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Potential Oncogenic and Immunosuppressive Roles of Multiple EGF-Like Domains 6 (MEGF6) in Colon Cancer: Insights from Bioinformatic Analysis

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Abstract

Multiple epidermal growth factor-like domains protein 6 (MEGF6) is a high molecular weight protein with several EGF-like domains. Although it has been demonstrated to promote metastasis and chemoresistance in colon cancer cells, its specific oncogenic and immunologic functions remain largely unexplored. This study aims to comprehensively analyze publicly available datasets to define the role of MEGF6 in colon cancer development and immune response modulation. The expression of MEGF6 in colon adenocarcinoma (COAD) and normal tissues at both mRNA and protein levels was assessed using the GEPIA2 and HPA databases, respectively. The UALCAN database was employed to examine the association between MEGF6 expression and clinicopathological outcomes in COAD patients, and survival analysis was conducted using the KM plotter database. Functional enrichment analysis of MEGF6-correlated genes was performed using the ShinyGO online tool. Additionally, the correlation of MEGF6 with immune cell infiltration and immunosuppressive molecules was explored through the TIMER and TISIDB databases. Our analysis revealed significantly higher mRNA and protein expressions of MEGF6 in COAD tissues compared to normal tissues, with associations to cancer stage, nodal metastasis status, and histological subtype. High MEGF6 expression was correlated with poorer survival outcomes, and genes correlated with MEGF6 were enriched in biological processes related to cellular component organization, cell adhesion, and extracellular matrix interaction. Furthermore, MEGF6 expression demonstrated a significant correlation with immune cell infiltration and the expression of immunosuppressive molecules, particularly CTLA-4, PD-1, PD-L1, TGF-β, and IL-10. In conclusion, our findings suggest that MEGF6 may play an oncogenic role by influencing cell and extracellular matrix interactions. Its overexpression may indicate immunosuppressive properties within the cancer microenvironment. Therefore, MEGF6 holds promise as a potential biomarker for predicting both prognosis and therapeutic responses in colon cancer.

Keywords: MEGF6, Colon cancer, Prognosis, Biomarker, Immunomodulation, Bioinformatics

Introduction

Colon adenocarcinoma (COAD), a prevalent type of colon cancer, poses a significant health challenge due to its widespread occurrence and clinical complexities [1, 2]. According to global cancer statistics from 2022, colorectal cancer is ranked 3rd and 2nd for incidence and mortality, respectively. There were about 1.9 million new cases and approximately 900,000 deaths worldwide for both sexes combined [2]. As one of

the most common malignancies, COAD substantially contributes to the overall cancer burden in both males and females [3]. Despite advancements in diagnostic and treatment modalities, COAD patients are often diagnosed at advanced stages and exhibit suboptimal responses to therapy, resulting in a less favorable prognosis [4, 5]. Consequently, there is a critical need to identify biomarkers for diagnosis and therapeutic targets for effective intervention in colon cancer.

Multiple epidermal growth factor-like domains protein 6 (MEGF6) is a high molecular weight protein with several EGF-like domains, playing a crucial role in embryogenic development [6] and bone formation [7]. Alteration in MEGF6 expression is associated with patient survival in neuroblastoma and B-cell lymphoma [8]. In the context of colon cancer, MEGF6 has been identified as a promoter of cancer metastasis through the epithelial-to-mesenchymal transition (EMT) [9]. The knockdown of MEGF6 has been shown to induce resistance to oxaliplatin in colorectal cancer cells [10]. However, the specific roles of MEGF6 in oncogenic processes in colon cancer remain largely unexplored.

Recent research has demonstrated a growing interest in understanding the complex molecular mechanisms driving the progression and treatment resistance in colon cancer [11, 12]. Within the tumor microenvironment, intricate interactions occur among cancer cells, stromal cells, and various immune cell types. This immune cell infiltration plays a pivotal role in shaping the immune landscape of tumors and influencing cancer development and therapeutic responses [13, 14]. Furthermore, immunoregulatory molecules, such as programmed cell death protein 1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), are crucial for immune evasion and suppression within the tumor microenvironment [15-17]. Thus, exploring the relationship between MEGF6 and immune cell infiltration, along with its impact on the expression of immunoregulatory molecules, could facilitate the development of targeted immunotherapies in colon cancer.

In recent years, numerous high-throughput datasets and bioinformatic tools have become freely accessible, offering valuable resources for comprehensive analysis to gain deeper insights into cancer biology and discover potential new biomarkers [18-20]. In this study, we investigated the role of MEGF6 in colon cancer development and immune response modulation through bioinformatics analyses. The expression of MEGF6 and its association with clinicopathological outcomes in COAD patients were analyzed using the GEPIA2, HPA, and UALCAN databases. The KM plotter database was utilized for survival analysis. The potential roles of MEGF6 in carcinogenesis, immune cell infiltration, and the expression of immunosuppressive molecules were explored using Shiny GO, TIMER, and TISIDB databases.

Materials and methods

Analysis of MEGF6 mRNA and protein level

The investigation into the differential expression of MEGF6 in COAD compared to normal tissues was conducted through the Gene Expression Profiling Interactive Analysis 2 (GEPIA2) database (http://gepia2.cancer-pku.cn/) [21]. The mRNA expression of MEGF6 was assessed in COAD (n = 275) and normal (n = 41) tissue samples within The Cancer Genome Atlas (TCGA) dataset. Additionally, the Human Protein Atlas (HPA) database (http://www.proteinatlas.org) [22, 23] was utilized to explore the protein expression level of MEGF6 in both colon cancer and normal colon tissues.

