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Original Article

Clinical and Prognostic Values of REEP2 in Colorectal Cancer

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Abstract : REEP2 (Receptor Expression-Enhancing Protein 2) has been implicated in various cellular processes, but its clinical relevance in colorectal cancer in colorectal cancer (CRC) remains unclear. This study aimed to evaluate the association between REEP2 expression and clinicopathologic features, molecular correlations, and patient prognosis in colon and rectal cancers using The Cancer Genome Atlas (TCGA) data. In rectal cancer, higher REEP2 expression has statistically significant relation with venous invasion, advanced pathologic stage, advanced M stage, and advanced N stage. In colon cancer, higher REEP2 expression has statistically significant relation with lymphatic invasion, venous invasion, advanced N stage, colon mucinous adenocarcinoma type, and anatomic neoplasm. Survival analysis showed that higher REEP2 expression was significantly associated with poorer overall survival in colon cancer ($p=0.020$), and showed a trend toward worse prognosis in rectal cancer ($p=0.078$). High REEP2 expression is associated with aggressive tumor characteristics and poor survival outcomes in colorectal cancer, particularly in colon cancer. To enhance our knowledge, further studies to demonstrate the molecular pathogenesis and clinical characteristics of REEP2 gene in colorectal cancer should be needed.

Keywords : REEP2, Colorectal cancer, TCGA, Cancer prognosis

INTRODUCTION

Colorectal cancer (CRC) is third most commonly diagnosed and second most fatal cancer in the world [1]. In 2020, 9.4% of cancer-related deaths were caused by CRC. The pathogenesis of CRC is associated with both genetic and environmental factors. The majority of 70~80% of CRC are sporadic, while 20~30% of CRC have a hereditary component, due to either uncommon or rare, high-risk, susceptibility syndromes, such as Lynch Syndrome (3~4%) and familial adenomatous polyposis (approximately 1%) [2]. A major feature of CRC is genetic instability caused by at least two different mechanisms [3]. The adenoma-carcinoma series mainly represents the majority of human CRCs with the accumulation of mutation including APC, K-ras, and p53 genes [4]. Although the molecular genetics in CRC pathogenesis have been widely studied, further studies are still needed.

Receptor Expression-Enhancing Protein 2 (REEP2) is encoded by the REEP2 gene located on chromosome 5q31.2 [5]. It belongs to the REEP (Receptor Expression-Enhancing Protein) family, which is known to facilitate the

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surface expression of G protein-coupled receptors (GPCRs), including olfactory receptors (ORs) [6]. REEP proteins play a crucial role in enhancing the trafficking and functional expression of GPCRs, thereby influencing a variety of cellular signaling pathways.

Mutations in REEP1 are a well-established genetic cause of hereditary spastic paraplegia (HSP), and similar pathogenic mutations in REEP2 have also been identified in families with HSP [7-9]. Beyond their neurological implications, recent studies have highlighted the broader biological significance of the REEP family. These proteins are involved in diverse cellular processes such as endoplasmic reticulum (ER) morphogenesis and remodeling, regulation of the microtubule cytoskeleton, and intracellular trafficking of membrane proteins, particularly GPCRs [8,10].

Additionally, the REEP family has been implicated in a wide range of diseases, including neurological disorders, diabetes, retinal and cardiac diseases, infertility, obesity, oligoarticular juvenile idiopathic arthritis, COVID-19, and various types of cancer [10]. Specifically, altered expression of REEP family members has been associated with breast cancer [11], hepatocellular carcinoma [12], lung cancer [13], and kidney clear cell carcinoma [14]. Despite these associations, the role of REEP2 in colorectal cancer (CRC) remains largely unexplored.

Therefore, the aim of this study is to investigate the clinical and prognostic significance of REEP2 expression in colorectal cancer and to explore its potential molecular correlations using data from The Cancer Genome Atlas (TCGA). In particular, this study focuses on analyzing the clinical features of REEP2 in colorectal cancer and provides preliminary data to support future research.

