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Expression and clinical significance of FGL1 and YAP1 in colorectal cancer

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Abstract: Objective To investigate the expression characteristics and the reationship with clinical prognostic of fibrinogen-like protein 1 (FGL1) and Yes-associated protein 1 (YAP1) in colorectal cancer. **Methods** Tissue microarray technique was used to detect FGL1 and YAP1 expression in 101 colorectal cancer tissues and 79 adjacent tissues from June 2007 to April 2008. Spearman test was employed to assess the correlation between FGL1 and YAP1 expressions. The relationship between FGL1/YAP1 expression and clinicopathological parameters was analyzed. Survival analysis was performed using Kaplan-Meier method, and Cox proportional hazards model was used to identify risk factors influencing prognosis. **Results** The high expression rate of FGL1 in cancer tissues was 58.42% (59/101), significantly higher than 30.38% (24/79) in adjacent tissues (χ^2=14.022, P<0.013). YAP1 high expression rate was 58.42% (59/101) in cancer tissues, significantly higher than 34.18% (27/79) in adjacent tissues (χ^2=10.438, P<0.01). FGL1 and YAP1 expressions showed positive correlation (r^2=0.226, P<0.05), and their high expressions were significantly associated with lymph node metastasis and advanced TNM stage(P<0.05). The overall survival of FGL1/YAP1 high-expression group was significantly lower than that of the low-expression group(P<0.05). Multivariate Cox analysis revealed TNM stage (*HR*=2.664, *P*=0.001), FGL1 (*HR*=2.208, *P*=0.016), and YAP1 (*HR*=1.980, *P*=0.030) as independent factors. affecting the prognosis of colorectal cancer patients. **Conclusion** FGL1 and YAP1 are highly expressed in colorectal cancer tissues and associated with poor prognosis of patient, serving as an important reference for predicting cancer progression and evaluating prognosis.

Keywords: Colorectal cancer; Fibrinogen-like protein 1; Yes-associated protein 1; Prognosis

Colorectal cancer is the third most common malignancy worldwide and the second leading cause of cancer-related deaths, accounting for approximately 9.3% of all malignant tumors [1]. About 35% of colorectal cancer patients present with stage IV metastatic disease at diagnosis, while 20%~50% of stage Ⅱ or Ⅲ patients will progress to stage Ⅳ during the disease course, and their overall prognosis is poor [2]. Significant progress has been made in tumor immunotherapy in recent years, especially in basic research, technological innovation, and clinical translation, with tremendous potential in personalized treatment, combination strategies, and the development of novel drugs. The development of new prognostic markers and immune therapy targets is critical for the diagnosis and treatment of colorectal cancer.

Fibrinogen-like protein 1 (FGL1) is a protein secreted by hepatocytes under physiological conditions, playing a role in protecting liver cells and regulating metabolism. FGL1 is a high-affinity inhibitory ligand of lymphocyte activation gene 3 (LAG3), and through its binding with LAG3, it inhibits T-cell activation, thereby mediating immune evasion in tumors [3]. FGL1 is abnormally expressed in various cancers, including breast cancer, gastric cancer, lung adenocarcinoma, and liver cancer, and is associated with cancer prognosis [4-7].

Yes-associated protein 1 (YAP1) is a transcriptional co-activator that lacks a DNA-binding domain and regulates target gene expression by binding to transcription factors [8]. The activity of YAP1 is regulated and inhibited by the Hippo signaling pathway. In addition to its critical role in normal tissue homeostasis and regeneration, YAP1 also plays a prominent role in cancer initiation, invasiveness, metastasis, and drug resistance [9].

So far, studies on the correlation of FGL1 and YAP1 expression in colorectal cancer are scarce. This study used immunohistochemistry (IHC) to detect the expression levels of FGL1 and YAP1 in colorectal cancer and adjacent tissues, analyzing their expression patterns and their relationship with clinical pathology and prognosis, aiming to provide new references for colorectal cancer diagnosis and prognosis evaluation.

