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LAMA1 Is a Potential Molecule Associated with Poor Prognosis in Patients with Rectal Adenocarcinoma

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1. Abstract

1.1. Objectives: LAMA1 is expressed in a variety of tumors, but its role in rectal adenocarcinoma is not clear. This study was based on the tumor Genome Map (TCGA) database to explore the relationship between LAMA1 and rectal adenocarcinoma.

1.2. Materials and Methods: The patients with rectal adenocarcinoma were from TCGA. Wilcoxon rank sum test was used to compare the expression of LAMA1 in rectal adenocarcinoma and normal tissues. Cox regression and Kaplan-Meier methods were used to analyze the correlation between LAMA1 and survival rate. Besides, gene set enrichment analysis (GSEA) was used to investigate the biological functions of LAMA1.

1.3. Results: Kaplan-Meier survival analysis showed that the overall survival rate (OS) of patients with high expression of LAMA1 was significantly higher than that of patients with low expression of LAMA1(P=0.01). Univariate analysis showed that the low expression level of LAMA1 was associated with the deterioration of overall survival rate (OS) (P=0.010, HR = 0.276 (95%CI [0.104-0.733]). Multivariate analysis showed that LAMA1 was closely related to OS (P=0.026, HR=0.200 (95%CI [0.049-0.822]). GSEA shows that the high expression phenotype of LAMA1 has a significant enrichment effect on pathways in cancer, chemokine signaling pathway, IL18 signaling pathway, senescence and autophagy in cancer, T cell proliferation and regulation of cell morphogenesis. LAMA1 may be a prognostic indicator of low survival rate in patients with rectal adenocarcinoma.

1.4. Conclusion: Decreased LAMA1 level may be a potential biomarker for diagnosis and prognosis of rectal adenocarcinoma. In addition, LAMA1 may be involved in the occurrence and development of rectal adenocarcinoma through chemokine signaling pathway and IL18 signaling pathway.

2. Introduction

Colorectal cancer is a common malignant tumor, and its morbidity and mortality are increasing. The global cancer report in 2020 shows that colorectal cancer has become the third most common cancer in the world. In 2020, there were 1,931,590 cases of colorectal cancer diagnosed worldwide, 935,173 people died of colorectal cancer, and the mortality rate was the second-highest. Colorectal cancer is the first malignant tumor of the digestive system in the world [1,2], especially rectal cancer is the most common. According to the patients' clinical symptoms, the early lesions of colorectal cancer are not easy to be detected, but the treatment effect is not optimistic after the development of advanced cases. It is an urgent need for clinical treatment to reduce the incidence of patients and improve the survival rate of patients. However, the exploration of new molecular targets and markers for rectal adenocarcinoma is still in its infancy. Therefore, there is an urgent need to find new immune-related markers to achieve early diagnosis and treatment of rectal adenocarcinoma. The LAMA1 chromosome is located in 18p11.31. Because the α1 chain of laminin plays an important role in maintaining the structure and function of Laminin, if the LAMA1 gene is mutated or expressed abnormally, it will have an important effect on the synthesis, distribution, structure, and function of laminin [3]. The research found that LAMA1 regulates the number of Mesangial cells and the deposition of the Mesangial matrix through the TGF-β/Smad signal, which plays a key role in renal function and renal aging [4]. We further found that LAMA1 is up-regulated in a variety of cancers,

such as esophageal squamous cell carcinoma, melanoma, gastric cancer, and colorectal cancer [5-8]. It plays a key role in tumor metastasis and can be used as a biomarker for the diagnosis and prognosis of patients with colorectal cancer. However, so far, there are few reports on the relationship between LAMA1 and rectal adenocarcinoma. The purpose of this study was to demonstrate the correlation between protein LAMA1 and rectal adenocarcinoma and to analyze the prognostic role of LAMA1 in rectal adenocarcinoma based on The Cancer Genome Atlas (TCGA). Therefore, we analyzed the expression level of protein LAMA1 in rectal adenocarcinoma and normal tissues based on TCGA. What's more, we analyzed the incidence and clinical characteristics of LAMA1 and rectal adenocarcinoma patients. In addition, we examined the biological pathways associated with the protein LAMA1 and rectal adenocarcinoma by Gene set enrichment analysis (GSEA). GSEA analysis showed that the increase of LAMA1 was related to the poor prognosis of rectal adenocarcinoma. Furthermore, pathways in cancer, chemokine signaling pathway, IL18 signaling pathway, senescence and autophagy in cancer, T cell proliferation, and regulation of cell morphogenesis were all related to LAMA1 expression phenotype.

