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Original article

Role of miR-1 expression in clear cell renal cell carcinoma (ccRCC): A bioinformatics study based on GEO, ArrayExpress microarrays and TCGA database

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ABSTRACT

Purpose: To investigate the clinical value and potential molecular mechanisms of miR-1 in clear cell renal cell carcinoma (ccRCC).

Methods: We searched the Gene Expression Omnibus (GEO), ArrayExpress, several online publication databases and the Cancer Genome Atlas (TCGA). Continuous variable meta-analysis and diagnostic meta-analysis were conducted, both in Stata 14, to show the expression of miR-1 in ccRCC. Furthermore, we acquired the potential targets of miR-1 from datasets that transfected miR-1 into ccRCC cells, online prediction databases, differentially expressed genes from TCGA and literature. Subsequently bioinformatics analysis based on aforementioned selected target genes was conducted.

Results: The combined effect was −0.92 with the 95% confidence interval (CI) of −1.08 to −0.77 based on fixed effect model (I^2 = 81.3%, P < 0.001). No publication bias was found in our investigation. Sensitivity analysis showed that GSE47582 and 2 TCGA studies might cause heterogeneity. After eliminating them, the combined effect was −0.47 (95%CI: −0.78, −0.16) with I^2 = 18.3%. As for the diagnostic meta-analysis, the combined sensitivity and specificity were 0.90 (95%CI: 0.61, 0.98) and 0.63 (95%CI: 0.39, 0.82). The area under the curve (AUC) in the summarized receiver operating characteristic (SROC) curve was 0.83 (95%CI: 0.80, 0.86). No publication bias was found (P = 0.15). We finally got 67 genes which were defined the promising target genes of miR-1 in ccRCC. The most three significant KEGG pathways based on the aforementioned genes were Complement and coagulation cascades, ECM-receptor interaction and Focal adhesion.

Conclusion: The downregulation of miR-1 might play an important role in ccRCC by targeting its target genes.

1. Introduction

As an important member of the microRNA family, microRNA-1 (miR-1) is expressed specifically in the normal skeletal muscle and myocardium tissues [1]. MiR-1 plays a critical role in the development and physiological function of muscular tissues and the related diseases [2,3]. Ectopic expression of miR-1 has been also found in many heart diseases, including arrhythmias, myocardial infarction, and cardiac failure [4–6]. Additionally, miR-1 has been confirmed to inhibit cancer cell proliferation and metastasis and stimulate apoptosis as tumor suppressors in genitourinary cancer, lung cancer, hepatocellular cancer, head and neck cancer, and colon cancer by targeting MET, LASP1, PIK3CA, CCND2, TAGLN2, HDAC4, FoxP1, etc. [7–13]. Moreover, miR-1 is markedly down-regulated in renal cell carcinoma (RCC) cell lines as a tumor suppressor and could be targeted by the oncogenic target genes TAGLN2, CDK4, CDK6, Caprin1 and Slug [13,14,]. However, the previous studies were performed based on small sample sizes. Furthermore, only several target genes were identified for miR-1 in clear cell renal cell carcinoma (ccRCC). The clinical value of miR-1 in ccRCC and its complete potential molecular mechanisms still remain unknown.

As gene chip and RNA sequencing technologies are rapidly developing, Gene Expression Omnibus (GEO), ArrayExpress, and The Cancer Genome Atlas (TCGA) databases gradually play a more important role in bioinformatics analyses. With microarrays or miRNA sequencing containing high-throughput expression data of microRNAs in cancers, the above databases could be used to analyze miRNA expression, explore their function, screen differential expressed microRNAs, etc. [15–19]. Therefore, the microarrays and miRNA sequencing of ccRCC in the databases could be applied to the exploration of the relationship between miR-1 and ccRCC.

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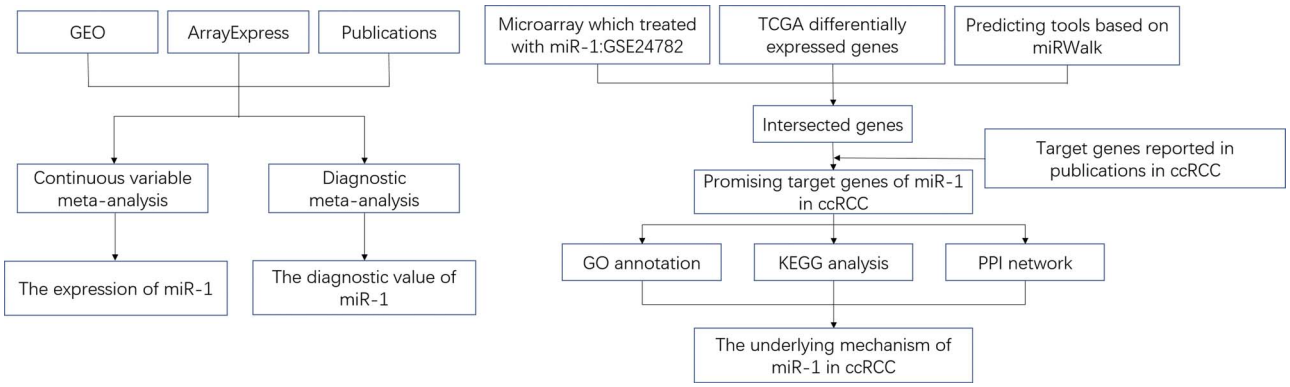