Analysis of the association between MEGF6 expression and clinicopathological features

The University of Alabama at Birmingham CANcer data analysis portal (UALCAN) database (http://ualcan.path.uab.edu) [24] was employed to explore the association between MEGF6 expression and

clinicopathological features including age, gender, race, cancer stage, nodal metastasis status, and histological subtypes within the TCGA dataset for COAD patients (n = 283).

Survival analysis

The survival analysis for MEGF6 expression in COAD patients was conducted using KM plotter (https://kmplot.com/analysis/) [25]. The Affymetrix probe ID: 213942_at was employed to evaluate the association of MEGF6 expression with overall survival (n = 1,061), post-progression survival (n = 311), and relapse-free survival (n = 1336) in colon cancer patients. The classification into low- and high-MEGF6 expression groups was achieved using the "Auto select best cut-off" option based on the median of expression values.

Functional enrichment analysis of MEGF6-related genes

To investigate the potential involvement of MEGF6 in COAD, the top 100 genes that exhibited a positive correlation with MEGF6 in the TCGA-COAD dataset, as determined by the Pearson correlation coefficient, were extracted from GEPIA2. Subsequently, these genes were subjected to Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses using the ShinyGO (version 0.80) (http://bioinformatics.sdstate.edu/go/) [26]. The threshold for significance in the enrichment analyses was set at a false discovery rate (FDR) ≤ 0.05.

Analysis of the correlation of MEGF6 with immune cell infiltration and immunosuppressive molecules

The correlation between MEGF6 expression and the infiltration level of immune cells in COAD, including B cells, $CD8^+$ T cells, CD4+ T cells, neutrophils, macrophages, and dendritic cells, was assessed using the Tumor Immune Estimation Resource (TIMER) database (https://cistrome.shinyapps.io/timer/) [27, 28]. Additionally, the Tumor and Immune System Interaction Database (TISIDB) (http://cis.hku.hk/TISIDB) [29] was employed to analyse the correlation between MEGF6 expression and the expression of immunosuppressive molecules.

Statistical analysis

The differential expression analysis was carried out using one-way ANOVA in GEPIA2 and Student's t-test with unequal variance in UALCAN, respectively. Survival analysis was conducted using the Kaplan-Meier method along with the log-rank test. The correlation between MEGF6 and immune cell infiltration and immunosuppressive molecules was assessed through Spearman's correlation test. A *p*-value less than 0.05 was statistically significant.

Results and discussion

Expression of MEGF6 mRNA and protein was increased in colon cancer tissue

We evaluated the differential expression of MEGF6 in COAD and normal colon tissues at both the mRNA and protein levels using the GEPIA2 and HPA databases, respectively. The results revealed a significant increase in MEGF6 expression in COAD compared to normal colon samples, as demonstrated in both mRNA (**Figure 1(A)**) and protein (**Figure 1(B)**) analyses.

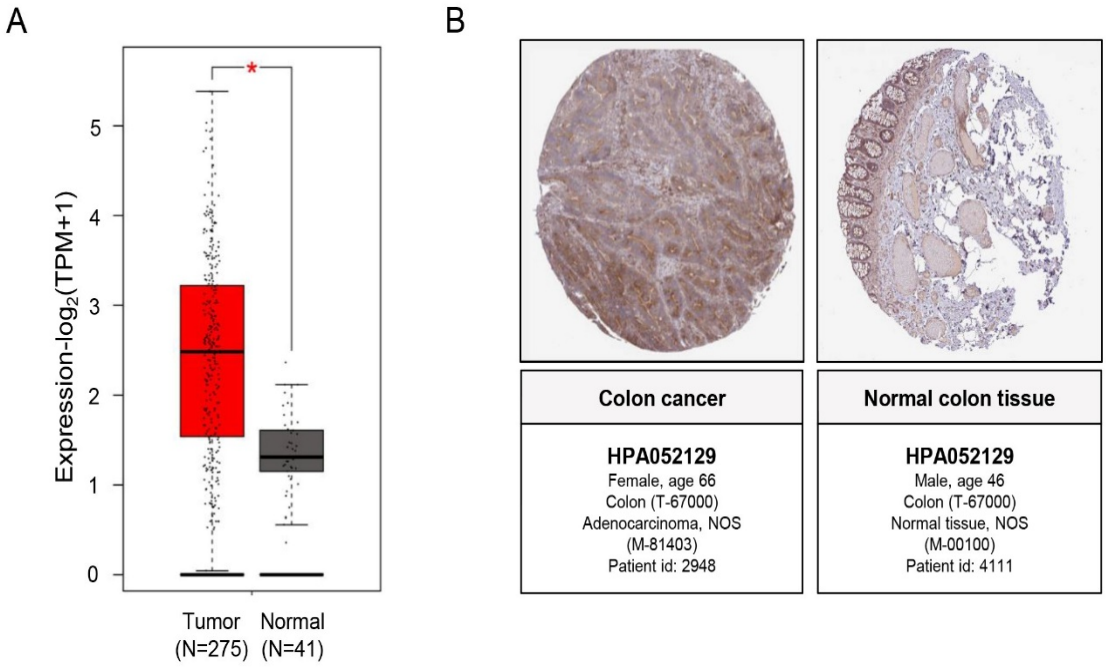

Figure 1 Expression of MEGF6 mRNA and protein in colon cancer compared to normal colon tissues. (A) The mRNA expression level of MEGF6 was investigated in the TCGA-COAD dataset through the GEPIA2. (B) Representative immunohistochemistry images of MEGF6 staining were obtained from the HPA database. *$p < 0.05$.

