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RESEARCH

Pathway Crosstalk Analysis of Microarray Gene Expression Profile in Human Hepatocellular Carcinoma

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Abstract Liver cancer is the third most common cause of cancer death in the world. Hepatocellular carcinoma (HCC) is the main pathological types in liver cancer, which amounts to 70–85 % of primary liver cancer in the world and 90 % in China. The aim of this study was to establish a PPI network and a pathway crosstalk network to isolate important dysfunctional pathways which play an important role in the pathogenesis of HCC. System biology approach was used in this research. A PPI network was firstly built and then a dysfunctional crosstalk network of HCC related pathways was constructed. Several important significant dysfunctional crosstalk pathways were identified. Basal transcription factors (hsa03022), Glycerophospholipid metabolism (hsa00564) and Metabolism of xenobiotics by cytochrome P450 (hsa00980) were significantly interact with Pathway in cancer (hsa05200). Besides, pathway Axon guidance (hsa04360) was also dysfunctional crosstalk with Pathway in cancer (hsa05200). The crosstalks among these pathways reveal some evidence that the pathways closely cooperated and play important tasks in HCC progression. Besides, the pathway hsa04360 dysfunctional crosstalk with the hsa05200 indicates there would be a same mechanism for HCC invasion and migration.

Keywords Human hepatocellular carcinoma · Pathway crosstalk · Protein-protein interaction network

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Introduction

Liver cancer is the third most common cause of cancer death in the world [1]. Hepatocellular carcinoma (HCC) is the main pathological types in liver cancer, which amounts to 70–85 % of primary liver cancer in the world and 90 % in China [2]. HCC is a complex multistep process and many different molecular pathways are implicated. For example, the recurrence and metastasis are considered to be the most important factors which influence the treatment of liver cancer [3]. When cancer cells obtain the ability of recurrence and metastasis, abnormal signal transduction is directly and inevitably generated. Therefore, inter-receptor crosstalk and positive feedback between different signaling systems are emerging as mechanisms of targeted therapy resistance. Identification of such interactions and revelation of the molecular mechanisms are benefit to improve therapeutic efficacy in prevention and treatment of HCC [4, 5].

Nowadays, several researches related to pathway crosstalk in HCC are carried out. In HCC cells, the crosstalk between the PI3K/Akt and MEK/ERK cascades under endoplasmic reticulum (ER) stress contributes to both cell cycle arrest and cell survival. ER stress-induced crosstalk between the PI3K/Akt and MEK/ERK cascades is a protective mechanism utilized by HCC cells to adapt to stress [6]. Epidermal growth factor receptor (EGFR) system is recognized as a signaling hub where different extracellular growth and survival signals converge. EGFR can be transactivated in response to multiple heterologous ligands through the physical interaction with multiple receptors. The crosstalk between EGFR and other signaling pathways could be relevant to liver cancer development and treatment [5]. Crosstalk between the IGF pathway

and ErbB1 has been demonstrated in various cellular backgrounds by showing that activation of IGF-1 receptor leads to the shedding of different ErbB1 ligands including AR, TGFα and HB-EGF. Besides, new researches have shown the proliferative effect of IGF-II on human HCC cell lines requires ErbB1 activation through the autocrine/paracrine release of AR, simultaneous targeting of both COX-2 and ErbB1 could result in synergistic antitumor effects with reduced toxicity. These results indicate the interaction between these two systems in liver carcinogenesis is significant [7].

Recently, system biology approaches have been successfully used for research on the pathway crosstalk, such as network-based methods [8–10]. The complexity of crosstalk depict via protein-protein interactions (PPI). Several computational methods [9] are used to detect functional pathways and the crosstalk between them. Construction of molecular interaction networks is available for understanding the underlying mechanisms of biological processes [11]. Significantly dysfunction crosstalk pathway is expected to provide intense insights into the pathogenetic mechanism. Nowadays, with the development of availability and integration high-throughput gene expression data and the genome-wide PPI data, more valuable information will be revealed. Thus, research on more crosstalk pathways will provide new ideas for prophylaxis and treatment of HCC.

Here, we integrate gene expression data informations to research PPI and dysfunctional crosstalks related to HCC. A PPI network was built and then a scoring scheme was utilized to define the dysfunctions of pathways crosstalk. Finally, several dysfunctional pathways significantly interact with the central pathway which directly related to HCC progression were found.