1. Materials and Methods

1.1 General Information

This study collected 101 colorectal cancer tissue samples and 79 adjacent tissue samples from patients who underwent colorectal cancer surgery between June 2007 and April 2008 (tissue microarrays were purchased from Shanghai Xinchao Biological Technology Co., Ltd.), with no prior radiotherapy, chemotherapy, or other anti-tumor treatments. General information of the patients was collected, including a median age of 69 years, with 50 patients aged ≥69 years and 51 patients aged <69 years. There were 50 males and 51 females. Regarding pathological grade, 74 cases (73.27%) were moderately to highly differentiated, and 27 cases (26.73%) were poorly

differentiated. The maximum tumor diameter was ≤5 cm in 67 cases (66.34%) and >5 cm in 34 cases (33.66%). Tumor invasion depth was T1-T2 in 20 cases (19.80%) and T3-T4 in 81 cases (80.20%). Lymph node metastasis was absent in 54 cases (53.47%) and present in 47 cases (46.53%). TNM stage was Ⅰ-Ⅱ in 54 cases (53.47%) and Ⅲ-Ⅳ in 47 cases (46.53%). This study was approved by the Ethics Committee of Shanghai Xinchao Biological Technology Co., Ltd. (Approval No.: SHYJS-CP-1801005), and informed consent was obtained from all patients or their families.

1.2 IHC Staining

The tissue microarray was baked at 60°C for 1 hour, followed by xylene gradient dewaxing and ethanol hydration. After antigen retrieval, the slides were cooled in distilled water at room temperature for >10 minutes. The tissue microarrays were washed with PBS buffer, and diluted anti-FGL1 and anti-YAP1 antibodies were added, incubating overnight at 4°C. The slides were then washed with PBS buffer for 45 minutes at room temperature, followed by the addition of secondary antibody (HRP-conjugated goat anti-rabbit antibody) and incubation at room temperature for 30 minutes. 3,3'-Diaminobenzidine (DAB) was used for color development. After hematoxylin counterstaining for 1 minute and differentiation in acidic ethanol (0.25% hydrochloric ethanol) for 10 seconds, the slides were washed with water for 5 minutes, dried at room temperature, and mounted with neutral resin. IHC was performed using the EnVision method. Anti-FGL1 antibody was purchased from Abcam (Catalog No.: ab275091), and anti-YAP1 antibody was purchased from Proteintech (Catalog No.: 66900-1-lg).

1.3 Interpretation of Results

FGL1 protein was primarily expressed in the cytoplasm, and YAP1 was mainly expressed in both the nucleus and cytoplasm. The expression levels of FGL1 and YAP1 were semi-quantified using a combined score system. The formula for the combined score was: combined score = staining intensity score × percentage of positive cells. The staining intensity was scored as follows: 0 (no staining), 1 (light yellow), 2 (brownish yellow), 3 (brown). The percentage of positive cells was defined as the percentage of positive cells in all tumor cells, ranging from 0 to 100%. The scoring range was 0-300%, and based on the median score, the groups were classified as low expression and high expression. FGL1 expression ≤30% was considered low expression, and FGL1 >30% was considered high expression; YAP1 expression ≤12.5% was considered low expression, and YAP1 >12.5% was considered high expression.

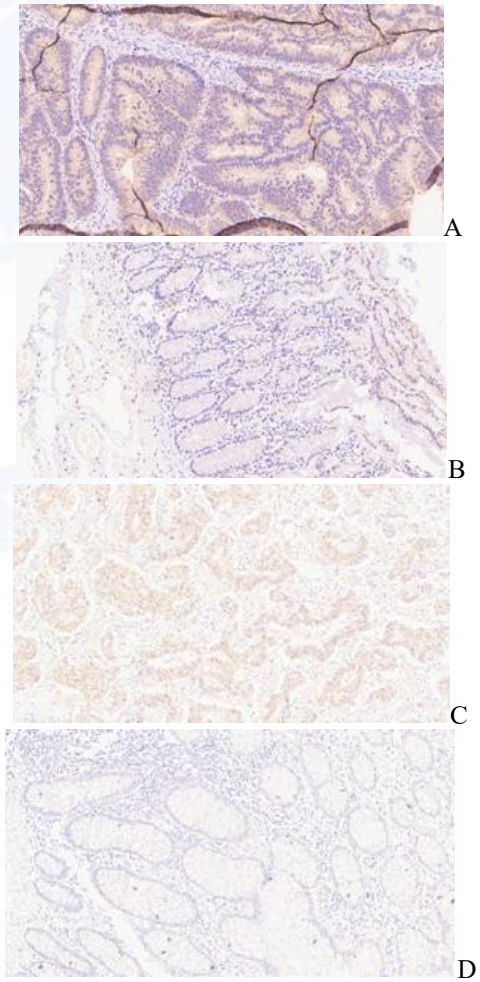
1.4 Statistical Methods

Data were analyzed using SPSS 26.0 software, with categorical data presented as n (%). The correlation between FGL1 and YAP1 expression in colorectal cancer tissue and clinical pathological features was assessed using the chi-square test. Spearman's correlation coefficient was used to analyze the correlation between FGL1 and YAP1 expression levels. Kaplan-Meier survival curves and log-rank tests were used to evaluate patient survival. Multivariate Cox regression analysis was performed to assess independent prognostic factors. The significance level was set at $\alpha = 0.05$.