MEGF6 expression was correlated with cancer stage, nodal metastasis status, and histological subtypes of colon cancer

The relationship between MEGF6 expression and clinicopathological features among COAD patients was investigated using the UALCAN database. The findings indicated that patient age, gender, and race did not exhibit significant correlations with MEGF6 expression (**Figures 2(A)** to **2(C)**, respectively). However, MEGF6 expression demonstrated a correlation with cancer stage, nodal metastasis status, and histological subtypes. Elevated expression levels were observed in higher cancer stages (**Figure 2(D)**) and nodal metastasis statuses (**Figure 2(E)**). Additionally, patients diagnosed with mucinous adenocarcinoma in COAD exhibited significantly higher MEGF6 expression levels compared to those with adenocarcinoma (**Figure 2(F)**).

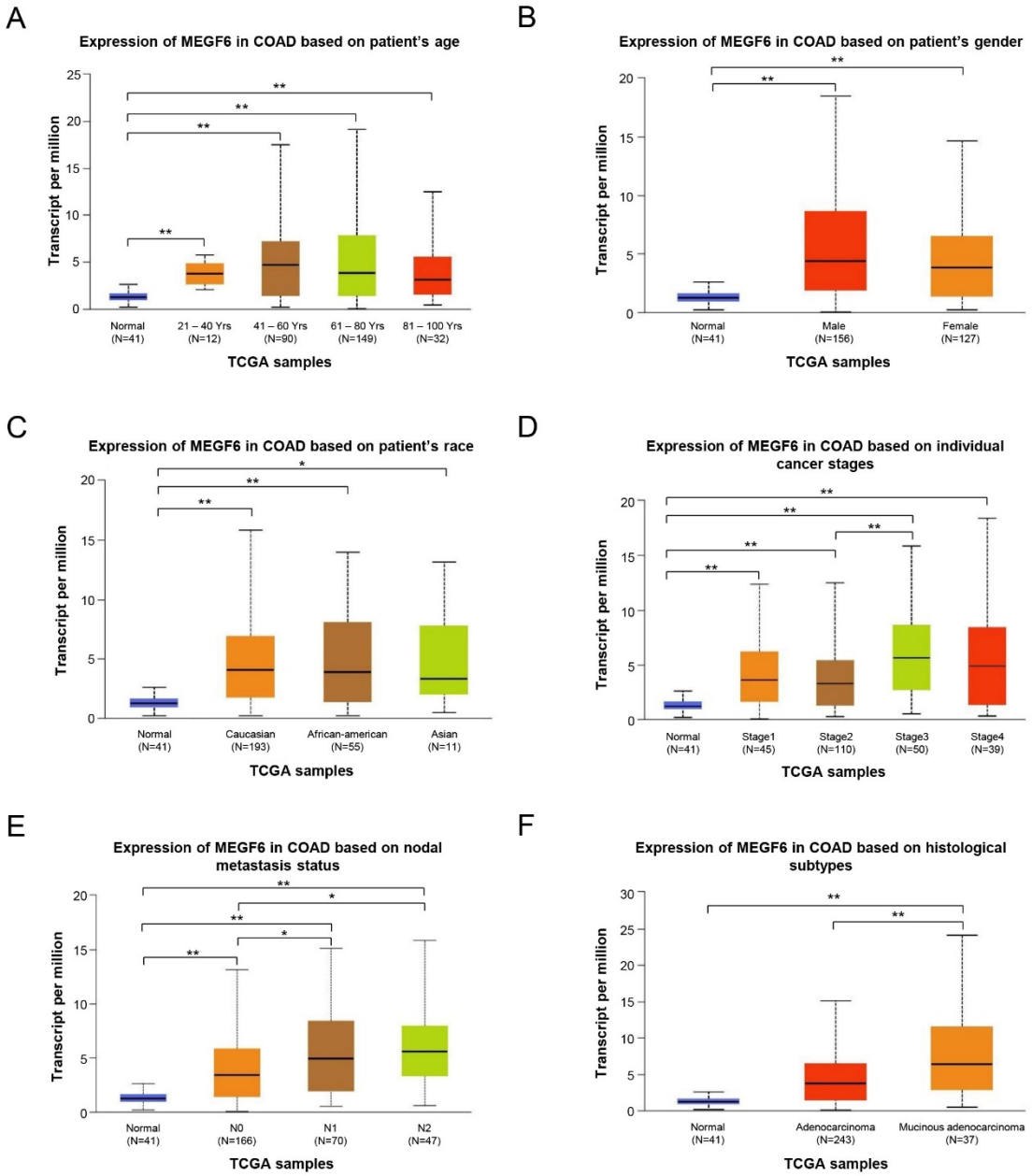

Figure 2 Association between MEGF6 expression and clinicopathological features of COAD patients. Bar plots represent the expression of MEGF6 in patients based on age (A), gender (B), race (C), cancer stage (D), nodal metastasis status (E), and histological subtypes (F), obtained from the UALCAN database. *$p <$ 0.05. **$p < 0.01$.