Materials and Methods

1. Microarray Data

The gene profile of GSE29721 was downloaded from Gene Expression Omnibus (http://www.ncbi.nlm.nih.gov/geo/), which was deposited by Matthew Suderman [12]. A total of 10 cancerous and 10 corresponding adjacent tissue samples obtained from 10 patients with HCC in Chinese National Human Genome Center at Shanghai, China (Dr. Ze-Guang Han) were available. Tissues were dissected using the laser capture microdissection technique, and total RNA was isolated from these tissues using TRIzol (Invitrogen, Life Technologies, Carlsbad, CA, USA) (1 μg RNA served as template for cDNA synthesis using reverse transcriptase). Finally, these samples were hybridized to HG-U133 Plus 2.0 high-density oligonucleotide arrays (Affymetrix).

2. Data processing and identification of differential expression analysis

R package (v.2.13.0) [13] was used to analyze the gene expression profile. CEL source files from all conditions were processed into expression estimates and performed background correction and quartile data normalization using RMA (Robust Multi-array Average) algorithm [14]. The probability of genes being differentially expressed between liver cancer samples and normal samples was computed using the limma package [15]. Bayesian method [16] was used to adjust the raw p-values into false discovery rate (FDR). A total of 13433 genes were detected.

3. Pathway Analysis and PPI Construction

The KEGG (Kyoto Encyclopedia of Genes and Genomes) PATHWAY database records networks of molecular interactions in cells, and variants of them specific to particular organisms (http://www.genome.jp/kegg/) [17]. We downloaded the Non-small cell lung cancer pathway (hsa05223) and all its neighbor pathways from KEGG. Here the neighbor pathways are defined as those pathways which have at least one overlapping gene with hsa05223. A pathway set related to HCC was constructed and all genes in this set were extracted. Then these genes were mapping into PPI database. PPI pairs were isolated by PPI database (intersection set of database mint [18], hprd [19] and grid [20]). Finally, the PPI networks were constructed.

4. Analysis of Correlation of co-expressed genes

To determine the correlation among co-expressed genes, the Pearson correlated coefficient in protein pairs were measured. P-value was calculated as a reference of correlation. Fisher's method [21] is used to define a function as the combination of statistical significance of an interaction by a scoring scheme in the following formula:

$$S(e(x,y)) = f(diff(x), corr(x,y), diff(y)) = -2\sum_{i=1}^{k} \log_e(p_i),$$

Where S(e(x,y)) exhibit scores of correlation, diff(x) and diff(y) are differential expression assessments of gene x and gene y, respectively. Corr(x,y) represents their correlation between gene x and gene y. Where k =3, p1 and p2 are the p-values of differential expression of two nodes, p3 is the p-value of their co-expression.

5. Significance analysis of pathway crosstalk

We defined an interaction function to evaluate the significance of all non-empty overlaps between two pathways. The interaction score between two pathways is estimated by their overlapping status of weighted pathways in the following formula:

$$C(P_i, P_j) = \sum_{e \in O_{ij}} S(e).$$

We random sample 10^6 times of the same size two pathways in the edges of the pathway network and calculate their overlapping scores. The frequency larger than C is regarded as the interaction significant p-value [22].

6. Dysregulation of related pathways

To define the dysfunction of a pathway P, we summarize all the scores of edges S(e) of every pathway, i.e.,

$$S_p = \sum_{e \in P} S(e)$$

To estimate a p-value for significance of this pathway, we iteratively compute similar scores 10^6 times randomly generated pathways of the same size as that of pathway P. The frequency of scores that are larger than Sp is used as the significant p-value of pathway P to describe its dysregulation. Then we get a ranked list of dysfunctional pathways.

Results

1. Excavation of HCC related pathways and PPI construction

In total 108 pathways related to HCC were isolated from the database, including one cancer pathway hsa05200 (pathway in cancer) and 107 neighbor pathways. There were in total 2099 genes in these pathways. Then we built a PPI network by mapping these genes into PPI database. In this network, there were 5036 PPI pairs in total. The interaction protein exist in the 108 pathways and do not interact with itself. Figure 1 shows the PPI network where the genes in the KEGG hsa05200 pathway were highlighted in red.