2. Results

2.1 Comparison of FGL1 and YAP1 Expression in Colorectal Cancer and Adjacent Tissues

In colorectal cancer, FGL1 was located in the cytoplasm, and YAP1 was located in the cell membrane and cytoplasm (Figure 1). The expression levels of FGL1 and YAP1 were significantly higher in colorectal cancer tissues than in adjacent tissues. The high expression rate of FGL1 in colorectal cancer tissues was 58.42% (59/101), significantly higher than the 30.38% (24/79) in adjacent tissues. The high expression rate of YAP1 in colorectal cancer tissues was 58.42% (59/101), significantly higher than the 34.18% (27/79) in adjacent tissues. The differences were statistically significant (P<0.05) (Table 1).



Note: A represents the expression of FGL1 in colorectal cancer tissues; B represents the expression of FGL1 in adjacent non-cancerous tissues; C represents the expression of YAP1 in colorectal cancer tissues; D represents the expression of YAP1 in adjacent non-cancerous tissues.

Fig.1 Expression of FGL1 and YAP1 in colorectal cancer and adjacent tissues (SP staining, ×200)

2.2 Correlation of FGL1 and YAP1 Expression in Colorectal Cancer Tissues

Of the 101 colorectal cancer samples, 39.60% (40/101) exhibited high expression of both FGL1 and YAP1, while 22.77% (23/101) had low expression of both. Spearman correlation analysis showed a positive correlation between FGL1 and YAP1 expression levels (r^2 = 0.226, P = 0.023) (Table 2).

2.3 Relationship Between FGL1 and YAP1 Expression and Clinical Pathological Features

In colorectal cancer, the expression of FGL1 and YAP1 was significantly correlated with lymph node metastasis and TNM stage (P <0.05), but not with patient gender, age, pathological grade, maximum tumor diameter, or invasion depth (P >0.05) (Table 3).

Tab.1 Comparison of FGL1 and YAP1 expressions in colorectal cancer and adjacent tissue

Site	n	FGL1		YAP1	
		Low Expression	High Expression	Low Expression	High Expression
Cancer Tissues	101	42	59	42	59
Paracancerous Tissues	79	55	24	52	27
χ^2 value		14.022		10.438	
P value		<0.001		0.001	

Tab.2 The correlation of FGL1 and YAP1 expression in colorectal cancer tissues

Expression status		YAP1 Low Expression	YAP1 High Expression	Total	r^2 value	*P* value
FGL1 Expression	Low	23	19	42	0.226	0.023
FGL1 Expression	High	19	40	59		
Total		42	59	101		

Tab.3 The relationship between the expressions of FGL1 and YAP1 in colorectal cancer tissues and clinicopathological parameters

Clinicopathological Characteristics	n	FGL1		χ^2 value	*P* value	YAP1		χ^2 value	*P* value
		Low Expression	High Expression			Low Expression	High Expression		
Age				0.102	0.749			0.238	0.626
≥69 years old	50	20(40.00)	30(60.00)			22(44.00)	28(56.00)		
＜69 years old	51	22(43.14)	29(56.86)			20(39.22)	31(60.78)		
Gender				1.271	0.260			1.271	0.260
Male	50	18(36.00)	32(64.00)			18(36.00)	32(64.00)		
Female	51	24(47.06)	27(52.94)			24(47.06)	27(52.94)		
Pathological Grade				0.011	0.917			0.654	0.419
Moderately to Highly Differentiated	74	31(41.89)	43(58.11)			29(39.19)	45(60.81)		
Poorly Differentiated	27	11(40.74)	16(59.26)			13(48.15)	14(51.85)		
Maximum Tumor Diameter				0.835	0.361			0.004	0.953
≤5 cm	67	30(44.78)	37(55.22)			28(41.79)	39(58.21)		
＞5 cm	34	12(35.29)	22(64.71)			14(41.18)	20(58.82)		
Invasion Depth				1.378	0.241			0.445	0.505
T1-T2	20	6(30.00)	14(70.00)			7(35.00)	13(65.00)		
T3-T4	81	36(44.44)	45(55.56)			35(43.21)	46(56.79)		
Lymph Node Metastasis				9.325	0.002			5.036	0.025
None	54	30(55.56)	24(44.44)			28(51.85)	26(48.15)		
present	47	12(25.53)	35(74.47)			14(29.79)	33(70.21)		
TNM Stage				9.325	0.002			5.036	0.025
I-II	54	30(55.56)	24(44.44)			28(51.85)	26(48.15)		
III-IV	47	12(25.53)	35(74.47)			14(29.79)	33(70.21)		

