Identification of Key Genes and Pathways in Renal Cell Carcinoma Through Expression Profiling Data

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Key Words
Renal cell carcinoma • Differentially expressed genes • Network • Functional enrichment • Pathways

Abstract
Background/Aims: To isolate key genes and pathways in renal cell carcinoma (RCC), which might reveal more evidences on the regulation network and contribute to pathogenic mechanisms of RCC. Methods: Microarray data of GSE34676, GSE23926 and GSE48008 were downloaded from Gene Expression Omnibus. Differentially expressed genes (DEGs) and differentially expressed miRNAs were respectively screened using Limma package, followed by the selection of CNV associated genes and miRNAs. A multi-molecular regulation interaction network was constructed, and significant modules were subsequently isolated from the network by Molecular Complex Detection (Mcode) of Cytoscape. Finally, GO terms and KEGG pathways of these genes and miRNAs in significant modules were enriched using DAVID. Results: Total 403 DEGs and 231 differentially expressed miRNAs were screened in RCC samples and normal group. Moreover, 1369 genes and 68 miRNAs were isolated by CNV analysis. Besides, a total of 59 miRNAs and 209 genes that related to 340 interaction pairs were analyzed and used to construct the network and 2 significant modules were identified. In the modules, CAV1 and CAV2 were shown to correlate with RCC. GNAI1, GPSM2 and GNAO1 were likely involved in the regulation of RCC through G protein signal transduction. Besides, G-protein coupled receptor protein signaling pathway, focal adhesion, MAPK signaling pathway and neuroactive ligand receptor interaction were enriched. Conclusion: Our study suggests that several crucial genes including CAV1, CAV2, GNAI1, GPSM2, and GNAO1 and pathways may play key roles in RCC progression.
Introduction

Renal cell carcinoma (RCC) is one of the most common cancers in urinary system. The annual incidence of RCC represents 3% of all malignancies in 2010 in the United States [1, 2]. Moreover, the incidence of RCC continues to be steadily rising over the past two decades [3]. In the treatment of RCC, it is still complicated due to different morphological characteristics and clinical phenotype, such as clear-cell RCC (82%), type 1 or 2 papillary tumors (11%), chromophobe tumors (5%), and collecting duct carcinoma (1%) [2, 4]. RCC is known to be resistant to all chemotherapeutic and radiation therapies, and surgical resection remains the mainstay of curative treatment to data [5]. However, studies have found that RCC partially responds to targeted therapies or immunotherapy [6, 7]. Exploring new therapeutic strategies for the treatment of this disease is imperative.

RCC is a disease with complex etiologies, which may be caused by the combined effect of multiple genes. Extensive efforts have been made to explore the underlying molecular pathogenesis of it. VHL (von Hippel-Lindau), p53, p16, p21 and p27 were shown as the main tumor suppressor genes in RCC, in which VHL and p53 were clearly certified to result in the development of RCC [8]. Dysfunction of VHL will lead to constitutively aberrant activation of the hypoxic response, like upregulation of vascular endothelial growth factor (VEGF), which is considered to play important roles in tumor development and angiogenesis [5, 9]. p53 is shown to suppress tumor growth and induce cell apoptosis in RCC [10, 11]. Moreover, miRNA-21 (miR-21) can post-transcriptionally downregulate the expression of programmed cell death 4 (PDCD4) and consequently promotes the proliferation and metastasis in RCC [12]. Besides, some factors involved in relevant biological pathways have been demonstrated as potential therapeutic targets, such as small-molecule multikinase inhibitors that target VEGF receptors (sunitinib and sorafenib) [13], the anti-VEGF antibody bevacizumab [14], and a mammalian target of rapamycin inhibitor temsirolimus [15]. Despite these great progresses in pathogenesis of RCC, the molecular mechanisms underlying this disease have not been fully elucidated.

Recently, microarray profiling of human RCC has increasingly been used to identify the potential genes and critical pathways involved in RCC [16]. In this study, expression profiles of gene, miRNA and SNP from RCC and normal group were respectively used to isolate differentially expressed genes (DEGs) and differentially expressed miRNAs. A multi-molecular regulation interaction network that related to RCC was constructed and significant modules were subsequently identified. Moreover, functional enrichment analyses of these genes and miRNAs were performed. This study aimed to select several key genes and significant pathways that associated with RCC progression. These key genes and pathways might reveal some regulatory mechanisms and provide a new therapy approach in RCC.

Materials and Methods

Microarray data and data preprocessing

The gene expression profile of GSE23926 deposited by Gan et al. [17], miRNA expression profile of GSE48008 deposited by Zaravinos et al. [18], and SNP profile of GSE34676 deposited by Krill-Burger et al. [19] were downloaded from Gene Expression Omnibus (GEO, http://www.ncbi.nlm.nih.gov/geo/), which were based on the platforms of

- GPL570: [HG-U133_Plus_2] Affymetrix Human Genome U133 Plus 2.0 Array,
- GPL11434: miRCURY LNA microRNA Array, 6th generation - hsa, mmu & rno, and
- GPL6801: [GenomeWideSNP_6] Affymetrix Genome-Wide Human SNP 6.0 Array, respectively.

