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ORIGINAL ARTICLE

The Key Genes of Chronic Pancreatitis which Bridge Chronic Pancreatitis and Pancreatic Cancer Can be Therapeutic Targets

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Abstract An important question in systems biology is what role the underlying molecular mechanisms play in disease progression. The relationship between chronic pancreatitis and pancreatic cancer needs further exploration in a system view. We constructed the disease network based on gene expression data and protein-protein interaction. We proposed an approach to discover the underlying core network and molecular factors in the progression of pancreatic diseases, which contain stages of chronic pancreatitis and pancreatic cancer. The chronic pancreatitis and pancreatic cancer core network and key factors were revealed and then verified by gene set enrichment analysis of pathways and diseases. The key factors provide the microenvironment for tumor initiation and the change of gene expression level of key factors bridge chronic pancreatitis and pancreatic cancer. Some new candidate genes need further verification by experiments. Transcriptome profiling-based network analysis reveals the importance of chronic pancreatitis genes and pathways in pancreatic cancer development on a system level by computational method and they can be therapeutic targets.

Keywords Transcriptome · Chronic pancreatitis · Pancreatic cancer · Network analysis · Key factors

Background

Exploring themechanism of disease progression is a meaningful challenge in biomedicine. Many approaches have been developed to identify disease-associated genes and pathways in recent years [1]. Biological function is usually not produced by a single gene or its products but by multiple genes, their expression products, their interactions with each other and with the external environment. Therefore, the biological network is the basis of complex biological systems and a leading method deciphering in complex diseases [2–6]. Genetics and environment jointly determine the risk of disease progression [7]. Conventional approaches are not enough in clarifying complex diseases, because most molecules function in an integrated fashion. [[8].]

To investigate the relationship between inflammation and cancer on a system level is useful to explore the new treatment of cancer [9, 10]. Network-based approaches to cancer research are developed with the accumulation of high-throughput data. A structured network knowledge-base approach to analyze genome-wide transcriptional responses and identify significant functional modules perturbed in human subjects receiving an inflammatory stimulus was presented [11]. This paper focuses on inflammation which is one of the important drivers of cancer [12–14]. Integrating the information from inflammation and cancer is helpful to understand the nature of cancer. Inflammation and cancer are complex processes regulated by both environment and genetics [15]. The relationships have been raised, but have never been analyzed from a computational perspective. Here, we emphasize the relationships between chronic pancreatitis and pancreatic

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cancer at a network level since chronic inflammation is a process of gradual decay of homeostasis increasing the susceptibility to cancer. Moreover, the risk of pancreatic cancer (PC) is significantly elevated in subjects with chronic pancreatitis (CP) [15]. Many components have been identified to function in regulation of inflammation and cancer by biological experiments, but a description of the relationship from a computational perspective is still not available. There is an urgent need to connect chronic inflammation with cancer because it can help to explain cancer initiation and progression. Several observations indicate that a variety of human diseases might be biologically connected. In particular, some data suggest that metabolic, inflammatory and autoimmune diseases increase the risk of developing cancer. How the underlying biology of these diseases overlaps has been investigated based on transcriptome data [16].

In this paper, we used the transcriptional profiles, protein-protein interaction (PPI), pathway into network, and constructed a chronic pancreatitis-pancreatic cancer network (CP-PCN) in gene level and a characteristic sub pathway