2.4 Relationship Between FGL1 and YAP1 Expression and Patient Prognosis

Survival curve analysis revealed that patients with high expression of FGL1 had a lower overall survival rate than those with low expression, with a statistically significant difference (log-rank test P<0.01, Figure 2A). High expression levels of FGL1 were associated with shorter overall survival. Similarly, patients with high expression of YAP1 had a lower overall survival rate than those with low expression, with statistical significance (log-rank test P<0.01, Figure 2B). High expression levels of YAP1 were associated with a lower overall survival rate.

2.5 Prognostic Factors in Colorectal Cancer Patients

Multivariate Cox regression analysis revealed that TNM stage (P=0.001), FGL1 expression (P=0.016), and YAP1 expression (P=0.030) were independent prognostic factors for colorectal cancer (Table 4).

Tab.4 Univariate and multivariate analyses of factors influencing the prognosis of patients with colorectal cancer

Clinicopathological Characteristics	Univariate analysis		Multivariate analysis	
	HR (95%*CI*)	*P*	*HR* (95%*CI*)	*P*
Age	1.342(0.778-2.316)	0.290		
Gender	1.070(0.621-1.843)	0.809		
Pathological Grade	1.638(0.917-2.926)	0.095		
Maximum Tumor Diameter	1.225(0.696-2.155)	0.481		
Invasion Depth	0.745(0.390-1.422)	0.372		
TNM Stage	3.490(1.947-6.257)	<0.001	2.664(1.471-4.824)	0.001
FGL1 Expression	3.017(1.605-5.669)	0.001	2.208(1.162-4.192)	0.016
YAP1 Expression	2.525(1.365-4.668)	0.003	1.980(1.067-3.674)	0.030

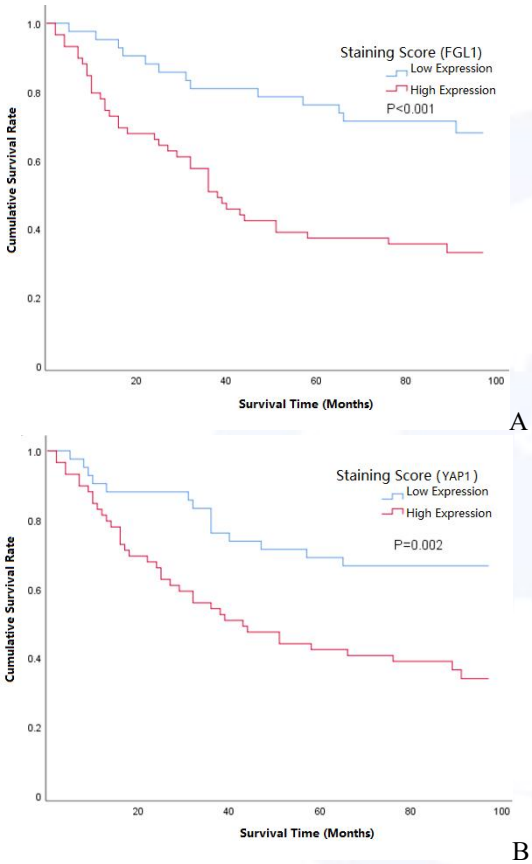


Fig.2 Kaplan-Meier curves of FGL1 and YAP1 expressions in patients with colorectal cancer

3 Discussion

Colorectal cancer (CRC) ranked third in global incidence and second in mortality among malignant tumors in 2022 [10]. In China, it ranked second in incidence and fourth in mortality among all malignant tumors [11]. With increasing attention to healthy dietary patterns and colorectal cancer screening, both the incidence and mortality rates have decreased; however, the overall situation remains severe, with most patients diagnosed at advanced stages [12]. Therefore, it is crucial to identify molecules that can effectively assess patient prognosis and provide new therapeutic targets, helping to improve the diagnostic efficiency of colorectal cancer and prolong patient survival.