3. Materials and Methods

3.1. RNA Sequencing and Clinic Information From TCGA Data Repository

Meaningless cases were excluded and 166 cases of rectal adenocarcinoma were included for further analysis to extract relevant RNA-seq data and clinicopathological data. In addition, considering the fact that the relationship between LAMA1 expression and tumor development is independent of follow-up days, we used 167 RNA-seq data for further association analysis and 166 data for survival analysis. What's more, the characteristics of patients including gender, race, pathologic stage, history of colon polyps, colon polyps present, lymphatic or perineural invasion, TNM stage, and residual tumor were recorded. This study does not include direct research of human participants or animals exerted by any authors.

3.2. Gene Set Enrichment Analysis

GSEA approaches represent a computational means of establishing whether a given set of genes differ significantly between a given set of biological states [9]. GSEA analyses were performed based on patients in the TCGA READ datasets with low and high LAMA1 expression levels using the clusterPorfiler package [10]. Ordered gene lists were generated based on the strength of individual correlations with LAMA1 in this analysis, with GSEA being conducted to clarify differences in survival outcomes between patients with low and high LAMA1expression levels. A preliminary GSEA version was utilized for data analysis [11]. Analyses were conducted with 10,000 genome permutations, with LAMA1 expression levels as a phenotypic label. Pathway enrichment was assessed according to nominal P-values and normalized enrichment score (NES) value.

3.3. ssGSEA-Based Immune Cell Analysis

A single-sample GSEA 9(ssGSEA) analysis was used to evaluate immune cell infiltration into rectal adenocarcinoma with the R GSVA package [12]. This approach allowed for GSEA-based analyses of 24 different immune cell populations including natural killer (NK) cells, eosinophils, CD8+ T cells, B cells, Th17 cells, T cells, gamma delta T cells (Tgd), immature dendritic cells (iDCs), mast cells, eosinophils, Th1 cells, plasmacytoid DCs (pDCs), neutrophils, activated DCs (aDCs), DCs, T helper cells, NK CD56dim cells, T follicular helper (Tfh) cells, T effector memory (Tem) cells, macrophages, Th2 cells, central memory T (Tcm) cells, and cytotoxic cells. Based upon characteristic gene expression patterns for these cell types [13], their relative enrichment in each tumor sample was established. Spearman correlation analyses and Wilcoxon rank-sum tests were then used to assess correlations between LAMA1 expression and such immune cell infiltration in patients with different levels of LAMA1 expression.

3.4. Statistical Analysis

R (3.6.3) was used to analyze all data in the present study. Associations between LAMA1 expression levels and clinicopathological variables were assessed via Wilcoxon rank-sum tests and logistic regression analyses, while the associations between patient OS and specific clinicopathological variables were assessed through Kaplan-Meier and Cox regression analyses. The relationship between LAMA1 expression levels, other variables of interest, and patient survival was assessed via a multivariate Cox analysis. median values were used to stratify patients into subgroups with low and high levels of LAMA1 expression. $P < 0.05$ was the threshold of significance.

4. Results

4.1. Clinical Characteristics

In total, 166 patients were identified for inclusion in this study (91 male, 75 female, Table 1). Of these patients, 64 (43.2%) exhibited lymphatic invasion, 32 (21.7%) had a pre-treatment history of colon polyps, and 12 (16.2%) exhibited colonic polyps. Patients with Stage I, II, III, and IV disease accounted for 19.2% (n=30), 32.7% (n=51), 32.6% (n=51), and 15.4% (n=24) of the overall cohort. With respect to staging, 5.4% (n = 8), 17% (n = 28), 68.9% (n = 113), and 8.6% (n = 14) of patients had T1, T2, T3, and T4 disease; 51.9% (n =84), 27.8% (n = 45), and 20.3% (n = 33) had N0, N1, and N2 disease; and 84.6% (n =126) and 15.4% (n = 23) had M0 and M1 disease, 89.7% (n =122), 1.4% (n = 2), and 8.8% (n = 12) had R0, R1, and R2 residual tumor, respectively. In addition, 47 patients (42%) had pre-treatment CEA levels greater that five.