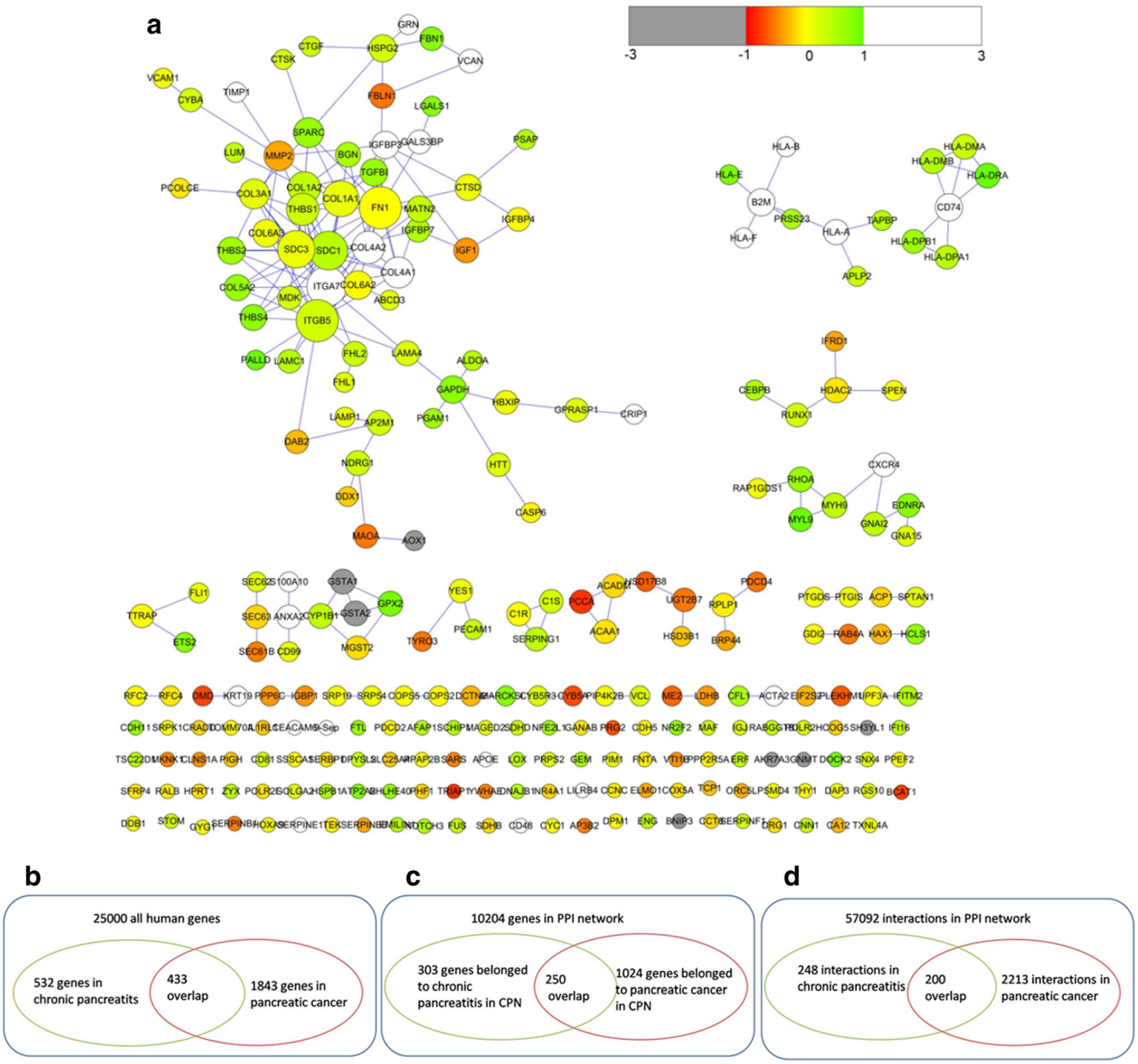

Fig. 1 The further analysis of CP-PCN. **a** The core network of CP-PCN. Each node in the network is both related to chronic pancreatitis and pancreatic cancer genes. The size of nodes corresponds to the degree and the color of nodes corresponds to gene expression level. **b**-**d** Venn graph of overlapping between chronic pancreatitis genes and pancreatic cancer genes. Universal sets are all human genes, genes with interactions in human PPI network and all gene interactions in human PPI network respectively. Both genes and gene interactions show significant overlapping than random

network. Their topological properties, interactions and the differential expression on the overlapped /shared genes of CP-PCN were used to estimate the main function of core pathway and the connectivity between different network layers. We proposed a method to find key genes during diseases progression. Functions of bridging genes were annotated with enrichment and topological analysis. A novel concept that the difference of overlapped / shared genesexpression may cause CP to progress into PC is suggested.

Hypothesis

The key genes of chronic pancreatitis which bridge chronic pancreatitis and pancreatic cancer can be therapeutic targets. The key genes of chronic pancreatitis and pancreatic cancer may function in tumor-associated immune cells in the tumor microenvironment and, thus, may be used as immunotherapeutic targets to induce an improved immune status against cancer.