LAG3 is an important immune checkpoint molecule, belonging to the immunoglobulin superfamily. It is predominantly expressed on the surface of activated T cells, regulatory T cells (Treg), B cells, and natural killer (NK) cells [13]. The binding of FGL1 to LAG3 occurs independently of the major histocompatibility complex (MHC)-II/LAG3 interaction. FGL1 can activate LAG3 through its fibrinogen-like domain, interacting with the D1 and D2 domains of LAG3, thereby inhibiting T cell function and promoting tumor progression [3]. The discovery of programmed death-1 (PD-1) and its ligand PD-L1 was a milestone in tumor immunotherapy and has become a hot research topic in recent years. The FGL1/LAG3 pathway and the PD-1/PD-L1 immune checkpoint pathway are independent, but they act synergistically in T cell function inhibition and promoting tumor immune evasion, further enhancing the research value of FGL1 [14]. Zhou *et al.* [15] reported that FGL1 is significantly expressed in gastric adenocarcinoma and inhibits $CD8^+$ T cell activation by activating the Notch signaling pathway, leading to immune evasion of gastric adenocarcinoma cells. Studies have shown that FGL1 is expressed at significantly higher levels in non-small cell lung cancer (NSCLC) tissues compared to adjacent normal tissues. Overexpression of FGL1 promotes the proliferation, migration, and invasion of NSCLC cells and is closely associated with poor prognosis in NSCLC patients [16]. However, there is limited research on the role of FGL1 in colorectal cancer. Our study found that FGL1 is significantly more highly expressed in colorectal cancer tissues than in adjacent non-cancerous tissues, suggesting that FGL1 may be closely related to the initiation and progression of colorectal cancer. Further analysis revealed that the expression of FGL1 is associated with TNM staging (stage III-IV) and lymph node metastasis, indicating that FGL1 promotes tumor progression in colorectal cancer. Moreover, Kaplan-Meier survival analysis demonstrated that patients with high FGL1 expression had significantly lower overall survival compared to those with low expression. Both univariate and multivariate Cox regression analyses indicated that FGL1 could serve as a prognostic marker for poor outcomes in colorectal cancer patients, suggesting its potential as a prognostic biomarker for colorectal cancer.

The Hippo signaling pathway is a highly conserved kinase cascade system whose core function is to regulate cell proliferation, differentiation, apoptosis, as well as organ size and regeneration [17]. YAP1 activity is tightly regulated by the Hippo pathway and plays a critical role in cell proliferation, differentiation, organ development, and tissue homeostasis. Under physiological conditions, the Hippo pathway phosphorylates YAP1 through a kinase cascade (such as MST1/2 and LATS1/2), leading to its sequestration in the cytoplasm where it is degraded or inactivated. When the Hippo pathway is inhibited, YAP1 becomes dephosphorylated and translocates to the nucleus, where it interacts with transcriptional enhanced associate domain (TEAD) and other transcription factors to activate downstream target genes, thereby promoting cell proliferation and survival [9]. YAP1 fusion proteins,

which retain the TEAD binding domain, have been found in tumors such as meningiomas, epithelioid hemangioendotheliomas, and cervical squamous cell carcinoma. These fusion proteins resist the negative regulation of the Hippo pathway due to continuous nuclear localization and loss of the S397 residue, thereby persistently driving tumor proliferation [18]. In this study, we used immunohistochemistry (IHC) to show that YAP1 is highly expressed in colorectal cancer, suggesting its oncogenic role in colorectal cancer, which is consistent with the findings of Shu *et al.* [19]. YAP1 expression is associated with lymph node metastasis and clinical staging, indicating that YAP1 may promote lymph node metastasis in colorectal cancer and be involved in tumor development and metastasis. Furthermore, Kaplan-Meier survival analysis revealed that patients with high YAP1 expression had poorer survival compared to those with low expression. This suggests that high YAP1 expression impacts the prognosis of colorectal cancer patients, and detection of YAP1 could help assess disease progression and prognosis. Recent studies suggest that in lung adenocarcinoma with Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations, KRAS activates the extracellular regulated protein kinase (ERK) 1/2 signaling pathway, leading to phosphorylation and stabilization of SET domain containing 1A (SETD1A), which further mediates the methylation modification of YAP1, promoting its nuclear retention and enhancing its transcriptional activity, thus activating FGL1 transcription and promoting KRAS-mutant lung adenocarcinoma progression [20]. Therefore, we hypothesize that YAP1 may drive FGL1 expression in colorectal cancer through a similar transcriptional regulation mechanism, with both synergistically promoting tumor immune evasion and malignant progression. Future research should focus on elucidating the dynamic interaction network between YAP1 and FGL1 and their relationship with the tumor microenvironment to develop more precise therapeutic strategies.