Tabel 1: TCGA rectal adenocarcinoma patient characteristics.

Clinical characteristic	Level	Overall(166)
T stage (%)	T1	9 (5.4%)
	T2	28 (17%)
	T3	113 (68.9%)
	T4	14 (8.6%)
N stage (%)	N0	84 (51.9%)
	N1	45(27.8%)
	N2	33 (18.6%)
M stage (%)	M0	126 (84.6%)
	M1	23 (15.4%)
Pathologic stage (%)	Stage I	30 (19.2%)
	Stage II	51 (32.7%)
	Stage III	51 (32.6%)
	Stage IV	24 (15.4%)
Perineural invasion (%)	NO	40(74%)
	YES	14(26%)
CEA level (%)	<=5	64 (58.1%)
	>5	47 (42%)
Lymphatic invasion (%)	No	84 (56.8%)
	Yes	64 (43.2%)
History of colon polyps (%)	No	115 (78.3%)
	Yes	32 (21.7%)
Colon polyps present (%)	No	62 (83.7%)
	Yes	12 (16.2%)
Residual tumor (%)	R0	122(89.7%)
	R1	2 (1.4%)
	R2	12(8.8%)
Gender (%)	Female	301 (46.7%)
	Male	343 (53.3%)
Race (%)	Asian	1 (1.1%)
	Black or African American	6 (6.8%)
	White	81 (92.1%)

4.1. Assessment of LAMA1 Expression and Diagnostic Utility in Rectal Adenocarcinoma

Using a Wilcoxon rank-sum test, LAMA1 expression was next compared between 167 rectal adenocarcinoma tumor samples and 10 normal tissue samples, revealing the LAMA1 to be significantly downregulated in tumor tissue samples relative to healthy control tissues (P <0.001) (Figure 1A). When LAMA1 levels were compared between rectal adenocarcinoma patient tumors and matched paracancerous tissues, the LAMA1 was similarly found to be downregulated in tumor tissues (P<0.001) (Figure 1B), suggesting that it may be linked to rectal adenocarcinoma development and/or progression. The area under the curve (AUC) of LAMA1 in Figure 1C is 0.973, which indicates that the expression of LAMA1 has a good discrimination ability in tumor and healthy tissues (Under the ROC curve area value from 0.5 to 1, the closer AUC is to 1, the better the diagnostic effect will be. AUC 0.5 ~ 0.7 leads to lower accuracy, while AUC 0.7 ~ 0.9 results in moderate accuracy, and higher accuracy can be guaranteed as AUC is higher than 0.9).

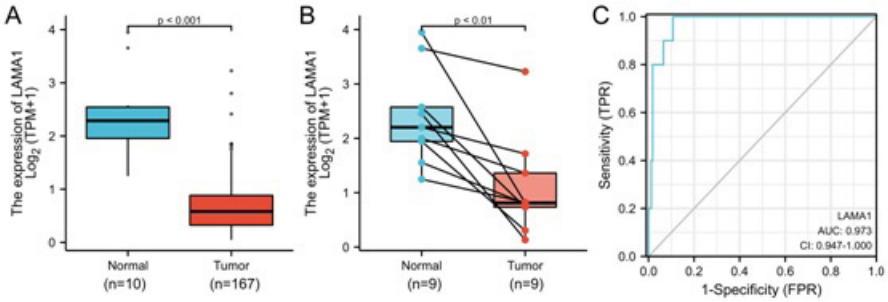

Figure 1: The expression and diagnostic value of LAMA1 in colorectal tissues. (A) LAMA1 showed significantly lower expression in cancer tissues than in normal tissues. (B) LAMA1 was prominently lower expressed in colorectal cancer (p<0.001) compared with 9 pairs non-cancerous adjacent tissues. (C) Receiver Operating Characteristic Curve, FPR, False Positive Rate; TPR, True Positive Rate; CI, Confidence interval.