MATERIALS AND METHODS

1. TCGA data analysis

We used primary data from TCGA portal (http://cancergenome.nih.gov/) in Feburary 2025. This provided the p-value ranking for REEP2 prognosis for each cancer type (Fig. 1). The cancer type that showed the most promising results (colon cancer and rectal cancer) was selected, and a detailed analysis was performed. In total, 440 colon cancer patients and 158 rectal cancer patients were profiled for the survival analysis. Survival was defined as the time interval from surgery until the date of death.

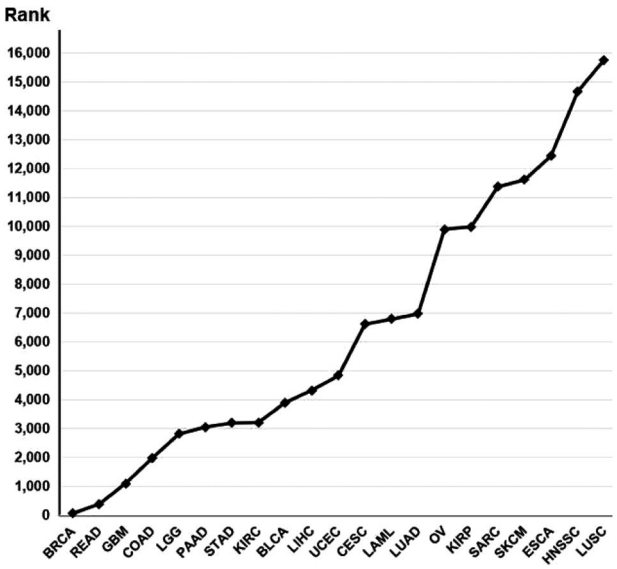

Fig. 1. The rank of survival value of REEP2 in various cancers.

2. Statistical analysis

Data were analyzed using SPSS (version 25.0; IBM SPSS, Armonk, NY, USA). The TNM stage was determined according to the seventh edition of the American Joint Committee on Cancer staging system. Clinicopathological characteristics, including age, sex, carcinoembryonic antigen level, and pathological TNM stage, were analyzed using the chi-square test. Spearman's correlation coefficient was used for the correlation analyses between the REEP2 genes and variables related to rectal cancer. Univariate survival analysis was performed using Kaplan-Meier curves and the log-rank test. Overall survival was defined as the time between diagnosis and mortality. Statistical significance was set at $p < 0.05$.

RESULTS

To assess the clinical significance of REEP2 expression, patients were divided into two subgroups based on the median REEP2 expression level. The clinical correlations of REEP2 expression are summarized in Tables 1 and 2. In rectal cancer, high REEP2 expression was significantly associated with venous invasion ($p = 0.044$), advanced pathologic stage ($p = 0.039$), advanced M stage ($p = 0.020$), and advanced N stage ($p = 0.026$). Although not statistically significant, there was a trend toward associations with lymphatic invasion ($p = 0.088$) and higher T stage ($p = 0.055$).

Table 1. Clinical characteristics of REEP2 gene in rectal cancer

	REEP2		
	High	Low	*P*-value
Age			
<65	39	36	0.687
≥65	40	42	
Gender			
Female	38	33	0.466
Male	41	45	
Lymphatic invasion			
No	34	48	**0.088**
Yes	32	25	
CEA			
≤5	26	35	0.328
>5	23	21	
Venous invasion			
No	44	58	**0.044**
Yes	22	13	
Pathologic stage			
Stage I	9	20	**0.039**
Stage II	24	23	
Stage III	24	24	
Stage IV	17	7	
M stage			
M0	56	62	**0.020**
M1	17	6	
N stage			
N0	35	44	**0.026**
N1	20	23	
N2	23	9	
T stage			
T1	1	8	**0.055**
T2	13	14	
T3	56	51	
T4	9	4	