Evaluation and Discussion

Gene Expression Data and Differential Expressed Genes

Gene expression profiling data E-EMBL-6 were obtained from the EMBL European Bioinformatics Institute database [17], which contain the stages of normal state, chronic pancreatitis and pancreatic cancer, each with 9 samples. The 27 samples of normal state, chronic pancreatitis, pancreatic cancer

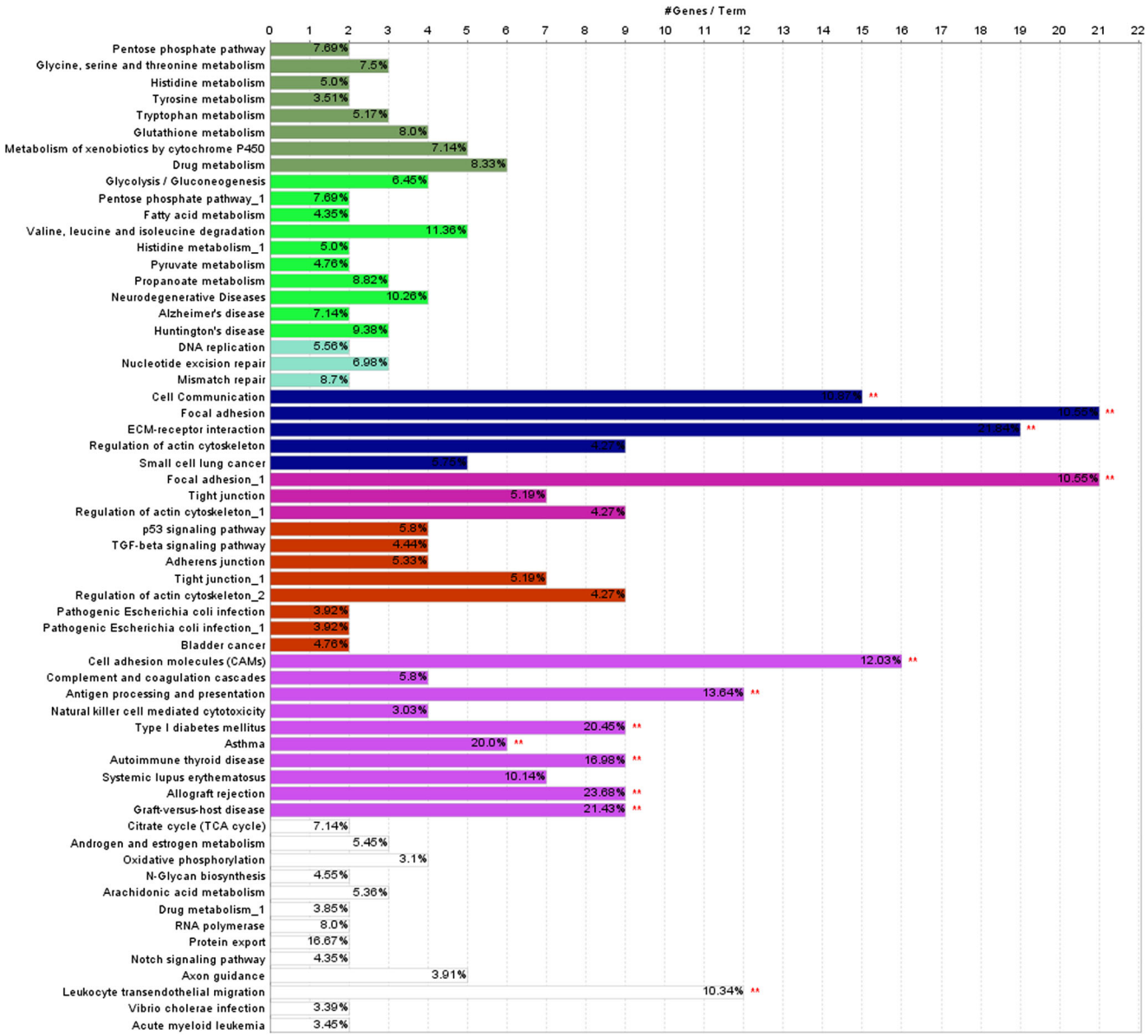

Fig. 2 Graph to show genes in the core network of CP-PCN belong to different KEGG pathways. The bars represent the number of genes (≥2) associated with the term.The percentage of genes per term is shown as bar label

were used in this research. The differential expressed genes of CP and PC were obtained by t-test with the local false discovery rates (FDR) < 0.05 using the fdrtool package [18].