4.2. Examination of the Relationship between LAMA1 and Patient Survival

Kaplan-Meier survival analyses revealed rectal adenocarcinoma patients with low LAMA1 levels to exhibit a worse prognosis than that of patients expressing higher levels of the LAMA1 (P = 0.01) (Figure 2A), with similar results being obtained when assessing the disease-specific survival (P = 0.019) (Figure 2B). In univariate analyses, low LAMA1 expression was associated with poorer OS (hazard ratio [HR]: 0.276; 95% confidence interval [CI]: 0.104-0.733; P = 0.010), and other variables associated with lower survival rates included age, residual tumor, pathological stage, and NM stage. In multivariate analyses, an independent association between LAMA1 expression and OS was detected (HR = 0.200; 95% CI: 0.049-0.822, P = 0.026), with the same being true for age (Table 2).

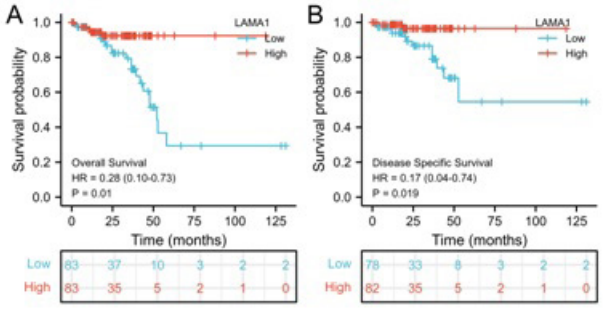

Figure 2: Low expression of LAMA1 is associated with poor OS and PFI in patients with rectal adenocarcinoma. (A) Effect of LAMA1 expression on OS of rectal adenocarcinoma patients in TCGA cohort. (B) Effect of LAMA1 expression on DSS of rectal adenocarcinoma patients in TCGA cohort. TCGA, The Cancer Genome Atlas; OS, overall survival; DSS, disease specific survival.

Table 2: Univariate and multivariate Cox proportional hazards regression analysis of LAMA1 expression.

Characteristics	Total(N)	Univariate analysis			Multivariate analysis	
		Hazard ratio (95% CI)	*P*-value		Hazard ratio (95% CI)	*P*-value
T stage (T1&T2 vs. T3&T4)	164	1.408 (0.476-4.159)	0.536			
Nstage (N0&N1vs. N2)	162	2.609 (1.148-5.929)	0.022		3.534 (0.925-13.494)	0.065
M stage (M0 vs. M1)	149	3.412 (1.424-8.174)	0.006		0.756 (0.081-7.070)	0.806
Pathologic stage (Stage I&Stage II vs. Stage III&Stage IV)	156	3.380 (1.311-8.712)	0.012		1.240 (0.263-5.848)	0.786
Residual tumor(R0&R1 vs. R2)	136	4.937 (1.834-13.286)	0.002		2.500 (0.271-23.061)	0.419
CEA level (<=5 vs. >5)	112	1.453 (0.489-4.316)	0.501		1.178 (0.296-4.687)	0.816
Perineural invasion (No vs. Yes)	54	1.025 (0.203-5.175)	0.977			
Lymphatic invasion(No vs. Yes)	148	1.245 (0.530-2.927)	0.615			
Colon polyps present (No vs. Yes)	74	1.204 (0.331-4.383)	0.778			
History of colon polyps (No vs. Yes)	147	0.952 (0.319-2.844)	0.930			
Race (Asian&Black or African American vs. White)	88	2.612 (0.334-20.412)	0.360			
Gender (Female vs. Male)	166	0.916 (0.422-1.988)	0.824			
Weight (<=90 vs. >90)	75	0.890 (0.308-2.572)	0.829			
BMI(<25 vs. >=25)	73	1.218 (0.341-4.351)	0.762			
Height(<170 vs. >=170)	73	0.756 (0.269-2.127)	0.596			
Age (<=65 vs. >65)	166	3.843 (1.535-9.622)	0.004		6.823 (1.980-23.510)	0.002
LAMA1 (Low vs. High)	166	0.276 (0.104-0.733)	0.010		0.200 (0.049-0.822)	0.026

4.3. GSEA-Based Identification of Signaling Pathways Associated with LAMA1

Next, a GSEA approach was used to compare patterns of gene expression between rectal adenocarcinoma tumors with low and high levels of LAMA1 expression, revealing significant differences in enrichment levels for MSigDB collections (c2.cp.v7.2.symbols.gmt) and (c5.all.v7.2.symbols.gmt) (FDR <0.05, normalized P < 0.05). NES values were then used to select the most enriched signaling pathways (Figure 3 and Table 3), revealing high levels of LAMA1 expression to be associated with the enrichment of pathways in cancer, chemokine signaling pathway, IL 18 signaling pathway, senescence, and autophagy in cancer, T cell proliferation, and regulation of cell morphogenesis.