Table 2. Clinical characteristics of REEP2 gene in colon cancer

	REEP2		
	High	Low	*P*-value
Age			
<65	91	70	**0.085**
≥65	129	140	
Gender			
Female	106	99	0.532
Male	114	120	
Lymphatic invasion			
No	111	132	**0.004**
Yes	92	60	
CEA			
≤5	93	96	0.638
>5	47	43	
Venous invasion			
No	138	152	**0.003**
Yes	59	31	
Pathologic stage			
Stage I	40	32	**0.056**
Stage II	72	98	
Stage III	72	54	
Stage IV	32	29	
M stage			
M0	162	163	0.708
M1	32	29	
N stage			
N0	116	141	**0.027**
N1	56	48	
N2	48	30	
T stage			
T1	6	5	0.947
T2	38	36	
T3	149	153	
T4	27	24	
Histological type			
Colon adenocarcinoma	180	194	**0.029**
Colon mucinous adenocarcinoma	38	22	
MSI			
Indeterminate	0	2	0.111
MSI-H	40	36	
MSI-L	37	42	
MSS	138	136	
Colon polyps			
No	117	125	0.761
Yes	65	65	
Anatomic neoplasm			
Ascending colon	46	39	**0.008**
Cecum	46	55	
Descending colon	9	10	
Hepatic flexure	19	8	
Sigmoid colon	74	71	
Splenic flexure	4	3	
Transverse colon	16	22	

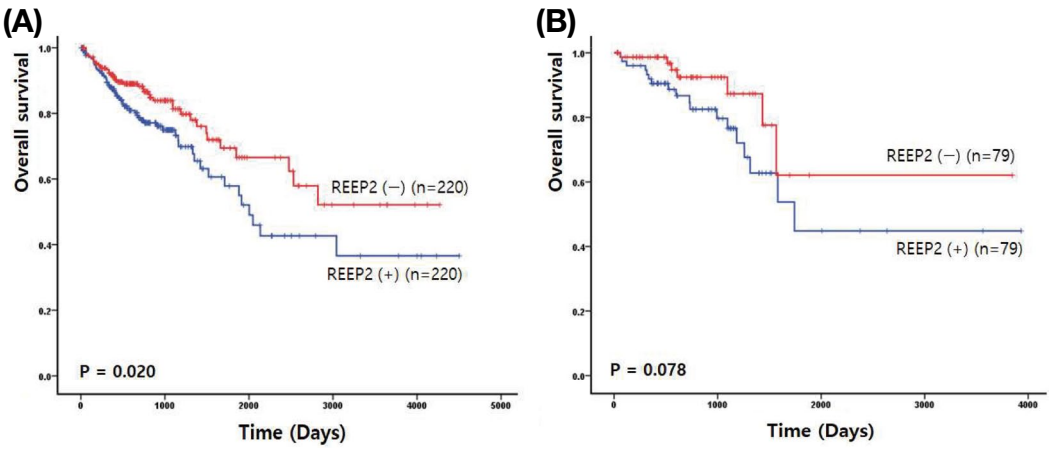

Fig. 2. Univariate survival analysis in colon cancer (A) and rectal cancer (B). Blue line: High REEP2 expression group; Red line: Low REEP2 expression group.

In colon cancer, high REEP2 expression was significantly associated with lymphatic invasion ($p=0.004$), venous invasion ($p=0.003$), advanced N stage ($p=0.027$), mucinous adenocarcinoma subtype ($p=0.029$), and tumor location ($p=0.008$). Although not statistically significant, there were trends toward associations with older age ($p=0.085$) and more advanced pathologic stage ($p=0.056$).