Network Construction and Analysis

Core Network and key Factors from Inflammation to Cancer

Multiple sources of information containing gene expression and protein-protein interactions are integrated to find key factors. Firstly, the differential expressed genes of the chronic pancreatitis (CP) and pancreatic cancer (PC) were identified respectively, which were considered playing important roles for CP and PC respectively. The differential expressed genes represent genes playing important roles under special disease conditions. Secondly, the overlapping genes between CP and PC are extracted and connected by protein-protein interactions combining KEGG and Human Protein Reference Database (HPRD) [19], which were considered as the core network during the progression of CP to PC. The network parameters were analyzed by cytoscape [20] Thirdly, key factors are the genes in core network which gene expression level change during the progression of CP to PC. The Functional analysis of those key factors are done by the "Set Analyzer" tool (http://ctdbase.org/tools/analyzer.go) [21].

Results

The Core Network and key Factors of CP-PCN

It has been proved that PC is close to CP, but what genes bridge PC and CP? To answer this question, we provide a method of extracting pancreatic cancer-pancreatitis overlapping part as the core network and exploring the key factors.

The core of CP-PCN is extracted according to that the differentially expressed genes are in both CP and PC when compared with normal pancreas. The differential expressed genes are mapped to the PPI network and the connected components were extracted, CP, PC and CP-PC network were constructed.

There are totally 250 nodes with 200 edges in the core subnetwork of CP-PCN (Fig. 1a). The size of nodes corresponds to the degree and the color of nodes corresponds to log2gene expression ratio of PC/CP. We checked the KEGG pathway enrichment of the 250 overlapping genes (Fig. 2). They are significantly overrepresented in ECM-receptor interaction and focal adherence pathways which are important in cells-cell communication and cell-ECM contact. Cells receive the signals from niche and react to the signals mostly by ECM-receptor interaction and focal adherence pathways.

The range of interesting genes needs to be narrowed. The overlapping genes can be grouped by expression pattern. The expression pattern of 217(86.8%) genes in the core of CP-PCN does not change from CP to PC (−1 < log2 PC/CP gene expression ratio < 1). Most chronic pancreatitis genes provide the constant inflammatory microenvironment for tumor initiation. 33 genes which expression level changed from CP to PC are key factors to drive pancreatic cancer. The function of key factors is verified by gene set analysis.

Table 1 Genes from the core CP-PCN up-regulated in pancreatic cancer (Pan/Chr > 2). (n = 26)

Gene ID	Gene symbol	Pan/Chr	Degree
3486	IGFBP3	6.819554	5
7852	CXCR4	4.920701	2
2335	FN1	4.416979	17
348	APOE	4.104358	0
3880	KRT19	2.813848	1
1396	CRIP1	2.784572	1
6281	S100A10	2.731218	1
3106	HLA-B	2.696158	1
3134	HLA-F	2.603329	1
3105	HLA-A	2.525671	3
1282	COL4A1	2.493855	8
3959	LGALS3BP	2.469681	2
10,801	SEPT9	2.434348	0
962	CD48	2.403551	0
1284	COL4A2	2.355477	9
567	B2M	2.307632	5
972	CD74	2.251239	5
4680	CEACAM6	2.242435	0
7076	TIMP1	2.216513	1
11,006	LILRB4	2.176155	0
59	ACTA2	2.170962	1
5054	SERPINE1	2.123345	0
1462	VCAN	2.09605	2
3679	ITGA7	2.090289	15
302	ANXA2	2.079634	2
2896	GRN	2.033424	1

Table 2 Genes from the core CP-PCN down-regulated in pancreatic cancer (Pan/Chr < 0.5).(n = 7)

Gene ID	Symbol	Pan/Chr	degree
22,977	AKR7A3	0.264792	0
2938	GSTA1	0.312429	3
2939	GSTA2	0.357226	3
27,232	GNMT	0.405741	0
664	BNIP3	0.438629	0
26,751	SH3YL1	0.478277	0
316	AOX1	0.483607	1

Table 3 Pathway analysis of the up-regulated genes in pancreatic cancer from core CP-PCN ($P < 0.001$)