2. Dysfunctional crosstalk of HCC related pathways

Significantly changed crosstalk were isolated according to p value ($p < 0.05$). These pathways were neighbor pathways significantly crosstalk with hsa05223 (Non-small-cell lung cancer) and then a pathway crosstalk network was constructed by Cytoscape (Fig. 2). According to hsa05223 related pathways, significance of dysfunctions was identified through dysfunction score and its significance criterion. The top 10 ranked pathways were listed in Table 1. In this network, the interaction significance of two pathways was represented by the width of their edge. The dysfunction significance of a pathway was shown by the corresponding gradient node color. The node size represents the number of proteins involved in the pathway. As shown in Fig. 2, several pathways were found significantly crosstalk with hsa05200 (Pathway in cancer), such as hsa03022 (Basal transcription factors), hsa00980 (Metabolism of xenobiotics by cytochrome P450), hsa00564 (Glycerophospholipid metabolism) and hsa04360 (Axon guidance). This result gives evidence for the strong relationship between these pathways with hsa05200. Some of the pathways provide valuable infromations for the mechanism of HCC,

Discussion

HCC is the main pathological types of Liver cancer and is one of the most common cause of cancer death in the world. Currently, network-based method is an important way to understand the underlying mechanisms of biological processes. Identify signaling pathways and crosstalk between them play significant roles in the development of disease. Besides, significantly pathway crosstalk dysfunction expect to provide intense insights into the pathogenetic mechanism. In this study, Non-small cell lung cancer (NSCLC) hsa05223 related pathways were isolated from database, a PPI network was built by integrating the microarray data information. Then a dysfunctional crosstalk network was constructed. Several significant dysfunctional crosstalk pathways were identified. In these pathways, we found that hsa03022, hsa00980, hsa00564 and hsa04360 were significant pathways with the cancer centre pathway hsa05200. The identified dysfunctional crosstalk between the pathways provides valuable information for HCC mechanism, The interaction of these dysfunctional pathways provides more insights for the HCC progression in various regions.

We identified the crosstalk of pathways in the clustered groups as well as their neighbor pathways. Ten significant crosstalk pathways were isolated. They are highly interact with pathway hsa05223. The pathway hsa05223 is a centre pathway in NSCLC. Several genes in this pathway are essential in NSCLC. For example, K-RAS and c-erbB-2 activate oncogenes, p53, p16INK4a, RAR-beta, and RASSF1 inactivate tumor suppressor genes[23, 24]. In details, function loss of K-RAS inhibit GTPase activity and the p21-RAS protein continuously transmits growth signals to the nucleus [25]; Overexpression of c-erbB-2 or EGFR leads to a proliferative

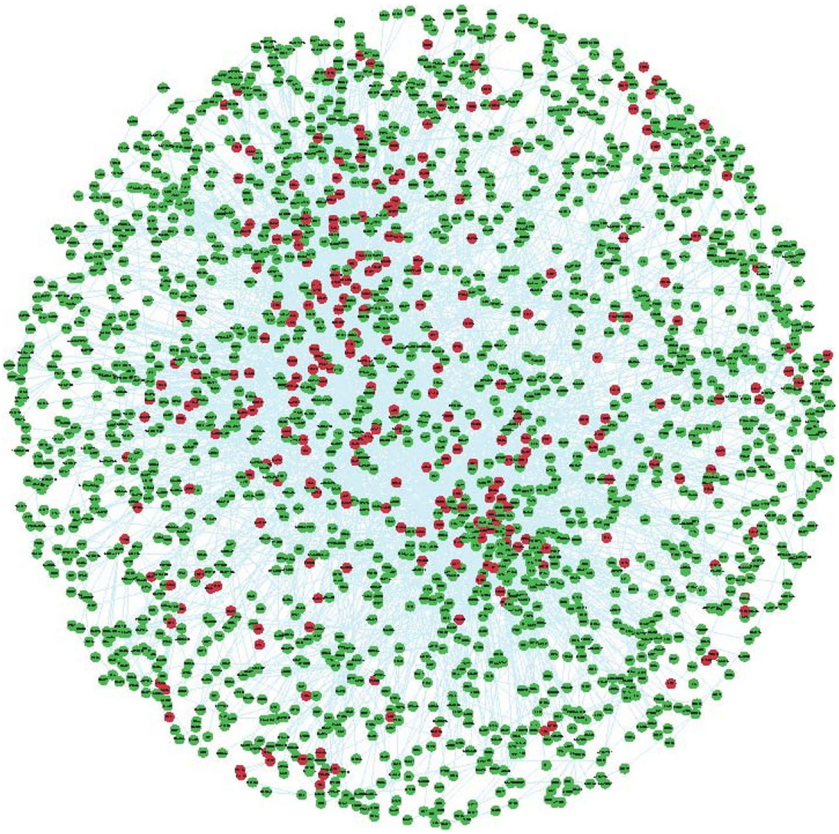

Fig. 1 Network of pathways. The proteins of KEGG hsa05200 pathway and its neighbor pathways were involved in the ensemble protein-protein interaction network. The red dots represent genes involved in hsa05200. The green dots represent genes involved in neighbor pathway. There are 2099 nodes and 5036 edges in total