In conclusion, our study demonstrates that FGL1 and YAP1 play significant roles in the initiation and progression of colorectal cancer. We speculate that YAP1 may be involved in the regulation of FGL1 expression in colorectal cancer, and their high expression levels indicate poor prognosis. Therefore, FGL1 and YAP1 hold potential as prognostic biomarkers for colorectal cancer and could provide new insights for immune-suppressive therapies.

Conflict of interest None

Reference

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·论 著·

FGL1和YAP1在结直肠癌中的表达与临床意义

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摘要：目的 探讨纤维蛋白原样蛋白1(FGL1)与Yes相关蛋白1(YAP1)在结直肠癌中的表达特征及其与临床预后的关系。**方法** 采用组织芯片技术检测2007年6月至2008年4月101例结直肠癌及79例癌旁组织中FGL1和YAP1表达，通过Spearman检验评估FGL1和YAP1表达关联性；分析FGL1、YAP1表达与临床病理参数的相关性；绘制Kaplan-Meier曲线进行生存分析。Cox比例风险模型分析影响结直肠癌预后的危险因素。**结果** FGL1在癌组织中的高表达率为58.42%(59/101)，显著高于癌旁组织30.38%(24/79)，YAP1高表达率为58.42%(59/101)显著高于癌旁组织34.18%(27/79)，差异有统计学意义(χ^2=14.022、10.438，P<0.01)。FGL1表达与YAP1表达呈正相关(r^2=0.226，P<0.05)，且高表达均与淋巴结转移、晚期TNM分期显著相关(P<0.05)。FGL1、YAP1高表达组总生存期显著低于表达组(P<0.05)。多因素Cox分析显示TNM分期(HR=2.664，P=0.001)、FGL1(HR=2.208，P=0.016)及YAP1(HR=1.980，P=0.030)为影响结直肠癌患者预后的独立因素。**结论** FGL1和YAP1在结直肠癌组织中高表达，且与患者不良预后相关，其表达对预测结直肠癌进展及判断预后具有重要的参考价值。

关键词： 结直肠癌；纤维蛋白原样蛋白1；Yes相关蛋白1；预后
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Expression and clinical significance of FGL1 and YAP1 in colorectal cancer

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Abstract: Objective To investigate the expression characteristics and the reationship with clinical prognostic of fibrinogen-like protein 1 (FGL1) and Yes-associated protein 1 (YAP1) in colorectal cancer. **Methods** Tissue microarray technique was used to detect FGL1 and YAP1 expression in 101 colorectal cancer tissues and 79 adjacent tissues from June 2007 to April 2008. Spearman test was employed to assess the correlation between FGL1 and YAP1 expressions. The relationship between FGL1/YAP1 expression and clinicopathological parameters was analyzed. Survival analysis was performed using Kaplan-Meier method, and Cox proportional hazards model was used to identify risk factors influencing prognosis. **Results** The high expression rate of FGL1 in cancer tissues was 58.42% (59/101), significantly higher than 30.38% (24/79) in adjacent tissues (χ^2=14.022, P<0.01). YAP1 high expression rate was 58.42% (59/101) in cancer tissues, significantly higher than 34.18% (27/79) in adjacent tissues (χ^2=10.438, P<0.01). FGL1 and YAP1 expressions showed positive correlation (r^2=0.226, P<0.05), and their high expressions were significantly associated with lymph node metastasis and advanced TNM stage (P<0.05). The overall survival of FGL1/YAP1 high-expression group was significantly lower than that of the low-expression group respectively (P<0.05). Multivariate Cox analysis revealed TNM stage (HR=2.664, P=0.001), FGL1(HR=2.208, P=0.016), and YAP1(HR=1.980, P=0.030) as independent factors affecting the prognosis of colorectal cancer patients. **Conclusion** FGL1 and YAP1 are highly expressed in colorectal cancer tissues and associated with poor prognosis of patient, serving as an important reference for predicting cancer progression and evaluating prognosis.