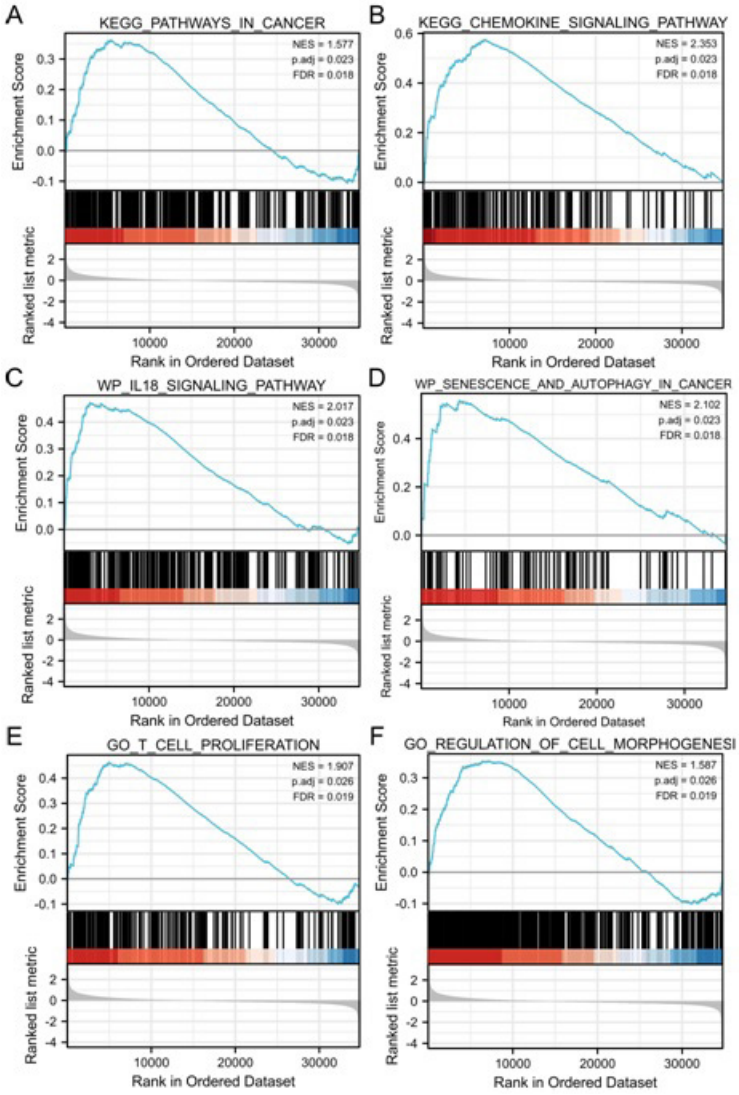

Figure 3: Enrichment plots from gene set enrichment analysis (GSEA). GSEA results showing pathway in cancer (A), chemokine signaling pathway (B), IL 18 signaling pathway (C), senescence and autophagy in cancer (D), T cell proliferation (E), regulation of cell morphogenesis (F) differentially enriched in LAMA1-related rectal adenocarcinoma. NES, normalized ES; FDR, false discovery rate.

Table 3: Gene sets enriched in phenotype high.