The information of patients in different samples from the three selected microarrays were shown in Table 1. The gene expression profile and miRNA expression profile was preprocessed using R language (v.2.13.0) [20]. CEL source files from all conditions were performed background correction and quartile data norma-
gene or miRNA. However, if a probe was mapped to multiple genes or miRNAs, the probe was considered unspecific and was then removed.

In addition, APT (apt-probeset-genotype program in Affymetrix Power Tools) was used to analyze original CEL source files to obtain genotyping data and isolate SNP signal intensities of A, B allele [22]. Standard genotype clustering files were generated by genotyping data and signal intensities of normal samples. Finally, the signal intensities of A, B allele in cancer samples were consulted with standard genotype clustering files in order to evaluate Log R Ratio (LRR) and B Allele Frequency (BAF) of every locus in cancer samples.

Identification of DEGs and differentially expressed miRNAs

The T test in Limma package [23] was used to select the DEGs in RCC samples from GSE23926 and the differentially expressed miRNAs from GSE48008 compared with the normal samples. Fold change (FC) of the gene expression was also observed for differential expression test. The p-value < 0.05 and |log2 FC| > 1 were considered as the threshold.

Copy number variation analysis

PennCNV [24] and Hidden Markov model (HMM) [25] were used to deduce the CNV (Copy number variation) regments in the genomes of microarray data GSE34676 based on the LRR and BAF of RCC samples. Then the occurrence of a same CNV sessions was counted in RCC samples. Sessions were retained which appeared in more than 7 samples. Finally, CNV sessions were annotated to select the genes or miRNAs related to CNV.

Prediction of miRNA target genes

In order to improve the accuracy and reduce false positive, the target genes of differentially expressed miRNAs were predicted by 6 prediction algorithm, including PicTar [26], DIANA-microT [27], miRanda [28], RNAhybrid [29], RNA22 [30] and TargetScan [31]. The target genes which were appeared in at least three algorithms were identified as the truly target genes for the differentially expressed miRNAs.

Network analysis and module mining

The selected DEGs and differentially expressed miRNAs associated with CNV, and the target genes for miRNAs were used to construct the regulatory network of RCC using Mocde (Molecular Complex Detection) in Cytoscape [32]. Key biomoleculars were isolated in this network and significant modules with degree cutoff to 2 (degree > 2) from the constructed network were analyzed.

Functional enrichment analysis of the genes in modules

Gene Ontology (GO) [33] and KEGG pathway [34] enrichment analysis for the selected DEGs in the modules were performed to explore significant biological processes and pathways using the DAVID (Database...
Fig. 1. Network constructed by regulation and protein-protein interactions. Circle represents related genes of RCC; triangle represents related miRNAs of RCC; green represents DEGs and miRNAs; red represent CNV related genes and miRNAs; blue represents both differentially expressed and CNV related genes and miRNAs.
Results

Screening of DEGs and differentially expressed miRNAs

Totally, 403 DEGs and 231 differentially expressed miRNAs were identified in RCC samples compared with normal controls with the p-value < 0.05 and |log2 FC| > 1, respectively. Besides, the results of CNV analysis showed that 1369 genes and 68 miRNAs were isolated from the genome regments with CNV.

Network construction and functional modules

A total of 209 target genes related to 59 differentially expressed miRNAs that associated with RCC was selected based on the 6 miRNA prediction algorithm. Finally, 340 interaction pairs among these CNV related genes and miRNAs were predicted to construct the network (Fig. 1). As a result, a high level of connectivity is shown in the network. All these nodes were related to RCC and several nodes were highly in degrees in the network.

In addition, 2 significant modules with degree > 2 in specific RCC regulatory network were isolated. As shown in Fig. 2, CNV related genes caveolin 1 (CAV1) and caveolin 2 (CAV2) were linked with DEG mal-T-cell differentiation protein (MALL). Notably, MALL was downregulated genes. Besides, guanine nucleotide binding protein (G protein)-alpha inhibiting activity polypeptide 1 (GNAI1), G-protein signaling modulator 2 (GPSM2), opioid receptor-delta 1 (OPRD1) and guanine nucleotide binding protein-alpha O (GNAO1) were also closely correlated.

Functional annotation of GO and pathway

The functional enrichment analysis of all the selected genes showed that several important GO terms in biological process, such as regulation of transcription and DNA-dependent (GO: 0006355), G-protein coupled receptor protein signaling pathway (GO: 0007186), oxidation reduction (GO: 0055114) and cell adhesion (GO: 0007155) were enriched (Table 2). Besides, genes were also enriched in cell composition and molecular function through GO enrichment analysis.
function, and the most significant GO terms were nucleus (GO:0005634) and protein binding (GO:0005515), respectively (Table 3 and 4). On the other hand, the top 10 pathways of these genes were also enriched (Table 5). The results showed that the most significant pathway was neuroactive ligand-receptor interaction. In addition, the other significant pathways such as Cytokine-cytokine receptor interaction, Focal adhesion, Tight junction, MAPK signaling pathway, Olfactory transduction, Insulin signaling pathway, ErbB signaling pathway, Regulation of actin cytoskeleton and Glioma were also enriched.