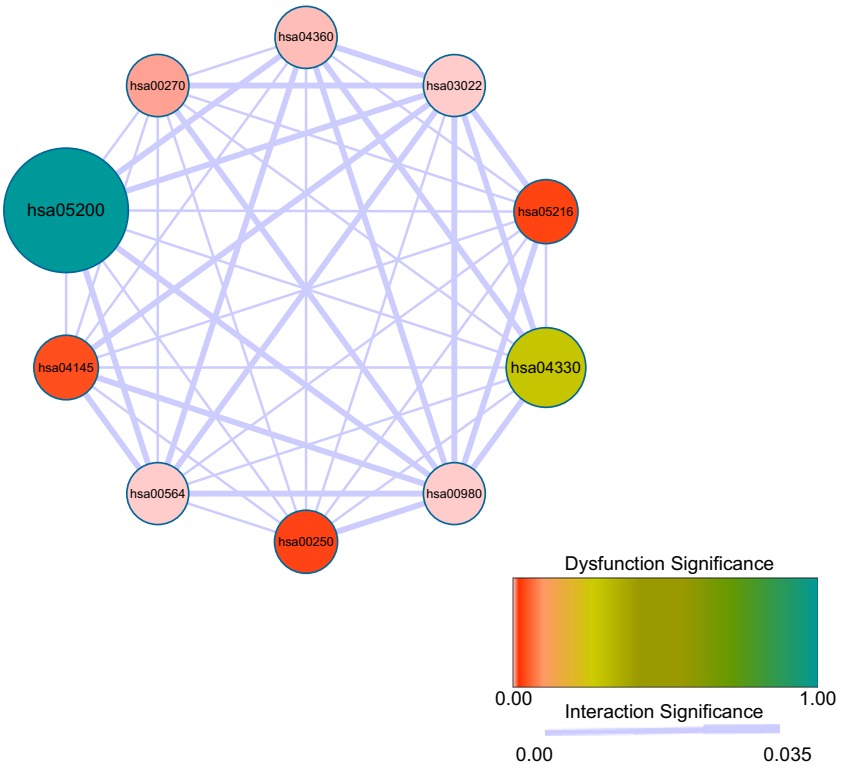

Fig. 2 Dysfunctional crosstalk of HCC related pathways. The nodes are neighbor pathways. The size of the nodes represents the number of genes in the pathways (increased with the size). The color of the nodes represents the dysfunction significance of these neighbor pathways (reduced from *red* to *blue*). The width of the edges represents the significance of dysfunctional relationship between the two pathways

Table 1 Rank of pathways

Pathway	p-value	size	description
hsa00564	0	78	Glycerophospholipid metabolism
hsa00980	0	70	Metabolism of xenobiotics by cytochrome P450
hsa03022	1.70E-05	36	Basal transcription factors
hsa04360	0.002132	129	Axon guidance
hsa00270	0.00578	34	Cysteine and methionine metabolism
hsa00250	0.018902	32	Alanine, aspartate and glutamate metabolism
hsa05216	0.034097	29	Thyroid cancer
hsa04145	0.042209	155	Phagosome
hsa04330	0.28337	47	Notch signaling pathway
hsa05200	0.999999	328	Pathway in cancer

advantage [26]; Inactivating of p53 leads to rapid proliferation and reduced apoptosis [27]; p16INK4a inhibits formation of CDK-cyclin-D complexes by competitive binding of CDK4 and CDK6 [28]; RAR-beta is a nuclear receptor that bears vitamin-A-dependent transcriptional activity [29]; Loss of RASSF1A might shift the balance of RAS activity towards a growth-promoting effect [30]. The crosstalk with hsa05223 between these pathways might contribute to HCC by their cooperative dysfunctions.

An crosstalk network was bulit by the 10 significant pathways. In this network, we found the pathway hsa03022, hsa00564 and hsa00980 were significant dysfunctional crosstalk with a pathway hsa05200. Hsa05200 is a pathway function in cancer. This certified hsa03022, hsa00564 and hsa00980 also played an important role in the regulation of cancer genes.

