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Analysis of metastasis associated signal regulatory network in colorectal cancer

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ABSTRACT

Metastasis is a key factor that affects the survival and prognosis of colorectal cancer patients. To elucidate molecular mechanism associated with the metastasis of colorectal cancer, genes related to the metastasis time of colorectal cancer were screened. Then, a network was constructed with this genes. Data was obtained from colorectal cancer expression profile. Molecular mechanism elucidated the time of tumor metastasis and the expression of genes related to colorectal cancer. We found that metastasis-promoting and metastasis-inhibiting networks included protein hubs of high connectivity. These protein hubs were components of organelles. Some ribosomal proteins promoted the metastasis of colorectal cancer. In some components of organelles, such as proteasomes, mitochondrial ribosome, ATP synthase, and splicing factors, the metastasis of colorectal cancer was inhibited by some sections of these organelles. After performing survival analysis of proteins in organelles, joint survival curve of proteins was constructed in ribosomal network. This joint survival curve showed metastasis was promoted in patients with colorectal cancer ($P = 0.0022939$). Joint survival curve of proteins was plotted against proteasomes ($P = 7\ e{-}07$), mitochondrial ribosome ($P = 0.0001157$), ATP synthase ($P = 0.0001936$), and splicing factors ($P = 1.35e{-}05$). These curves indicate that metastasis of colorectal cancer can be inhibited. After analyzing proteins that bind with organelle components, we also found that some proteins were associated with the time of colorectal cancer metastasis. Hence, different cellular components play different roles in the metastasis of colorectal cancer.

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1. Introduction

Health and life-expectancy of humans is severely impacted when there is metastasis of malignant tumor. Metastasis usually occurs due to the growth of malignant tumor. In some patients, micrometastasis occurs in early stages of malignant tumor. This troublesome condition cannot be treated with conventional methods of cancer treatment. For many solid tumors, the main routes of metastasis include lymph tract, vessels, and implantation metastasis. Malignant tumors can spread from its original site by local spread and lymphatic spread to regional lymph nodes or by hematogenous spread to distant organs, resulting in compression, embolism, secretion, and even cachexia in advanced stages. It is difficult and expensive to treat metastatic tumors, which severely affect the survival time and prognosis of patients. There has been unreliable on invasive resection of solid tumors because of limitations, such as inadequate resection and local recurrence. Although radiotherapy and chemotherapy are often used to treat cancerous tissues, their efficacy is often limited as they lack tumor specificity and concomitant cytotoxic effects. Recurrent tumor cells are refractory to conventional chemotherapy or radiotherapy, resulting in treatment failure and economic pressures on patients. Presently, conventional treatments of malignant tumors include resection, radiotherapy, and chemotherapy. Because of development in medical technology, many tumors can be treated effectively; however, some patients still die of cancer even after spending a lot of money. Therefore, it is important to identify genes related to metastasis; these genes can be used to predict and prolong the survival rate of colorectal cancer patients. Colorectal cancer is a common tumor of the digestive tract, easily resulting in compression and blocking. Due to blood supply is sufficient to colorectal tissues, metastasis and invasive tumor growth easily occurs. This study aims to investigate the time of metastasis in patients with

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colorectal cancer. We screened genes related to the time of metastasis. Metastasis and tissue expression information was obtained from colorectal cancer expression profile, which was constructed from protein-protein interaction network by using genes that promote or inhibit tumor metastasis. Network module, cellular components, and key molecules were analyzed subsequently. Furthermore, survival analysis was performed on network module and key molecules to determine the potential molecular mechanism that promotes and inhibits tumor metastasis in patients with colorectal cancer.

2. Materials and methods

2.1. Source of data

For screening genes related to metastasis of colorectal cancer, we used GEO (Gene Expression Omnibus) database in NCBI [1,2]. We searched colorectal cancer expression profile with metastasis-free survival time and chose the dataset GSE28722. The dataset GSE28722 included the data of 125 patients with colorectal cancer, including metastasis-free survival time and metastasis status information.