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结直肠癌是全世界范围内第三大恶性肿瘤，也是肿瘤相关死亡的第二大因素，约占所有恶性肿瘤的9.3%[1]。约35%的结直肠癌患者在确诊时即出现Ⅳ期转移性疾病，而20%~50%的Ⅱ期或Ⅲ期患者会在疾病过程中某个时间点进展为Ⅳ期且总体预后较差[2]。肿瘤免疫治疗近年来在基础研究、技术创新及临床转化方面均取得显著进展，尤其在个性化治疗、联合策略及新型药物开发等领域展现出巨大潜力，开发新的预后判断指标和免疫治疗靶点对结直肠癌诊疗十分重要。

纤维蛋白原样蛋白1（fibrinogen-like protein 1，FGL1）是一种在生理条件下由肝细胞分泌的蛋白，发挥保护肝细胞和调节代谢的功能，FGL1是淋巴细胞活化基因3（lymphocyte activation gene 3，LAG3）的高亲和力抑制性配体，FGL1可通过与LAG3结合抑制T细胞的活化，从而介导肿瘤的免疫逃逸[3]。FGL1在乳腺癌、胃癌、肺腺癌、肝癌等多种肿瘤中表达异常，并且与肿瘤的预后相关[4-7]。

Yes相关蛋白1（Yes-associated protein 1，YAP1）是一种转录共激活因子，YAP1不含有DNA结合结构域，它通过与转录因子结合调节靶基因表达[8]。YAP1的活性受Hippo信号通路的调节和抑制，除了在正常组织稳态和再生中的重要功能外，YAP1在恶性肿瘤发生、侵袭性、转移、耐药性方面也具有突出的功能[9]。

至今为止，关于在结直肠癌中FGL1和YAP1的表达相关性研究较少。因此，本研究应用免疫组织化学（immunohistochemistry，IHC）检测FGL1和YAP1在结直肠癌及癌旁组织中的表达水平，分析它们的表达情况与临床病理及预后的关系，希望可以为结直肠癌的诊治和预后评价提供新的参考。

1 资料与方法

1.1 一般资料 本研究收集2007年6月至2008年4月行结直肠癌手术切除患者的结直肠癌组织101例及癌旁组织79例（组织芯片购自上海芯超生物科技有限公司，芯片编号为HColA180Su17），且患者在术前未经放疗、化疗等抗肿瘤治疗。患者中位年龄69岁，≥69岁50例，<69岁51例；男性50例，女性51例；病理分级中、高分化74例（73.27%），低分化27例（26.73%）；肿瘤最大径≤5 cm 67例（66.34%），>5 cm 34例（33.66%）；浸润深度T1~T2 20例（19.80%），T3~T4 81例（80.20%）；无淋巴结转移54例（53.47%），有淋巴结转移47例（46.53%）；TNM分期Ⅰ~Ⅱ期54例（53.47%），Ⅲ~Ⅳ期47例（46.53%）。本研究已经通过上海芯超生物科技有限公司的伦理委员会批准（批件号：SHYJS-CP-1801005），并取得所有患者或其家属的知情同意。

1.2 IHC染色 将组织芯片经60 ℃恒温烘烤1 h后，依次进行二甲苯梯度脱蜡及乙醇水化处理。将玻片进行抗原修复后放置于常温蒸馏水中冷却，控制冷却时间>10 min。PBS缓冲液洗涤组织芯片，随后滴加稀释好的抗FGL1抗体、抗YAP1抗体，保存于4 ℃度冰箱过夜。取出玻片，45 min室温复温后，进行第2次PBS缓冲液洗涤。随后滴加二抗（辣根过氧化物酶标记山羊抗兔抗体），在室温下孵育30 min，使用3,3′-二氨基联苯胺（3,3′-diamino benzidine，DAB）显色。经苏木素对比染色1 min及酸性乙醇（0.25%盐酸乙醇）分化10 s后，再用清水冲洗5 min，使玻片在室温下干燥，通过中性树胶封片完成制片。应用EnVision法进行IHC。FGL1抗体购自Abcam公司（货号：ab275091）。YAP1抗体购自Proteintech公司（货号：66900-1-lg）。