The pathway hsa03022 is basal transcription factor. As reported, a limited list of transcription factors were overactive in most human cancer cells. Three main groups of transcription factors are known to be important in human cancer. They are steroid receptors, resident nuclear proteins and latent cytoplasmic factors [31]. Several detail researches were carried out. For example, some Sp proteins play a critical role in the growth and metastasis of many tumour types by regulating expression of cell cycle genes and vascular endothelial growth factor. Sp/KLF proteins are also potential targets for cancer chemotherapy [32]; YY1 are known to be intimately associated with progression through phases of the cell cycle. Overexpression or activation YY1 is associated with unchecked cellular proliferation, resistance to apoptotic stimuli, tumorigenesis and metastatic potential [33].

Another dysfunctional crosstalk pathway hsa00564 takes part in glycerophospholipid metabolism. As reported, increased tumour growth needed fatty acids to provide energy requirements. There are increasing evidences that lipid metabolism is deregulated in cancers and the expression and activity of lipogenic enzymes involved in lipid synthesis are increased. These genes are regulated by metabolic and oncogenic signalling pathways [34]. Lipids can also influence the invadopodia formation. Invadopodia are membrane protrusions that facilitate matrix degradation and cellular invasion; Inhibition of acetyl-CoA carboxylase 1(ACC1), the committed step of fatty acid synthesis, reduced invadopodia formation and also decreased the ability to degrade gelatin. At the same time, inhibition of fatty acid synthesis through AMP-activated kinase activation and ACC phosphorylation also decreased invadopodia incidence. The novel metabolic regulation of invadopodia and the invasive are processed by de novo fatty acid synthesis and lipogenesis [35]; In cancer pathogenesis, fatty acid synthase (FASN) is a key lipogenic enzyme in the de novo biogenesis of fatty acids. A recent identification of cross-talk between FASN and well-established cancer-controlling networks begins to delineate the oncogenic nature of FASN-driven lipogenesis [36].

The last one dysfunctional crosstalk pathway hsa00980 is treated as metabolism of xenobiotics by cytochrome P450. The cytochromes *P*450 (CYPs) are key enzymes in cancer formation and cancer treatment. They mediate the metabolic activation of numerous precarcinogens and participate in the inactivation and activation of anticancer drugs [37]. Several CYP enzymes metabolically activate procarcinogens to genotoxic intermediates. Phenotypic analyses revealed an association between CYP enzyme activity and the risk to develop several forms of cancer [38]. There are many genes in this family have been researched. For example, CYP1B1 is a key enzyme involved in the production of potentially carcinogenic estrogen metabolites and the activation of environmental carcinogens [39]; *CYP1A1* codes for an enzyme that contributes to aryl hydrocarbon hydroxylase activity, which is involved in the metabolism of polyaromatic hydrocarbons [40]. Finally, the significantly crosstalk between these critical pathways reveals amount of informations and offers new therapeutic opportunities for metabolically treating and preventing cancer.

The pathway hsa04360 function in Axon guidance is also dysfunctional crosstalk with the pathway hsa05200. Several researches related to Axon guidance have reported. Semaphorin 5A is identified as axonal guidance factor belongs to semaphorin family. Earlier studies demonstrate that the expression of Semaphorin 5A in pancreatic cancer cells regulates tumorigenesis, growth, invasion and metastasis [41]. Then the mechanism has also been revealed: semaphoring 5A could regulate MMP9 expression to promote the invasive and metastatic abilities of gastric cancer cell. This process is partially via the MEK/ERKs signal transduction pathway [42] . Deeply research is carried out and found that Semaphorin 5A could promote invasion and metastasis of gastric cancer through the PI3K/Akt/uPA signal transduction pathway [43]. In details, overpression of semaphorin 5A enhanced the expression of uPA and promoted the

phosphorylation of Akt. Blocking effects of PI3K/Akt abolished the ability of semaphorin 5A to induce uPA expression, cell invasion and migration. The significant dysfunctional crosstalk between hsa04360 and hsa05200 indicates there would be a same mechanism in HCC, and similar regulated molecules could be the potential targets for liver cancer therapy.

In conclusion, several pathways related to HCC were isolated by significant crosstalk with lung cancer pathway hsa05223. Among these pathways, Basal transcription factors (hsa03022), Glycerophospholipid metabolism (hsa00564) and Metabolism of xenobiotics by cytochrome P450 (hsa00980) were found to significant dysfunctional crosstalk with Pathway in cancer (hsa05200). Previous researches certified these pathways played an important role in regulation expression of cancer genes. The crosstalk between them reveals amount of informations and offers new therapeutic opportunities for HCC. Besides, another pathway hsa04360 which was dysfunctional crosstalk with hsa05200 indicates there would be a similar mechanism with hsa04360 in HCC.

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Conflict of Interest The authors have declared that no competing interests exist.

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