2.2. Metastasis-related genes screening based on the time of metastasis

After collecting data from GSE28722 dataset, SAM 3.01[3,4] software was used to screen metastasis-related genes with respect to following parameters: metastasis-free time, metastasis occurrence status, and gene expression. We identified genes that were positively and negatively related to the time of colorectal cancer metastasis. Hence, we also identified genes that promote or inhibit tumor metastasis.

2.3. Analysis of metastasis-related genes in biological process and cellular components

To determine the underlying biological process and cellular components of metastasis-related genes, enrichment analysis of metastasis-related genes was performed on biological process and cellular components by using Toppgene tool.

2.4. Network construction and network module analysis of metastasis-related genes

Protein-protein interaction network was constructed with String (Search Tool for the Retrieval of Interacting Genes/Proteins) [5,6], which was based on screened genes that promote and inhibit metastasis. An experiment parameter was performed to determine the reliability of protein connectivity. It was maked that all protein were screened metastasis-related proteins and protein-binding confidence score was greater than 0.7. By using MCODE plug-in[7] in Cytoscape software, [8,9] The score was used to calculate network modules and to determine modules of higher connectivity. Because most network modules were composed of organelle components, we considered the chosen network module as a whole. Furthermore, we only reserved grade 2 network hubs that were connected with network modules. By analyzing proteins bound with orgenelle components, we determined the potential molecular mechanism through which organelle components affected survival time.

2.5. Survival analysis of protein hubs in network

The PROGgeneV2 tool collects gene expression data for various types of cancer in the GEO (Gene Expression Omnibus) and TCGA (The Cancer Genome Atlas) databases and uses MySQL as a database to store these gene expression information, covariates data and metadata. Users can perform survival analysis by inputting a single gene or a combination of several genes, selected such different parameters as cancer types, survival variables (death, metastasis, recurrence) and gene expression bifurcation methods (average, median, 25th percentile and 75th percentile). After obtaining information input by the user, the PROGgeneV2 tool can retrieve related data sets (including gene expression data, survival variable data, and covariate data) from the MySQL database, and send the collected data to the back-end R script for Kaplan Meier survival analysis and graphing.

In order to verify the reliability of metastasis-related genes (These genes were screened by SAM 3.01 software.), survival analysis of genes in the network was performed with PROGgeneV2[10,11]. We found that GSE28722 dataset was included in the database of PROGgeneV2. In this study, metastasis-free survival analysis was performed on protein hubs of networks, which were based on the dataset GSE28722. The median of gene expression value was used to determine groups that showed high and low expression. Survival curve was used to determine the correlation between protein hubs and metastasis time in patients with colorectal cancer. Survival analysis of multiple proteins was performed by using PROGgeneV2. Most network modules consisted of organelle components, which could be analyzed to determine whether changes in different organelle components affected metastasis time of patients with colorectal cancer.

3. Results

3.1. Screening results of genes were related to metastasis time in patients with colorectal cancer

In 125 patients with colorectal cancer, genes related to metastasis time were screened. Based on positive and negative correlation between metastasis time and gene expression, 1406 metastasis-promoting genes and 1650 metastasis-inhibiting genes were identified. By increasing the expression of 1406 metastasis-promoting genes, we speculate the survival time of metastasis-free patients decreased. By increasing the expression of 1650 metastasis-inhibiting genes, we speculate the survival time of metastasis-free patients was increased.

3.2. Analysis of metastasis-related genes involved in biological process and cellular components

By performing enrichment analysis on 1406 metastasis-promoting genes, we identified genes involved in angiogenesis and extracellular matrix. This indicates that the key molecular event of colorectal cancer metastasis was angiogenesis. By performing enrichment analysis on 1650 metastasis-inhibiting genes, we identified genes involved in cell cycle and mitochondrion. This implies that metastasis-promoting genes were enriched in extracellular matrix, so they may be related to adhesion and migration of tumors. Meanwhile, metastasis-inhibiting genes were enriched in mitochondrion. By enhancing the function of mitochondrion, tumor metastasis can be inhibited (Table 1).

3.3. Construction of metastasis-related genes network and analysis of network module

Protein-protein interaction networks of 1406 metastasis-promoting genes and 1650 metastasis-inhibiting genes were constructed with String tool. Network modules were analyzed using MCODE plug in of Cytoscape software. Finally, we found one highly

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