIK3CA mutations and the loss of PTEN expression in Chinese patients with colorectal cancer. PLoS One 2012; 7: e36653.
[22] Cappellani A, Di Vita M, Zanghi A, Veroux P, Cavallaro A, Lo Menzo E, Cacopardo B, Canzonieri V, Murabito P, Tirelli U, Berretta M. Biological and clinical markers in colorectal cancer: state of the art. Front Biosci (Schol Ed) 2010; 2: 422-31.
[23] Delektorskaya VV, Golovkov DA and Kushlinskii NE. Clinical significance of levels of molecular biological markers in zones of invasive frontline of colorectal cancer. Bull Exp Biol Med 2008; 146: 616-619.
[24] Ryu JY, Kim HU and Lee SY. Human genes with a greater number of transcript variants tend to show biological features of housekeeping and essential genes. Mol Biosyst 2015; 11: 2798-807.
[25] Chen L, Wang H, Zhang L, Li W, Wang Q, Shang Y, He Y, He W, Li X, Tai J and Li X. Uncovering packaging features of co-regulated modules based on human protein interaction and transcriptional regulatory networks. BMC Bioinformatics 2010; 7: 392.
[26] Kovács IA, Palotai R, Szalay MS and Csermely P. Community landscapes: an integrative approach to determine overlapping network module hierarchy, identify key nodes and predict network dynamics. PLoS One 2010; 5: e12528.
[27] Yu SJ, Yu JK, Ge WT, Hu HG, Yuan Y and Zheng S. SPARCL1, Shp2, MSH2, E-cadherin, p53, ADCY-2 and MAPK are prognosis-related in colorectal cancer. World J Gastroenterol 2011; 17: 2028-2036.
[28] Frewer KA, Sanders AJ, Owen S, Frewer NC, Hargest R, Jiang WG. A role for WISP2 in colorectal cancer cell invasion and motility. Cancer Genomics Proteomics 2013; 10: 187-96.
[29] Goh KI, Cusick ME, Valle D, Childs B, Vidal M, Barabási AL. The human diseases net work. Proc Natl Acad Sci U S A 2007; 104: 8685-8690.
[30] Yildirim MA, Goh KI, Cusick ME, Barabási AL and Vidal M. Drug-target network. Nat Biotechnol 2007; 25: 1119-1126.
[31] Hopkins AL. Network pharmacology: the next paradigm in drug discovery. Nat Chen Biol 2008; 4: 682-690.