Fig. 1. Flow chart of this study's design.

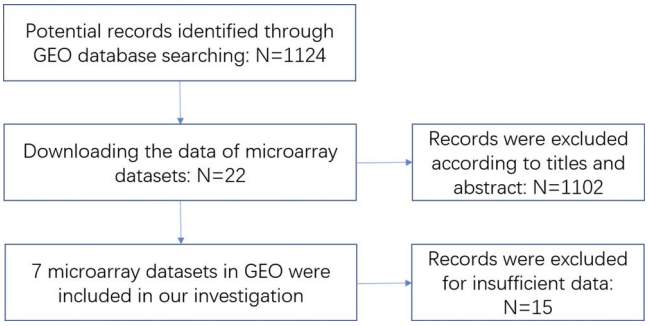

Fig. 2. The flow diagram of searching and screening process as well as the number of screened, excluded, and included microarrays datasets in GEO.

In the present study, we aimed to investigate the clinical value and potential molecular mechanisms of miR-1 in ccRCC. To explore the clinical value of miR-1 in ccRCC, we collected available miR-1 expression data in ccRCC tissues and normal control group tissues from GEO, ArrayExpress, and TCGA databases. Then, the prospective target genes were screened based on the intersection of the predictive genes in 12 online prediction databases, the differential expressed genes (DEGs) post miR-1 overexpression as assessed by microarray, and the DEGs of TCGA database. Based on the potential target genes, the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway, Gene Ontology (GO) analysis and the protein–protein interaction (PPI) network were used to reveal the potential molecular mechanisms for further bioinformatics analysis.

2. Material and methods

2.1. Collection of microarray datasets from GEO and ArrayExpress

The design of our study was shown in Fig. 1. To determine the expression of miR-1 in ccRCC, we searched the GEO and ArrayExpress. The following searching strategy was used: (renal or kidney) and (malignan* OR cancer OR tumor OR tumour OR neoplas* OR carcinoma). The search results were confined to Series and Homo sapiens. Microarray datasets covering the expression value of miR-1 between the ccRCC and control groups were included in the present study. The data in the individual gene chip was transformed to log2 scale. The number, the mean and the standard deviation of the control group and experimental group were calculated based on each single gene chip Fig. 2.

3. TCGA data acquisition

We downloaded miRNA data in the entry of KIRC. The Edge R package was applied to acquire the miRNA expression matrix. Subsequently, the miR-1 expression value was selected and converted into log2 scale. Similarly, the number, the mean and the standard deviation of the control group and experimental group were calculated.

4. Literatures screening

To explore additional information about the miR-1 in ccRCC, we searched PubMed, Science Direct, Google Scholar, Ovid, Wiley Online Library, EMBASE, Web of Science, Chong Qing VIP, CNKI, Wan Fang and China Biology Medicine Disc with the following key words: (renal or kidney) and (malignan* OR cancer OR tumor OR tumour OR neoplas* OR carcinoma) and "clear cell" and (miR-1 OR miRNA-1 OR microRNA-1 OR miR1 OR miRNA1 OR microRNA1 OR "miR 1" OR "miRNA 1" OR "microRNA 1" OR miR-1-3p OR miRNA-1-3p OR microRNA-1-3p OR miR-1-1 OR miR-1-2 OR miR1-1 OR miR1-2). Studies from which the number; the mean and the standard deviation of the control and experimental groups could be extracted were included in the current continuous variable meta-analysis. Moreover; studies from which true positive (TP); false positive (FP); false negative (FN) and true negative (TN) results could be extracted were included in the present diagnostic meta-analysis. Further; we recorded the target genes of miR-1 in ccRCC.

5. Expression of miR-1 in ccRCC based on the included individual study

We described scatter plots in GraphPad Prism 7 based on the included individual study. To further comprehend the expression of miR-1 in ccRCC, we applied another method, ROC curves, in SPSS 23(IBM, NEW YORK, USA).

6. Statistical analysis

In the continuous variable meta-analysis, fixed effects and random