High MEGF6 expression was significantly associated with poor survival outcomes in COAD patients

We conducted an investigation into the correlation between MEGF6 expression and the survival outcomes of COAD patients using the KM plotter database. High MEGF6 expression was found to be significantly associated with poor survival outcomes in COAD patients. Specifically, COAD patients with high MEGF6 expression exhibited shorter overall survival (**Figure 3(A)**), post-progression survival (**Figure 3(B)**) and relapse-free survival (**Figure 3(C)**) compared to their counterparts with low MEGF6

expression. These findings are consistent with a previous study [9], supporting the potential role of MEGF6 as a biomarker for colon cancer progression and prognosis.

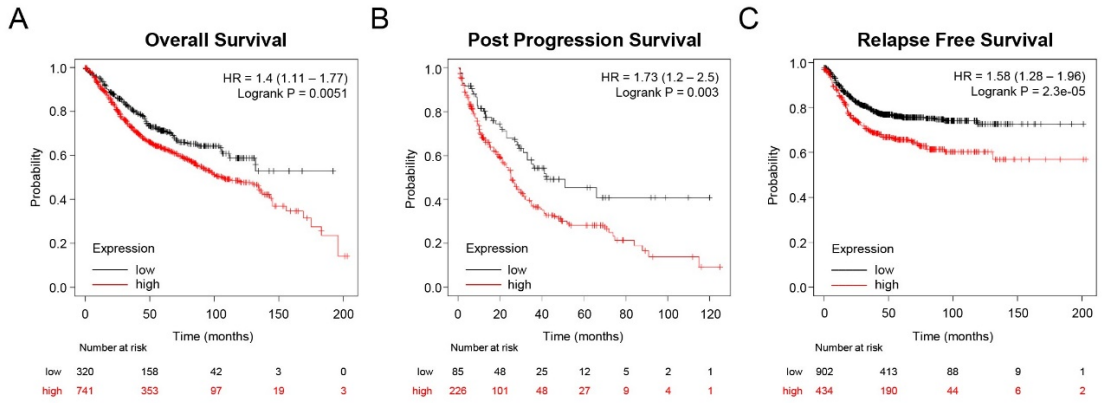

Figure 3 Association between MEGF6 expression and survival outcomes of COAD patients. Kaplan-Meier curves for overall survival (A), post-progression survival (B), and relapse-free survival (C) in COAD patients with low and high MEGF6 expression were obtained from the KM plotter database.

The MEGF6-correlated genes in COAD were mainly enriched in cellular processes related to cell adhesion and extracellular matrix interactions

To date, our understanding of the biological functions of MEGF6 remains limited. While it has been demonstrated to regulate the EMT process via the TGF-β/SMAD signaling pathway [9], the precise roles of MEGF6 in colon cancer remain largely unknown. To unravel the potential role of MEGF6 in colon cancer, we conducted a comprehensive functional enrichment analysis of genes correlated with MEGF6 using the ShinyGO tool. A detailed list of these genes is summarized in **Table S1**. The results revealed that MEGF6-correlated genes predominantly participated in several GO biological processes, including "supramolecular fiber organization", "regulation of Rab protein signal transduction" and "Ras protein signal transduction" (**Figure 4(A)**). Significant enrichment in GO cellular components mainly included "perinuclear region of cytoplasm", "focal adhesion" and "cell-substrate junction" (**Figure 4(B)**). The primary molecular functions associated with MEGF6-correlated genes were linked to "GTPase regulator activity", "nucleoside-triphosphatase regulator activity" and "GTPase activator activity" (**Figure 4(C)**). Furthermore, KEGG pathway enrichment analysis uncovered the significant involvement of MEGF6-correlated genes in pathways such as "ECM-receptor interaction", "phospholipase D signaling pathway", and "focal adhesion" (**Figure 4(D)**), indicating potential involvement of MEGF6 in cellular processes related to cell adhesion and interactions with the extracellular matrix.

It is known that cell-matrix interaction plays a critical role in cancer metastasis [30]. Among the various signaling pathways implicated, the Wnt signaling pathway is recognized as a key regulator of cell adhesion, linked to other cellular processes in colon cancer [30,31]. A previous study has reported that transcriptional factor 3 (TCF3) regulates the expression of several genes, including MEGF6, Wnt family member 2B (WNT2B), and TGF-β3 (TGFB3). Genes involved in cell adhesion, such as cadherin 3 (CDH3), protocadherin 7 (PCDH7), transglutaminase 2 (TGM2), and podocalyxin like (PODXL) is downregulated in TCF3-knockdown spermatogonial stem cells [32]. These findings suggest that MEGF6 may contribute to its oncogenic mechanism through the regulation of cell adhesion and may be linked to the Wnt signaling

pathway. Further elucidation of these mechanisms is warranted to better understand the role of MEGF6 in colon cancer development and progression.