Pathway ID	Pathway	Corrected *P*-value	Annotated Genes
REACT:118,779	Extracellular matrix organization	2.16E-08	7
KEGG:04612	Antigen processing and presentation	9.83E-08	5
KEGG:04512	ECM-receptor interaction	1.84E-05	4
KEGG:05330	Allograft rejection	1.02E-04	3
KEGG:04514	Cell adhesion molecules (CAMs)	1.21E-04	4
REACT:160,300	Binding and Uptake of Ligands by Scavenger Receptors	1.30E-04	3
KEGG:05332	Graft-versus-host disease	1.40E-04	3
KEGG:04650	Natural killer cell mediated cytotoxicity	1.43E-04	4
KEGG:04940	Type I diabetes mellitus	1.62E-04	3
KEGG:05320	Autoimmune thyroid disease	3.24E-04	3
KEGG:04510	Focal adhesion	5.97E-04	4
KEGG:04144	Endocytosis	7.16E-04	4
KEGG:05416	Viral myocarditis	7.72E-04	3

The up regulated 26 genes (listed in Table 1) are enriched in signal transduction in cancer, especially cell surface interaction ($P < 0.001$). For the pathway analysis, the up regulated genes are enriched in immunological process, for example antigen processing and presentation with 5 genes; in cell-ECM interaction process, such as ECM-receptor interaction and focal adherence pathway with 4 genes; cell adherence molecules (CAM) with 4 genes, focal adhesion with 4 genes (all pathway information listed in Tables 2 and 3).

The down regulated 7 genes (listed in Table 2) are enriched in metabolism-related pathway including Glutathione metabolism and Drug metabolism (all pathway information listed in Table 4). That is in coincidence with one metabolism hallmark of cancer-deregulating cellular energetic which involves reprogramming cellular metabolism to support neoplastic proliferation [22]. Therefore, down-regulation of metabolism pathways is important in the transition from CP to PC.

The network topological parameters between the key factors and other genes in CP are calculated, including Average Shortest Path Length, Betweenness Centrality, Closeness Centrality,Clustering Coefficient, Degree, Eccentricity, Neighborhood Connectivity and Topological Coefficient. Only Eccentricity of key factors are higher than that of other genes in CP ($P < 0.05$) (Fig. 3).

In conclusion, we suggest that the differential expression genes overlapping in inflammation and tumor form the core network of disease progression. There are two kinds of genes in core network. If the gene expression level doesn't change from inflammation to cancer, the genes provide microenvironment for disease progression; if the expression levels change in the transition, the genes are key factors mediating the disease progression. The key factors we found are proved to be enriched in cancer. The key factors and their specific function in pancreatic cancer need further computational validation by independent data sets and experimental investigation, since there is still no other available human data.

Pathway Network of CP-PC

We further explore the relationship between inflammation and cancer in pathway level by construct a CP-PC pathway network based on differentiated expression genes (Fig. 4, Table 5). Most of the CP pathways (16/19) are included in PC pathways and show higher degree than both CP specific and PC specific pathways. The results support that the therapies targeting the inflammatory factors have been developed in PC [23, 24]. CP-PC sharing pathways can be classified by their network characters. CP-PC sharing pathways are activated in both pancreatitis and pancreatic cancer. The degree of pancreatitis-specific pathways is higher than CP and PC individually.

Wnt signaling pathway in both CP and PC pathway network is proved to be candidate therapeutic target to prevent PC [25].

Table 4 Pathway analysis of the down-regulated genes in pancreatic cancer from core CP-PCN ($P < 0.001$)

Pathway ID	Pathway	Corrected *P*-value	Annotated Genes
KEGG:00982	Drug metabolism - cytochrome P450	3.35E-06	3
KEGG:00480	Glutathione metabolism	5.12E-04	2
REACT:111,217	Metabolism	9.66E-04	4
KEGG:00980	Metabolism of xenobiotics by cytochrome P450	9.12E-04	2