A univariate survival analysis was performed to determine the prognostic value of REEP2 in colon cancer (Fig. 2A) and rectal cancer (Fig. 2B). REEP2 expression had statistically significant prognostic value (2473.93 ± 221.35 vs 2924.70 ± 197.65 days, $\chi^2=5.39$, $p=0.020$) in colon cancer. In the overall survival analysis, REEP2 expression had statistically significant prognostic value (2368.96 ± 315.91 vs 2861.13 ± 389.82 days, $\chi^2=3.10$, $p=0.078$) in rectal cancer.

DISCUSSION

In this study, we demonstrated for the first time the clinical and prognostic significance of REEP2 expression in colorectal cancer (CRC), utilizing data from The Cancer Genome Atlas (TCGA). Members of the REEP family are known to facilitate the trafficking and surface expression of G protein-coupled receptors (GPCRs), and to contribute to the morphogenesis and remodeling of the endoplasmic reticulum (ER) [5,10].

GPCRs regulate a broad spectrum of biological processes involved in oncogenesis and tumor progression, including cell cycle control, proliferative signaling, evasion of growth suppressors, resistance to apoptosis, angiogenesis, and metastasis—collectively known as the hallmarks of cancer [15,16]. Furthermore, GPCRs are implicated in the regulation of cancer stem cell functions such as self-renewal, differentiation, and pluripotency, which are key contributors to tumor heterogeneity and therapeutic resistance [17]. Clinically, GPCRs are considered high-potential therapeutic targets for solid tumors, with approximately 36% of FDA-approved drugs acting on GPCRs, underscoring their centrality in current pharmacotherapy [15].

The ER is a highly dynamic organelle essential for various cellular functions, including protein synthesis, folding, and transport; lipid and steroid biosynthesis; calcium storage and signaling; and inter-organelle communication [18,19]. ER stress, resulting from disturbances in its homeostasis, disrupts critical cellular processes such as proliferation, differentiation, and apoptosis [20]. Sustained ER stress and the activation of its downstream signaling pathways have been shown to promote tumor growth, angiogenesis, resistance to radiotherapy, and modulation of immune responses [21-23]. Recent studies have also highlighted the role of ER stress in colorectal cancer pathogenesis [24,25].

Given REEP2's dual role in GPCR trafficking and ER function, our findings suggest that it may serve as a key molecular link between these two cancer-related pathways in CRC. We observed that high REEP2 expression was significantly associated with venous invasion, advanced pathological stage, and advanced M and N stages in rectal cancer, and with lymphatic and venous invasion, and advanced N stage in colon cancer. Additionally, survival analysis

revealed that elevated REEP2 expression was significantly correlated with poorer overall survival, particularly in colon cancer. These findings support the hypothesis that REEP2-mediated GPCR and ER stress pathways may contribute to key steps in oncogenesis, including angiogenesis and metastasis.

The observed associations between REEP2 expression and aggressive tumor characteristics, as well as its prognostic implications, highlight its potential as both a biomarker and a therapeutic target in CRC. While the REEP family has been previously associated with several cancers—such as breast cancer [11], hepatocellular carcinoma [12], lung cancer [13], and clear cell renal cell carcinoma [14]—its role in CRC remains underexplored. Notably, REEP5 has been reported to be upregulated in advanced-stage colorectal cancer and is known to neutralize HCCR1, a tumor-promoting protein that interferes with p53 function, thereby contributing to CRC progression [26,27]. Furthermore, REEP2 has been identified as a chemosensitivity-related gene in gastric cancer cells [28].

CONCLUSION

This study is the first to demonstrate a significant association between REEP2 expression and colorectal cancer using TCGA data. High REEP2 expression correlated with more aggressive clinical features and poorer survival, suggesting its potential as a prognostic biomarker and therapeutic target in CRC. While the findings are promising, limitations such as a relatively small sample size and lack of multivariate analysis warrant caution. Further research with larger cohorts and mechanistic studies is essential to clarify the biological role of REEP2 and its clinical relevance. Continued integration of bioinformatics tools such as GEPIA2, TIMER2, cBioPortal, UALCAN, Kaplan-Meier Plotter will support these future investigations [29].

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