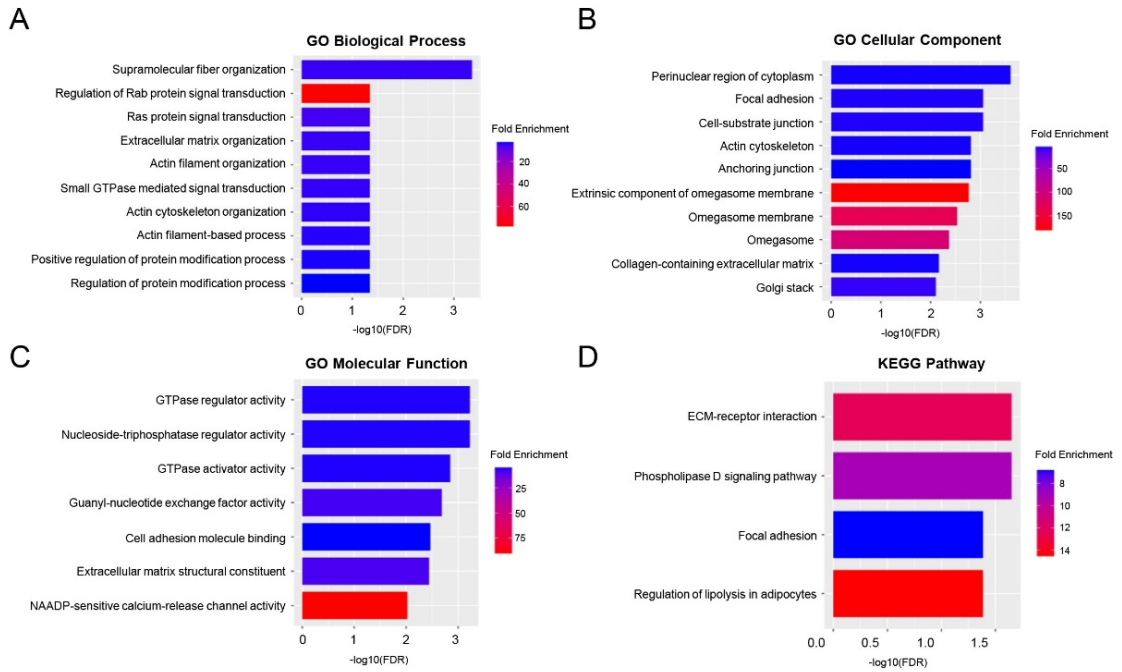

Figure 4 Functional enrichment of MEGF6-correlated genes in COAD. Gene ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment of the top 100 positively correlated with MEGF6 in the TCGA-COAD dataset were analyzed using the ShinyGO online tool. Bar plots represent significantly enriched GO terms for biological process (A), cellular component (B), molecular function (C), and KEGG pathway (D) assigned to MEGF6-correlated genes.

MEGF6 expression was correlated with the infiltration level of immune cells and the expression of immunosuppressive molecules

The tumor microenvironment significantly influences cancer development, progression, and responses to therapy in colorectal cancer [13, 14]. Immune cell infiltration levels and the expression of immunomodulatory molecules correlate with the survival outcomes and responses to immunotherapy in colorectal cancer patients [15-17]. Therefore, we further explored the relationship between MEGF6 expression and immune cell infiltration, as well as the expression of immunosuppressive molecules in COAD, using the TIMER and TISIDB databases, respectively. The results demonstrated a significant positive correlation between MEGF6 expression and B cells ($r = 0.146$, $p = 3.22\times10^{-3}$), CD4+ T cells ($r = 0.365$, $p = 4.36\times10^{-14}$), macrophages ($r = 0.279$, $p = 1.19\times10^{-8}$), neutrophils ($r = 0.318$, $p = 7.23\times10^{-11}$), and dendritic cells ($r = 0.323$, $p = 3.20\times10^{-11}$) in COAD. However, there was no significant correlation between MEGF6 and $CD8^+$ T cells ($r = 0.055$, $p = 2.70\times10^{-1}$) (**Figure 5(A)**). A previous study has shown that CRC patients with high neutrophil infiltration have a poorer prognosis compared to those with low neutrophil infiltration [16]. Additionally, tumor-associated macrophages have been found to promote colon cancer metastasis [33], suggesting that MEGF6 expression correlates with a tumor-promoting environment in colon cancer. Nevertheless, the underlying mechanisms of MEGF6 in regulating immune cell infiltration need further elucidation.

Regarding the relationship between MEGF6 and the immunosuppressive microenvironment, TISIDB database results revealed a positive correlation between MEGF6 expression and various immunosuppressive molecules (**Figure 5(B)**), with significant correlations observed with key immunosuppressive molecules, including CTLA4 (r = 0.138, $p = 3.15\times10^{-3}$), PD-1 (r = 0.24, $p = 2.05\times10^{-7}$), PD-L1 (r = 0.17, $p = 2.54\times10^{-4}$), transforming growth factor beta (TGF-β) (r = 0.435, $p < 2.2\times10^{-16}$), and interleukin-10 (IL-10) (r = 0.134, $p = 2.54\times10^{-4}$) (**Figure 5(C)**). Although the role of MEGF6 in immunity remains largely unknown, a previous study showed that MEGF6 levels in serum and lung increase in septic mice, and its overexpression prevents inflammation in mice with acute lung injury [34]. Collectively, these findings suggest that MEGF6 expression may indicate immunosuppressive properties within the cancer microenvironment and could serve as an indicator for predicting therapeutic responses in colon cancer.