### Discussion

RCC is a common cancer with complex mechanism by the combination of multiple genes. In this study, we utilized comprehensive bioinformatics methods to explore the potential molecular mechanism of RCC. The DEGs, differentially expressed miRNAs, CNV related...
genes and miRNAs, and target genes for miRNAs that associated with RCC were analyzed based on three microarrays. Moreover, we selected 2 significant modules with several key DEGs (like CAV1, CAV2, GNAI1, GPSM2 and GNAO1) in RCC regulatory network. Besides, functional enrichment analyses showed that some of the GO terms and pathways, such as signal transduction, G-protein coupled receptor protein signaling pathway, focal adhesion, MAPK signaling pathway and neuroactive ligand-receptor interaction, were also involved with the regulation of RCC.

Our data showed that several key genes had close relationships with RCC from the 2 significant modules. CAV1 is a tumor suppressor candidate and is a negative regulator of the Ras-p42/44 mitogen-activated kinase cascade. Loss of CAV1 in the tumour microenvironment contributes to the metastatic behaviour of tumour cells by up-regulation of TGF-β1 and SNCG through Akt activation [36]. Its expression is down-regulated in some tumors, however, many studies demonstrates that elevated expression of CAV1 is associated with tumor metastasis and a worse prognosis in several neoplasms, such as colon and urinary bladder cancer [37, 38]. In the kidney, one study verified that overexpression of CAV1 was related to the metastasis formation and cytogenetic abnormalities of kidney cancer [40]. Also, Zucchini et al. demonstrated that up-regulation of CAV1 that involved with cell-cell adhesion and cell growth was observed in kidney cancer cells [41]. Besides, CAV1 can be used in differentiating chromophobe RCC from oncocytoma and the effects are superior to CK7 [42]. Therefore, we speculate that CAV1 overexpression may contribute to RCC progression and correlate with a poor prognosis. Meanwhile, CAV2 belongs to the same family of CAV1, which also functions as a tumor suppressor. A silencing study of CAV2 revealed significant inhibition of cell proliferation, migration and invasion through dysregulation of the focal adhesion pathway, and its expression was significantly up-regulated in RCC clinical specimens [43].

On the other hand, GNAI1, GPSM2 and GNAO1 were members of the G protein signal transduction family. G-protein coupled receptor protein signaling pathway is frequently associated with tumorigenesis. It has been reported that there were 4.2% of tumours carry activating mutations in GNAS and nearly 20% of human tumours harbour mutations in G proteins and G-protein-coupled receptors (GPCRs). Besides, many human cancer-associated viruses also express constitutively active viral GPCRs [44]. As previous reported, GNAI1 can suppresses tumor cell migration and invasion [45], GPSM2 may influence the cell division in cancer [46], and GNAO1 is demonstrated to play an important role in oncogenesis [47]. Combination with these findings, we speculate that G-protein coupled receptor protein signaling pathway may play an important role in RCC initiation, and these genes are suspected to participate in the process of RCC through involved in this pathway.

Besides, RCC is shown to produce particular extracellular matrix components and expresses a characteristic repertoire of cell adhesion molecules. The expression of the alpha nu beta 3 integrin subunit is differentially expressed in all types of renal cell tumors [48]. Zucchini et al. demonstrated that up-regulation of CAV1 was involved with cell-cell adhesion in kidney cancer cells [41]. Therefore, focal adhesion factors are also certified to participate in the process of RCC. In polycystic kidney disease (PKD), MAPK signaling pathway and neuroactive ligand receptor interaction were enriched. The expression of genes involved in MAPK pathway is significantly higher in PKD, indicating the activation of MAPK signalling pathway [49]. Based on our results, we speculate that changes in the former pathways may cause tissue lesions and even lead to the generation of RCC.

No experimental validation is a limitation of our study, further experimental studies are still needed. Moreover, there are some sub-types of cancers with distinct phenotypes and control samples in the three datasets in this study, separate sub-analyses of the different sub-types of cancers versus the controls should be considered to validate these genes and pathways.
Conclusion

To sum up, CAV1 may contribute to the progression of RCC and correlate with a poor prognosis. Loss of CAV2 may reveal significant inhibition of cell proliferation, migration and invasion. GNAI1, GPSM2 and GNAO1 are likely involved in the regulation of RCC through G protein signal transduction. Besides, G-protein coupled receptor protein signaling pathway, focal adhesion, MAPK signaling pathway and neuroactive ligand receptor interaction are enriched in the development of RCC and may result in the development of this disease. Our study may provide the initial basis for the future study of RCC diagnosis or treatment.

Disclosure Statement

The authors declare that they have no conflict of interest.

Acknowledgements

We received no funding for this study.

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