MSigDB collection	Gene set name	NES	p.adj	FDR
c2.cp.v7.2.symbols.gmt	KEGG_PATHWAYS_IN_CANCER	1.577	0.023	0.018
	KEGG_CHEMOKINE_SIGNALING_PATHWAY	2.353	0.023	0.018
	WP_IL18_SIGNALING_PATHWAY	2.017	0.023	0.018
	WP_SENESCENCE_AND_AUTOPHAGY_IN_CANCER	2.102	0.023	0.018
c5.all.v7.2.symbols.gmt	GO_T_CELL_PROLIFERATION	1.907	0.026	0.019
	GO_REGULATION_OF_CELL_MORPHOGENESIS	1.587	0.026	0.019

4.4. Immune Cell Infiltration Analysis of LAMA1 in the Rectal Adenocarcinoma

Finally, we examined the relationship between LAMA1 expression and immune cell infiltration as quantified via an ssGSEA analysis in rectal adenocarcinoma samples through a Spearman correlation approach. This strategy revealed higher levels of LAMA1 expression to be positively correlated with Mast cells and DC infiltration ($P<0.001$, Figure 4).

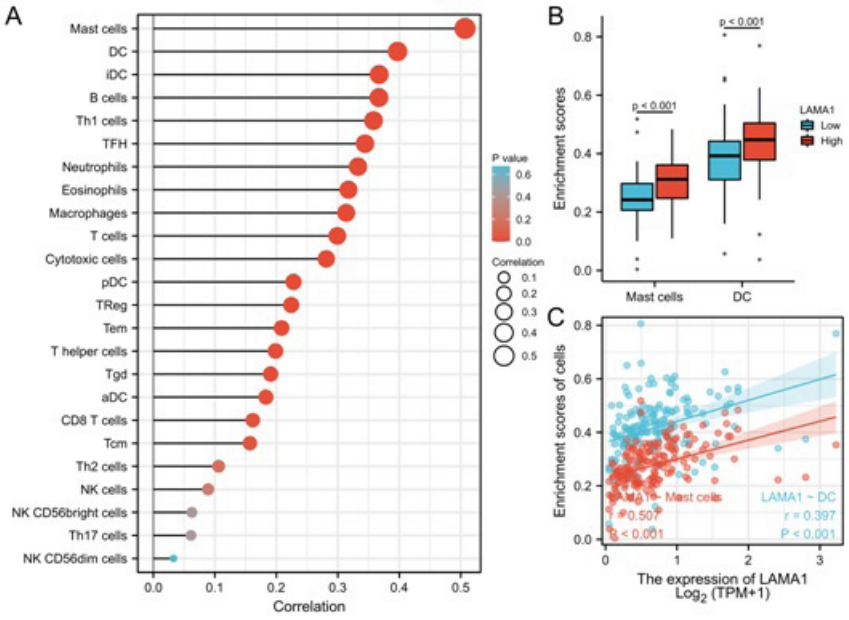

Figure 4: Immune Cell Infiltration Analysis of LAMA1 in the rectal adenocarcinoma. (**A**) The forest plot shows the correlation between LAMA1 expression level and 24 immune cells; (**B**) the enrichment scores of LAMA1 expression in Mast cells and DC; (**C**) The correlation between LAMA1 expression and Mast cells; the correlation between LAMA1 expression and DC.