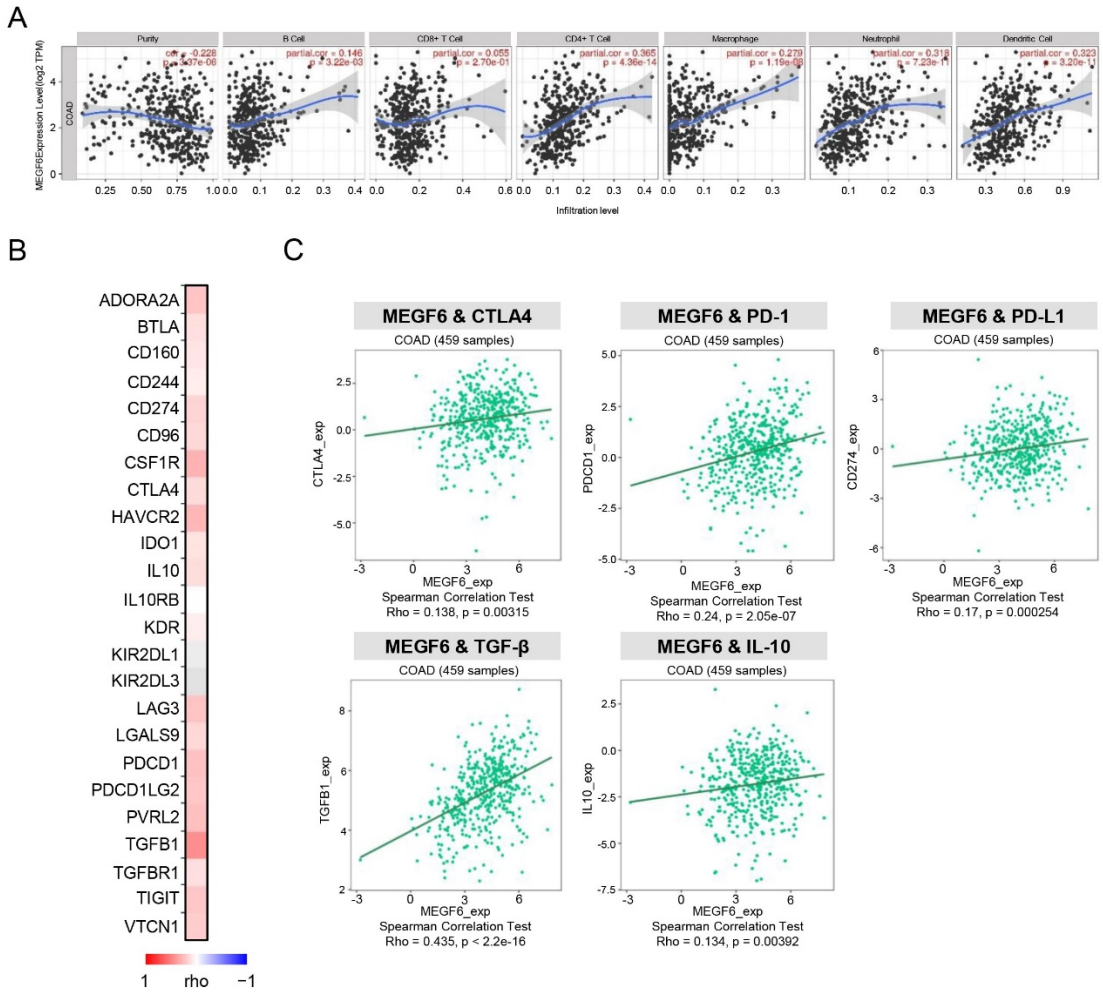

Figure 5 Correlation of MEGF6 with immune cell infiltration and immunosuppressive molecules. (A) Scatter plots represent the correlation between MEGF6 expression and the infiltration level of immune cells in the TIMER database. (B) The heatmap represents Spearman's correlation coefficient for the correlation of MEGF6 expression with immunosuppressive molecules in the TISIDB database. (C) Scatter plots depict the correlation of MEGF6 expression with CTLA4, PD-1, PD-L1, TGF-β, and IL-10 expressions in the TISIDB database.

Our study sheds light on the potential role of MEGF6 in colon cancer biology, offering implications for clinical applications and future investigations. Through our exploration of the relationship between MEGF6 and clinicopathological characteristics, disease prognosis, and immune responses in COAD, our findings contribute to a deeper understanding of colon cancer pathogenesis. This knowledge could potentially accelerate the development of precise treatments and predictive biomarkers. Targeting MEGF6 and its related pathways may serve as a potential therapeutic approach for COAD. However, it is crucial to acknowledge its limitations. First, our analyses relied on the availability of limited datasets accessible online, which may introduce inherent biases. The inclusion of more comprehensive datasets would enhance the robustness of our findings. Second, to validate our results, further experiments and prospective studies are necessary. Finally, the underlying mechanism and clinical significance of MEGF6 in COAD development and immunotherapeutic responses require further research with a more in-depth study.

Conclusions

In summary, our data revealed elevated levels of both MEGF6 mRNA and protein in COAD compared to normal tissues, and this overexpression was linked to reduced overall survival in COAD patients. MEGF6 may exert its oncogenic effects by influencing cell adhesion and interactions with the extracellular matrix. Furthermore, the expression of MEGF6 was correlated with immune cell infiltration and the expression of immunosuppressive molecules. These findings provide new insights into the potential role of MEGF6 in colon cancer and underscore its value as a prognostic and therapeutic response biomarker.

