Bioinformatic exploration of MTA1-regulated gene networks in colon cancer

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Abstract Metastasis-associated gene 1 (MTA1) controls a series of biological processes in tumor progression. Tumor progression is a complex process regulated by a gene network. The global cancer gene regulatory network must be analyzed to determine the position of MTA1 in the molecular network and its cooperative genes by further exploring the biological functions of this gene. We used TCGA data sets and GeneCards database to screen MTA1-related genes. GO and KEGG pathway analyses were conducted with DAVID and gene network analysis via STRING and Cytoscape. Results showed that in the development of colon cancer, MTA1 is linked to certain signal pathways, such as Wnt/Notch/nucleotide excision repair pathways. The findings also suggested that MTA1 demonstrates the closest relationship in a coregulation process with the key molecules AKT1, EP300, CREBBP, SMARCA4, RHOA, and CAD. These results lead MTA1 exploration to an in-depth investigation in different directions, such as Wnt, Notch, and DNA repair.

Keywords metastasis-associated gene 1; colon cancer; bioinformatics

Introduction

Cancer is the most fatal disease worldwide and costs over 8 000 000 lives in 2012. Cancer prevalence has also been rising in recent decades in China. The development and advancement of cancer involve delicate gene regulation network cascades, even with several feedback pathways. The multiple aspects of malignant behavior cannot be explained easily from the view of single-gene regulation mechanism, which is a traditional strategy to explore the mechanism of cancers. However, no gene is powerful enough to be responsible for all the cancer characteristics.

A new trend to investigate cancer mechanism is through gene regulation network analysis, i.e., system biology. Network analysis provides a global view of gene function, thereby facilitating the discovery of new clues on cancer progression.

The most notorious behavior of malignant cancer is metastasis. This process of cancer cells allows them to leave their original locations and circulate to other sites to settle down for new offspring. Metastasis, which is usually linked to the mortality of approximately 90% of patients with cancer, is a cutoff marker for the prognosis of these patients. Therefore, the mechanisms underlying metastasis should be highly prioritized in cancer research.

Metastasis-associated gene 1 (MTA1) has been shown to control a series of biological events related to cancer malignancy, particularly invasion and metastasis. MTA1 is first reported to be highly expressed in highly metastasis-potentiated breast cancers [1]. MTA1 is overexpressed in many cancers, such as breast, esophageal, gastric, colorectal, and pancreatic cancers and their corresponding cell lines [2,3]. MTA1 is an important component of the nucleosomal remodeling complex (NuRD), displaying dual regulatory functions as a corepressor and coactivator for numerous genes. MTA1 is first discovered and found to be correlated to cancer malignant behaviors. Previous reports indicate that this gene is a potent malignancy mediator through ER and NuRD. However, these individual gene regulation links cannot adequately provide a comprehensive overview of MTA1 function, and the most prominent effect that MTA1 exerts on cells, leading to their transformation into advanced cancer lesions, is not sufficiently screened. For instance, Ghanta et al. outlined

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a transcriptional profiling network in mouse embryonic fibroblasts, exploring p53-related MTA1 sublinks [4]. However, a network analysis from a global aspect remains lacking. In the present study, we investigated the enriched functions and pathways of MTA1 by analyzing the currently available gene regulation data in the TCGA database.

Materials and methods

Cancer sample-linked database for colorectal adenocarcinoma was retrieved from the TCGA website (http://tcga-data.nci.nih.gov/docs/publications/colorectal_2012/) [5]. The bioinformatic analysis procedures are described as follows: (1) cBioPortal [6,7] was used to screen genes that coexpressed (including upregulated and downregulated genes) with MTA1 by taking an absolute value of > 0.4 as the cutoff of Pearson correlation coefficient. (2) The identified gene set was overlapped with the colon-cancer-related gene list extracted from GeneCards [8] through Venny, thereby resulting in MTA1-related genes in colon cancer. (3) All the genes underwent GO and KEGG analyses on DAVID platform [9,10]. (4) We used the STRING online platform [11] to achieve the potential interactome of protein products of these genes; Cytoscape was further adopted [12] to identify the proteins at the key knots in the protein interactome. The gene regulation networks and protein interactions were visualized during analyses.

Results

We withdrew the MTA1-correlated gene set from the colon cancer gene expression profiling database with cBioPortal RNA-Seq-RPKM Co-Expression tool by setting the Pearson correlation efficient to > 0.4. Including MTA1 itself, 1103 genes were identified to be related to MTA1. The 1103 genes were overlapped with 3625 genes, which were defined as colon cancer genes in GeneCards with Venny. A total of 176 MTA1-related colon cancer genes, which were employed to analyze the gene regulation network (Fig. 1), were produced.

Gene function annotation and enrichment were performed by GO and KEGG analyses. In colon cancer, GO annotation suggested that MTA1-associated cancer genes were mostly enriched in several functions, such as chromatin modification and organization, large-molecule metabolism, and gene expression regulation (Fig. 2A). KEGG pathway exploration uncovered significant pathways in Wnt, Notch, cancer development, excision repair, and apoptosis, etc. (Fig. 2B).

Among the 176 MTA1-related colon cancer genes, the separately or loosely spotted gene products were filtered, and the 134 gene products showed potential physical interaction in the STRING database, thereby forming a complicated multicentric interactive network (Fig. 3). The significantly interacted genes were imported into Cytoscape to calculate the topological features. For colon cancer, the topography included 134 nodes and 427 edges with the maximal connectivity value of 43. A great connectivity value indicated a strong interaction among proteins, thereby contributing key properties to stabilize the network model. The top six genes with the highest connectivity values were AKT1 (43), EP300(31), CREBBP (27), SMARCA4(23), RHOA (22), and CAD (22) (the connectivity values are shown in parentheses) (Fig. 4).

Discussion

TCGA provides an increasingly large amount of genome sequencing and expression data in cancerous and corresponding normal samples. This database offers a series of tools to perform gene filtering and screening for differentially expressed genes. To date, TCGA has enrolled 458 cases of colon cancer samples with detailed transcriptional profiling data, as well as genomic abnormality and modification information, including amplification, mutation, deletion, methylation, and even noncoding RNA signatures. These data provide a precious and economic resource to identify potential targets that play key roles in cancer development or cancer treatment.

In this study, we extracted the gene expression data in a series of colon cancer cases from the TCGA database. We then used cBioPortal online tools to screen potential MTA1-regulated genes in colon cancer, followed by GO, KEGG, and protein interactome analyses to determine some clues for further mechanistic studies on colon cancer development and advancement.

MTA1 is first cloned from breast cancer with high metastasis potential, and it is demonstrated to be positively