5. Discussion

In recent years, a large number of studies have shown that LAMA1 plays a key role in tumor metastasis. For example, it can be concluded that laminin α1 (LAMA1) expression was frequently positive in ESCC tissues and LAMA1 overexpression rescued the proliferation inhibition and cell apoptosis elevation induced by miR-202 [14]. However, there are few studies on the relationship between LAMA1 and colorectal cancer. However, there was little correlation between LAMA1 and rectal adenocarcinoma. Therefore, the purpose of this study is to clarify the expression of LAMA1 in rectal adenocarcinoma and its potential therapeutic and prognostic value. In this study, we collected high-throughput RNA sequencing data of rectal adenocarcinoma from the TCGA database and found that the expression of LAMA1 in rectal adenocarcinoma was significantly lower than that in normal or paracancerous tissues. Therefore, the potential role of low expression of LAMA1 in rectal adenocarcinoma is the focus of this study. Studies have shown that the low expression of LAMA1 in rectal adenocarcinoma is related to advanced clinicopathological features (age, clinical stage, pathological stage, residual tumor, lymphatic invasion), short survival time, and poor prognosis. In addition, we also studied the function of LAMA1 in rectal adenocarcinoma by GSEA. The results showed that there were significant differences in cancer pathway, chemokine signal pathway, interleukin-18 signal pathway, senescence and autophagy in cancer, T cell proliferation, and regulation of cell morphogenesis among the high expression phenotypes of LAMA1. It is reported that these pathways are related to the proliferation, invasion, and metastasis of cancer cells [15-19]. It is suggested that LAMA1 may be a new target for the treatment and prognosis of rectal adenocarcinoma. Laminin regulates a variety of cell activities, such as cell adhesion, migration, metastasis, and tumor growth. Laminin is the main component of the extracellular matrix (ECM) structure, which is related to tumor cell metastasis [20]. In addition, the expression of LAMA1 is up-regulated in colorectal cancer. LM α 1 promotes tumorigenesis, growth, and angiogenesis by coordinating the complex crosstalk between cells and the LM-111 matrix [8]. In this study, we found that the expression of LAMA1 was low in rectal adenocarcinoma, and it was related to TNM stage, clinical stage, and pathological stage, suggesting that LAMA1 may play an important role in the occurrence and development of rectal adenocarcinoma. In this study, the prognosis was also analyzed, and the higher the level of LAMA1, the higher the survival rate. To enrich the data information related to LAMA1, we carried out functional annotations based on GSEA and proved that LAMA1 is involved in pathways in cancer, chemokine signaling pathway, IL18 signaling pathway, senescence, and autophagy in cancer, T cell proliferation, and regulation of cell morphogenesis. A recent GO analysis of rectal cancer showed that upregulated DEGs were enriched in the inflammatory response, signal transduction, cell adhesion, immune response, and positive regulation of cell proliferation. KEGG pathway analysis showed that upregulated DEGs were enriched in cytokine-cytokine receptor interaction, Pi3K-Akt signaling pathway, and chemokine signaling pathway [21]. IL-18 is a member of the IL-1 family of cytokines. Studies have shown that IL-18 is a cytokine that stimulates a variety of cell types and has pleiotropic functions [22]. Other studies have shown that neuron-derived IL-18 signaling controls tissue-wide intestinal immunity and has profound consequences on the mucosal barrier and invasive bacterial killing [23]. In addition, mtDNA in colorectal cancer patients

shows the ability of helper T cell proliferation to increase immunity that controls susceptibility to metastasis [24]. Further, a percentage imbalance in Vδ1 and Vδ2 T cells in rectal cancer patients may contribute to the development of rectal cancer [25]. Spearman correlation was used to analyze the relationship between LAMA1 and the quantitative immune cell infiltration level of ssGSEA in STAD, and we found that the expression of LAMA1 was closely related to the infiltration level of mast cells and dendritic cells. Studies have shown that the integrated gene biomarker group combined with immune cell infiltration can effectively indicate rectal cancer [26]. CBXs are not only associated with the overall survival of patients with rectal cancer but also may be a potential prognostic biomarker of patients with rectal cancer. The expression of CBXs is closely related to the infiltration of various immune cells, including CD4+ T cells, macrophages, neutrophils, B cells, CD8+ T cells, and dendritic cells in colon cancers and rectal cancers [27]. Although the relationship between LAMA1 and rectal adenocarcinoma was analyzed in detail in this study, some limitations remain. First, to elucidate in detail how LAMA1 is involved in the development and progression of rectal adenocarcinoma, other clinical factors, such as the course of treatment, should be considered comprehensively. But there is missing or inconsistent processing of this information. Second, there is a large gap between the number of healthy subjects in the control group and the number of patients in the study, so we may need to further balance the sample size. To sum up, retrospective studies still have their limitations, especially the inconsistent intervention methods and lack of specific information. Therefore, prospective studies should be carried out in future studies to avoid analysis bias caused by the retrospective nature of this study. Current studies are based on RNA sequencing in the TCGA database, so the direct mechanism of LAMA1 involvement in the occurrence and development of rectal adenocarcinoma cannot be evaluated. Therefore, further research on the direct mechanism of rectal adenocarcinoma is needed.

6. Conclusions

We observed a decrease in LAMA1 levels in rectal adenocarcinoma, which is associated with poor OS. In addition, LAMA1 may be involved in the occurrence and development of rectal adenocarcinoma through chemokine signaling pathway and IL18 signaling pathway. This study partially revealed the role of LAMA1 in rectal adenocarcinoma, providing a potential biomarker for the diagnosis and prognosis of rectal adenocarcinoma.

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