Acknowledgments

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Supplementary materials

Table S1 List of the top 100 genes that were positively correlated with *MEGF6* in TCGACOAD dataset in the GEPIA2 database.

No.	Gene symbol	Gene ID	Description	Pearson correlation coefficient
1	*ARRDC2*	ENSG00000105643.9	Arrestin domain containing 2	0.57
2	*ABTB1*	ENSG00000114626.17	Ankyrin repeat and BTB domain containing 1	0.54
3	*GSN-AS1*	ENSG00000235865.2	GSN antisense RNA 1	0.51
4	*PNPLA2*	ENSG00000177666.15	Patatin like phospholipase domain containing 2	0.51
5	*RAPGEF3*	ENSG00000079337.15	Rap guanine nucleotide exchange factor 3	0.51
6	*AHNAK*	ENSG00000124942.13	AHNAK nucleoprotein	0.5
7	*DENND3*	ENSG00000105339.10	DENN domain containing 3	0.5
8	*DENND6B*	ENSG00000205593.11	DENN domain containing 6B	0.5
9	*EHBP1L1*	ENSG00000173442.11	EH domain binding protein 1 like 1	0.5
10	*GSN*	ENSG00000148180.16	Gelsolin	0.5
11	*LTBP4*	ENSG00000090006.17	Latent transforming growth factor beta binding protein 4	0.5
12	*MYO9B*	ENSG00000099331.13	Myosin IXB	0.5
13	*MCOLN1*	ENSG00000090674.15	Mucolipin TRP cation channel 1	0.49
14	*PLEC*	ENSG00000178209.14	Plectin	0.49
15	*ULK1*	ENSG00000177169.9	Unc-51 like autophagy activating kinase 1	0.49
16	*BHLHE41*	ENSG00000123095.5	Basic helix-loop-helix family member e41	0.48
17	*CYTH1*	ENSG00000108669.16	Cytohesin 1	0.48
18	*ITGB5*	ENSG00000082781.11	Integrin subunit beta 5	0.48
19	*PHLDB1*	ENSG00000019144.16	Pleckstrin homology like domain family B member 1	0.48
20	*SFXN3*	ENSG00000107819.13	Sideroflexin 3	0.48
21	*SLC12A4*	ENSG00000124067.16	Solute carrier family 12 member 4	0.48
22	*AKAP13*	ENSG00000170776.19	A-kinase anchoring protein 13	0.47
23	*ARHGAP1*	ENSG00000175220.11	Rho GTPase activating protein 1	0.47
24	*ASAP2*	ENSG00000151693.9	ArfGAP with SH3 domain, ankyrin repeat and PH domain 2	0.47
25	*CBLN3*	ENSG00000139899.10	Cerebellin 3 precursor	0.47
26	*LAMB2*	ENSG00000172037.13	Laminin subunit beta 2	0.47
27	*MYOF*	ENSG00000138119.16	Myoferlin	0.47
28	*THBS3*	ENSG00000169231.13	Thrombospondin 3	0.47
29	*TNK2*	ENSG00000061938.16	Tyrosine kinase non receptor 2	0.47
30	*ZFYVE1*	ENSG00000165861.13	Zinc finger FYVE-type containing 1	0.47
31	*B3GALT4*	ENSG00000235863.3	Beta-1,3-galactosyltransferase 4	0.46
32	*CBLB*	ENSG00000114423.18	Cbl proto-oncogene B	0.46
33	*FAM65A*	ENSG00000039523.17	RHO Family Interacting Cell Polarization Regulator 1	0.46

