FABP4 Might be an Indicator of the Status of Tumor Microenvironment in Colorectal Cancer

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Research

Keywords: FABP4, tumor microenvironment, ESTIMATE, CIBERSORT, colorectal cancer

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Abstract

Background: As tumor microenvironment (TME) play an indispensable role in tumorigenesis of colorectal cancer, this study performs a bunch of bioinformatics analysis to identify the indicator of the status of TME in Colorectal cancer (CRC).

Results: In the presented study, we applied CIBERSORT and ESTIMATE computational methods to calculate the proportion of tumor-infiltrating immune cells (TICs) and the amount of immune and stromal components in 444 COAD-READ cases from The Cancer Genome Atlas (TCGA) database. The differentially expressed genes (DEGs) were analyzed by COX regression analysis and protein–protein interaction (PPI) network construction. Then, fatty acid-binding protein four (FABP4) was determined as a predictive factor by the intersection analysis of univariate COX and PPI. Further analysis revealed that FABP4 expression was positively correlated with the clinical pathologic characteristics (clinical stage, distant metastasis) and negatively correlated with the survival of CRC patients. Gene Set Enrichment Analysis (GSEA) showed that the genes in the high-expression FABP4 group were mainly enriched in immune-related activities. In the low-expression FABP4 group, the genes were enriched in metabolic pathways. CIBERSORT analysis for the proportion of TICs revealed that NK cell, CD4 + T cells and CD8 + T cells were negatively correlated with FABP4 expression, suggesting that FABP4 might be a potential prognostic factor of CRC patients.

Conclusion: Our study has developed a new biomarker (FABP4) that can predict the status of tumor microenvironment in Colorectal cancer. Keywords: FABP4, tumor microenvironment, ESTIMATE, CIBERSORT, colorectal cancer

Full Text

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Figures

Figure 1

Analysis workflow of this study.

Figure 2

Volcano plots, Heatmaps and Venn plots of DEGs. Volcano plots and Heatmap for DEGs generated by comparison of the high score group vs. the low score group in ImmuneScore (a, b) and StromalScore (c, d). Row name of heatmap is the gene name, and column name is the ID of samples which not shown in plot. Differentially expressed genes were determined by Wilcoxon rank sum test with $|\text{fold change}| > 1$ and false discovery rate (FDR) < 0.05 as the significance threshold. (e, f) Venn plots showing common up-

regulated and down-regulated DEGs shared by ImmuneScore and StromalScore, and $|\text{fold change}| > 1$ and false discovery rate (FDR) < 0.05 as the DEGs significance filtering threshold.

Figure 3

GO and KEGG of DEGs. (a, b, c, d) GO and KEGG enrichment analysis for 771 DEGs, terms with p and $q < 0.05$ were believed to be enriched significantly.

Figure 4

Protein–protein interaction network and univariate COX. (a) Interaction network constructed with the nodes with interaction confidence value >0.95. (b) Univariate COX regression analysis with 771 DEGs, listing the top significant factors with $p < 0.05$. (c) Venn plot showing the common factors shared by nodes in PPI and top significant factors in univariate COX.

Figure 5

The differentiated expression of FABP4 in samples and correlation with survival and clinicopathological staging characteristics of CRC patients. (a) Differentiated expression of FABP4 in the normal and tumor sample. Analyses were performed across all normal and tumor samples with p value closing to zero by Wilcoxon rank sum test. (b) Paired differentiation analysis for expression of FABP4 in the normal and tumor sample deriving from the same one patient ($p = 4e-04$ by the Wilcoxon rank sum test). (c) Survival

GSEA for samples with high FABP4 expression and low expression. (a) The enriched gene sets in KEGG collection by the high FABP4 expression sample. Each line representing one particular gene set with unique color, and up-regulated genes located in the left approaching the origin of the coordinates, by contrast the down-regulated lay on the right of x-axis. Only gene sets with P-value <0.05 and FDR < 25% were considered significant. And only several leading gene sets were displayed in the plot. (b) The enriched gene sets in KEGG by samples with low FABP4 expression. (c) The enriched gene sets in HALLMARK collection by the high FABP4 expression sample. Only several leading gene sets are shown in plot. (d) Enriched gene sets in HALLMARK by the low FABP4 expression. (e) Enriched gene sets in C7 collection, the immunologic gene sets, by samples of high FABP4 expression. Only several leading gene sets are shown in plot. (f) Enriched gene sets in C7 by the low FABP4 expression.

Figure 7

TIC profile in tumor samples and correlation analysis. (a) Barplot showing the proportion of 22 kinds of TICs in COAD-READ tumor samples. Column names of plot were sample ID. (b) Heatmap showing the correlation between 22 kinds of TICs and numeric in each tiny box indicating the p value of correlation between two kinds of cells. The shade of each tiny color box represented corresponding correlation value between two cells, and Pearson coefficient was used for significance test.

Figure 8

Correlation of TICs proportion with FABP4 expression. (a) Violin plot showed the ratio differentiation of 22 kinds of immune cells between COAD-READ tumor samples with low or high FABP4 expression relative to the median of FABP4 expression level, and Wilcoxon rank sum was used for the significance test. (b) Scatter plot showed the correlation of 6 kinds of TICs proportion with the FABP4 expression ($p < 0.05$).

The blue line in each plot was fitted linear model indicating the proportion tropism of the immune cell along with FABP4 expression, and Pearson coefficient was used for the correlation test.

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