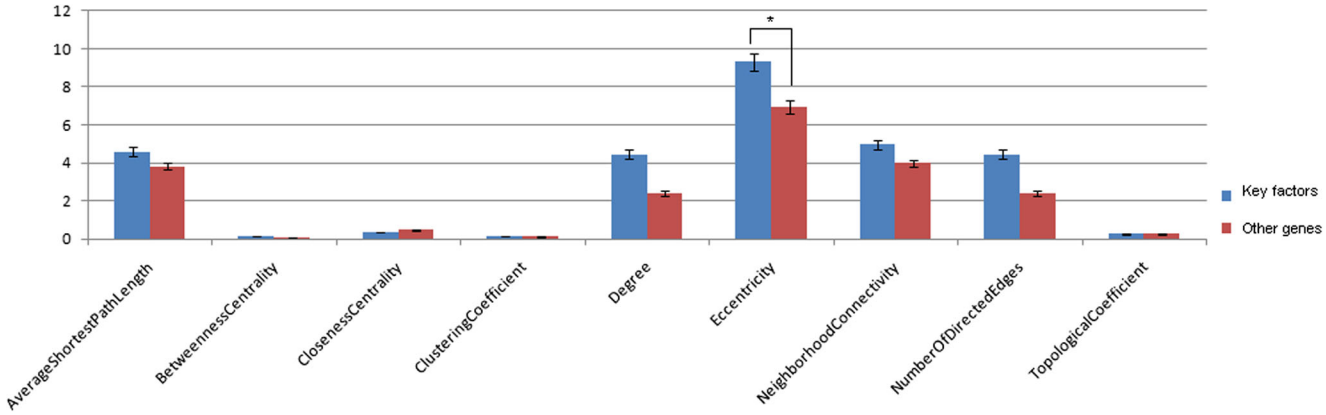

Fig. 3 The network topological parameters between the key factors and other genes in CP are calculated, including Average Shortest Path Length, Betweenness Centrality, Closeness Centrality, Clustering Coefficient, Degree, Eccentricity, Neighborhood Connectivity and Topological Coefficient

Discussion

Increasing evidence links inflammation and cancer. Although inflammation has been proved to promote all stages of cancer development through multiple mechanisms in preclinical and clinical researches, the system connection remains unclear. In this paper, we prove the connection between CP an PC in network level of genes and pathways and develop a method to identify important factors for understanding network-based disease relationship.

PC is one of the top lethal human cancers. CP is an important risk factor for PC. Chronic inflammation can create a microenvironment that contributes to malignant transformation. Immune pathways are the main mediator of CP and PC through their ability to communicate among PC cells and niche in a complicated network of interactions.

The enormous data accumulated from the researches of complex biological systems change our view on the pathogenesis and progression of human diseases [26]. The focus on the interaction of multiple components in biological systems deciphers disease better instead of the focus on individual components. A network analysis of diseases is a valid method to study their complex connections. Specific perturbations can trigger cascades of interactions, lead to the malfunction of cellular networks and contribute to the diseases [27].

Disease-specific network can be constructed by integration disease-related transcriptome, protein interaction and pathway (gene sets). The gene expression and network are integrated to prioritize disease genes in cancer [28]. We further apply the method in finding the key factors between diseases. It can be used to find the relationship between diseases and may be used to develop the new use of the old medicine. The eccentricity of key factors between CP and PC which is higher than that of other genes of PC and CP demonstrates that key factors are hubs during the transformation from CP to PC. Once key