No.	Gene symbol	Gene ID	Description	Pearson correlation coefficient
34	*MADD*	ENSG00000110514.18	MAP kinase activating death domain	0.46
35	*MGAT1*	ENSG00000131446.15	Alpha-1,3-mannosyl-glycoprotein 2-beta-N-acetylglucosaminyltransferase	0.46
36	*NOX4*	ENSG00000086991.12	NADPH oxidase 4	0.46
37	*RASA3*	ENSG00000185989.10	RAS p21 protein activator 3	0.46
38	*RIPK1*	ENSG00000137275.13	Receptor interacting serine/threonine kinase 1	0.46
39	*RP11-134L10.1*	ENSG00000272941.1	Novel Transcript, Antisense To C7orf49	0.46
40	*STAT2*	ENSG00000170581.13	Signal transducer and activator of transcription 2	0.46
41	*ADAMTS10*	ENSG00000142303.13	ADAM metallopeptidase with thrombospondin type 1 motif 10	0.45
42	*BTBD19*	ENSG00000222009.8	BTB domain containing 19	0.45
43	*C10orf54*	ENSG00000107738.19	Btb Domain Containing 19	0.45
44	*C1QTNF1*	ENSG00000173918.14	V-Set Immunoregulatory Receptor	0.45
45	*CTD-3035K23.7*	ENSG00000274565.1	Lnc-MARCH10-4	0.45
46	*FAM214B*	ENSG00000005238.19	Atos Homolog Protein B	0.45
47	*IFFO1*	ENSG00000010295.19	Intermediate filament family orphan 1	0.45
48	*LINC01429*	ENSG00000227964.1	Long intergenic non-protein coding RNA 1429	0.45
49	*MAFK*	ENSG00000198517.9	MAF bZIP transcription factor K	0.45
50	*MPRIP*	ENSG00000133030.19	Myosin phosphatase Rho interacting protein	0.45
51	*MXRA8*	ENSG00000162576.16	Matrix remodeling associated 8	0.45
52	*PIAS3*	ENSG00000131788.15	Protein inhibitor of activated STAT 3	0.45
53	*RP11-426C22.4*	ENSG00000259807.1	Lnc-NPIPB11-2	0.45
54	*RP11-426C22.5*	ENSG00000260517.2	Lnc-SLX1B-3	0.45
55	*SLC25A45*	ENSG00000162241.12	Solute carrier family 25 member 45	0.45
56	*SLC39A13*	ENSG00000165915.13	Solute carrier family 39 member 13	0.45
57	*TPCN1*	ENSG00000186815.12	Two pore segment channel 1	0.45
58	*WDR86*	ENSG00000187260.15	WD repeat domain 86	0.45
59	*AEBP1*	ENSG00000106624.8	AE binding protein 1	0.44
60	*AHDC1*	ENSG00000126705.13	AT-hook DNA binding motif containing 1	0.44
61	*CRY2*	ENSG00000121671.11	Cryptochrome circadian regulator 2	0.44
62	*EPG5*	ENSG00000152223.12	Ectopic P-granules 5 autophagy tethering factor	0.44
63	*GOLGA2*	ENSG00000167110.16	Golgin A2	0.44
64	*HDAC7*	ENSG00000061273.17	Histone deacetylase 7	0.44
65	*IL4R*	ENSG00000077238.13	Interleukin 4 receptor	0.44
66	*INAFM1*	ENSG00000257704.3	InaF motif containing 1	0.44
67	*INSR*	ENSG00000171105.13	Insulin receptor	0.44
68	*KDM4B*	ENSG00000127663.14	Lysine demethylase 4B	0.44
69	*LCAT*	ENSG00000213398.7	Lecithin-cholesterol acyltransferase	0.44
70	*LTBP2*	ENSG00000119681.11	Latent transforming growth factor beta binding protein 2	0.44
71	*PIM1*	ENSG00000137193.13	Pim-1 proto-oncogene, serine/threonine kinase	0.44

No.	Gene symbol	Gene ID	Description	Pearson correlation coefficient
72	*PIP5K1C*	ENSG00000186111.8	Phosphatidylinositol-4-phosphate 5-kinase type 1 gamma	0.44
73	*PTTG1IP*	ENSG00000183255.11	PTTG1 interacting protein	0.44
74	*SWAP70*	ENSG00000133789.14	Switching B cell complex subunit SWAP70	0.44
75	*TCP11L2*	ENSG00000166046.10	T-complex 11 like 2	0.44
76	*THBS2*	ENSG00000186340.14	Thrombospondin 2	0.44
77	*TRAK1*	ENSG00000182606.14	Trafficking kinesin protein 1	0.44
78	*UNC5B*	ENSG00000107731.12	Unc-5 netrin receptor B	0.44
79	*AC068580.6*	ENSG00000235027.1	PRC2 And DDX5 Associated LncRNA	0.43
80	*ADCY7*	ENSG00000121281.12	Adenylate cyclase 7	0.43
81	*ARHGEF2*	ENSG00000116584.17	Rho/Rac guanine nucleotide exchange factor 2	0.43
82	*CTIF*	ENSG00000134030.13	Cap binding complex dependent translation initiation factor	0.43
83	*DSTNP1*	ENSG00000230982.1	DSTN pseudogene 1	0.43
84	*FUT11*	ENSG00000196968.10	Fucosyltransferase 11	0.43
85	*GOLGB1*	ENSG00000173230.15	Golgin B1	0.43
86	*HCG4B*	ENSG00000227262.3	HLA complex group 4B	0.43
87	*KLC1*	ENSG00000126214.20	Kinesin light chain 1	0.43
88	*LOXL1*	ENSG00000129038.15	Lysyl oxidase like 1	0.43
89	*PFKFB3*	ENSG00000170525.18	6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3	0.43
90	*PSTPIP1*	ENSG00000140368.12	Proline-serine-threonine phosphatase interacting protein 1	0.43
91	*RP1-137D17.1*	ENSG00000226194.5	Lnc-WDR27-1	0.43
92	*SCARF2*	ENSG00000244486.7	Scavenger receptor class F member 2	0.43
93	*SUN1*	ENSG00000164828.17	Sad1 and UNC84 domain containing 1	0.43
94	*SUSD6*	ENSG00000100647.7	Sushi domain containing 6	0.43
95	*TMEM140*	ENSG00000146859.6	Transmembrane protein 140	0.43
96	*UACA*	ENSG00000137831.14	Uveal autoantigen with coiled-coil domains and ankyrin repeats	0.43
97	*YPEL3*	ENSG00000090238.11	Yippee like 3	0.43
98	*KCTD11*	ENSG00000213859.4	Potassium channel tetramerization domain containing 11	0.42
99	*TRIM8*	ENSG00000171206.13	Tripartite motif containing 8	0.42
100	*TSPAN4*	ENSG00000214063.10	Tetraspanin 4	0.42