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Bioinformatic Prediction of Hub Genes by Analysis of Signaling Pathways, Transcriptional Regulatory Networks and DNA Methylation Pattern in Colon Cancer

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Abstract : Anomalous nexus of complex topological assemblies and spatiotemporal epigenetic choreography at chromosomal territory may forms the most sophisticated regulatory layer of gene expression in cancer. Colon cancer is one of the leading malignant neoplasms of the lower gastrointestinal tract worldwide. There is still a paucity of information about the complex molecular mechanisms of colonic cancerogenesis. Bioinformatics prediction and analysis helps to identify essential genes and significant pathways for monitoring and conquering this deadly disease. The present study investigates and explores potential hub genes as biomarkers and effective therapeutic targets for colon cancer treatment. Colon cancer patient sample containing gene expression profile datasets, such as GSE44076, GSE20916, and GSE37364 were downloaded from Gene Expression Omnibus (GEO) database and thoroughly screened using the GEO2R tool and Funrich software to find out common 2 differentially expressed genes (DEGs). Other approaches, including Gene Ontology (GO) and KEGG pathway analysis, Protein-Protein Interaction (PPI) network construction and hub gene investigation, Overall Survival (OS) analysis, gene correlation analysis, methylation pattern analysis, and hub gene-Transcription factors regulatory network construction, were performed and validated using various bioinformatics tool. Initially, we identified 166 DEGs, including 68 up-regulated and 98 down-regulated genes. Up-regulated genes are mainly associated with the Cytokine-cytokine receptor interaction, IL17 signaling pathway, ECM-receptor interaction, Focal adhesion and PI3K-Akt pathway. Downregulated genes are enriched in metabolic pathways, retinol metabolism, Steroid hormone biosynthesis, and bile secretion. From the protein-protein interaction network, thirty hub genes with high connectivity are selected using the MCODE and cytoHubba plugin. Survival analysis, expression validation, correlation analysis, and methylation pattern analysis were further verified using TCGA data. Finally, we predicted COL1A1, COL1A2, COL4A1, SPP1, SPARC, and THBS2 as potential master regulators in colonic cancerogenesis. Moreover, our experimental data highlights that disruption of lipid raft and RAS/MAPK signaling cascade affects this gene hub at mRNA level. We identified COL1A1, COL1A2, COL4A1, SPP1, SPARC, and THBS2 as determinant hub genes in colon cancer progression. They can be considered as biomarkers for diagnosis and promising therapeutic targets in colon cancer treatment. Additionally, our experimental data advertise that signaling pathway act as connecting link between membrane hub and gene hub.

Keywords : hub genes, colon cancer, DNA methylation, epigenetic engineering, bioinformatic predictions
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