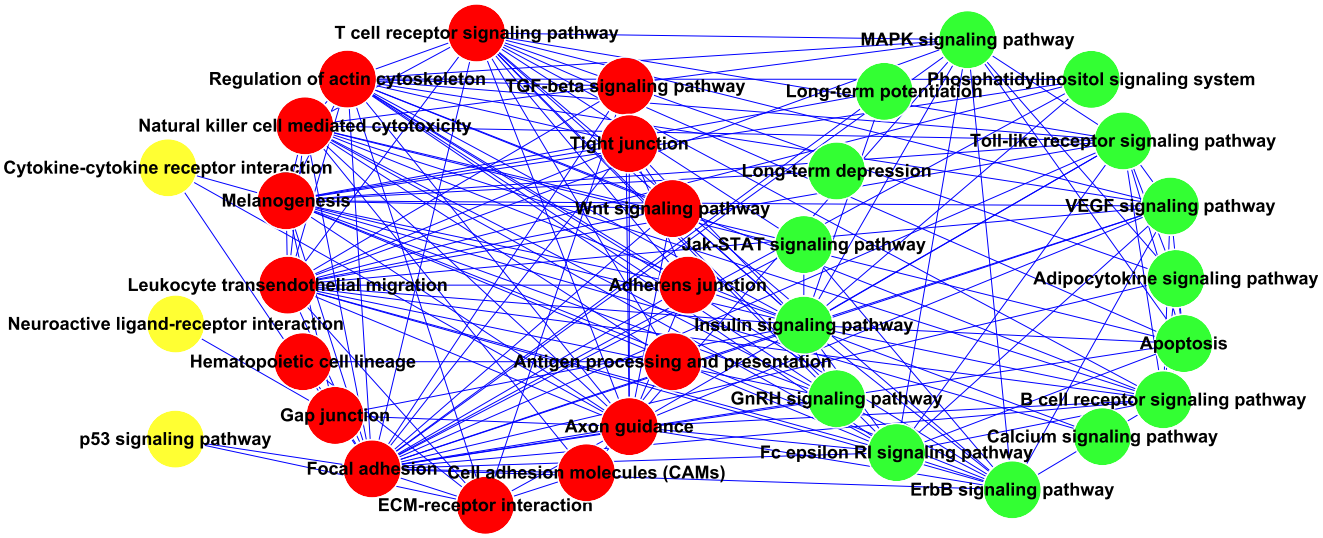

Fig. 4 Pathway networks of chronic pancreatitis and pancreatic cancer. Chronic pancreatitis-specific pathways are colored in yellow; pancreatic cancer pathways are colored in green; chronic pancreatitis and pancreatic cancer shared pathways are colored in red

Table 5 Pathway network in CP-PC

Pathway Category	Pathway name	Degree
Chronic pancreatitis	Cytokine-cytokine receptor interaction	3
	Neuroactive ligand-receptor interaction	1
	p53 signaling pathway	2
CP-PC sharing	Adherens junction	8
	Antigen processing and presentation	4
	Axon guidance	20
	Cell adhesion molecules (CAMs)	5
	ECM-receptor interaction	8
	Focal adhesion	28
	Gap junction	6
	Hematopoietic cell lineage	3
	Leukocyte transendothelial migration	20
	Melanogenesis	20
	Natural killer cell mediated cytotoxicity	16
	Regulation of actin cytoskeleton	20
	T cell receptor signaling pathway	18
	TGF-beta signaling pathway	5
	Tight junction	8
	Wnt signaling pathway	7
Pancreatic cancer	Adipocytokine signaling pathway	6
	Apoptosis	10
	B cell receptor signaling pathway	13
	Calcium signaling pathway	2
	ErbB signaling pathway	13
	Fc epsilon RI signaling pathway	14
	GnRH signaling pathway	6
	Insulin signaling pathway	22
	Jak-STAT signaling pathway	5
	Long-term depression	1
	Long-term potentiation	3
	MAPK signaling pathway	12
	Phosphatidylinositol signaling system	5
	Toll-like receptor signaling pathway	14
	VEGF signaling pathway	12

factor are disturbed, the connection between CP and PC would be interrupted.

The methods of network analysis are helpful to deeply understand the correlation between CP and PC. The methods can also be used in disease relationship. In future research, we shall exactly quantify the different expression by deep sequencing technology, and provide further network basis for malignant transformation. Disease-specific network can be constructed by integration disease-related transcriptome, protein interaction and pathway (gene sets). Different layer networks provide various information. Molecular networks conduce to find disease genes among differentially expressed genes and pathway networks help to the understanding of the cooperation among pathways by reconstruction of interactions networks among transcriptome profiles including differentially expressed genes and non-differentially expressed genes. In this work, the methods are helpful to deeply understand the correlation between chronic pancreatitis and pancreatic cancer.

Taken together, combing the transcriptome data and protein-protein interaction data, the connection of chronic pancreatitis and pancreatic cancer is proved in system at molecule level and pathway levels. Collectively, this finding not only helps to understand the importance of chronic pancreatitis in pancreatic cancer, but also gives us a strong rationale to further investigate anti-inflammation as a potential therapeutic target for pancreatic cancer.

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Contributions S.L. and L.L. designed the study. R. Li. and H.W. designed and accrued the samples. H. L., L.L. and Y.L. prepared the manuscript. All authors reviewed the manuscript.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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