1.3 结果判读 FGL1蛋白主要表达于胞浆，YAP1主要表达于胞核和胞浆。FGL1、YAP1蛋白表达量化方法：基于半定量综合评分系统，其计算公式为综合评分=染色强度评分×阳性细胞占比。根据细胞的染色强度分级：0分（无着色）、1分（浅黄色）、2分（棕黄色）、3分（黄褐色）。阳性细胞占比：阳性细胞占全部肿瘤细胞的百分比，记为0~100%。综合评分范围为0~300%，根据染色评分的中位数分为低表达组和高表达组。FGL1≤30%为低表达，FGL1>30%为高表达；YAP1≤12.5%为低表达，YAP1>12.5%为高表达。

1.4 统计学方法 数据以SPSS 26.0软件进行统计分析，计数资料以例（%）表示。结直肠癌组织中FGL1、YAP1表达与临床病理特征的相关性采用χ^2检验；FGL1与YAP1表达水平的相关性研究采用Spearman相关系数分析方法；使用Kaplan-Meier生存曲线、log-rank检验对患者生存情况进行评价；采用多因素Cox回归分析法评估影响预后的独立危险因素。检验水准α=0.05。

2 结 果

2.1 结直肠癌组织及癌旁组织中FGL1与YAP1表达的比较 结直肠癌中，FGL1定位于细胞质，YAP1定位于细胞膜和细胞质。见图1。

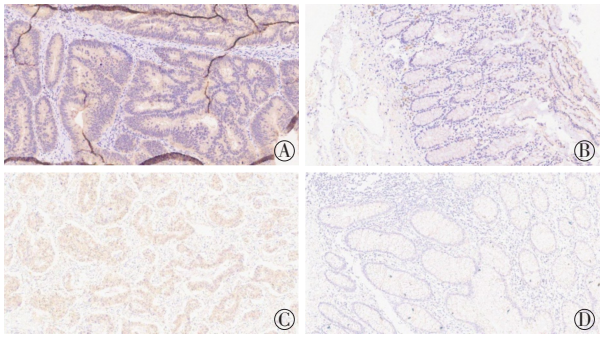
FGL1蛋白、YAP1蛋白在结直肠癌组织中的表达水平显著高于癌旁组织，结直肠癌组织中FGL1的高表达率为58.42%（59/101），高于癌旁组织的30.38%

(24/79)，YAP1 的高表达率的 58.42%(59/101)，高于癌旁组织的 34.18%(27/79)，差异有统计学意义(P<0.05)。见表 1。

2.2　结直肠癌组织中 FGL1 与 YAP1 表达的相关性　101 例结直肠癌组织标本中 39.60%(40/101)表现为双高表达，22.77%(23/101)为双低表达。Spearman 相关性分析显示，FGL1 与 YAP1 的表达水平呈正相关(r^2=0.226，P=0.023)。见表 2。

2.3　结直肠癌组织中 FGL1 和 YAP1 表达与患者临床病理特征的关系　在结直肠癌中，FGL1、YAP1 的表达与肿瘤的淋巴结转移、TNM 分期显著相关(P<0.05)，与患者性别、年龄、病理分级、肿瘤最大径、浸润深度无相关性(P>0.05)。见表 3。

2.4　结直癌组织中 FGL1 和 YAP1 表达与患者预后的关系　Kaplan-Meier 生存曲线结果示：随访截止至 2015 年 7 月，FGL1 高表达患者的总生存率低于低表达患者，差异有统计学意义(log-rank 检验 P<0.01，图 2A)，即高表达水平的 FGL1 与患者较短的总生存率相关。YAP1 高表达患者的总生存率低于低表达患者，差异有统计学意义(log-rank 检验 P<0.01，图 2B)，即高表达水平的 YAP1 与患者较低的总生存率相关。



注：A 为 FGL1 在结直肠癌组织中的表达；B 为 FGL1 在癌旁组织中的表达；C 为 YAP1 在结直肠癌组织中的表达；D 为 YAP1 在癌旁组织中的表达。

图 1　FGL1 及 YAP1 在结直肠癌和癌旁组织中的表达(IHC，×200)

Fig.1　Expression of FGL1 and YAP1 in colorectal cancer and adjacent tissues (IHC, ×200)

表 1　FGL1 和 YAP1 在结直肠癌组织和癌旁组织表达比较(例)

Tab.1　Comparison of FGL1 and YAP1 expressions in colorectal cancer and adjacent tissues (case)

部位	例数	FGL1		YAP1	
		低表达	高表达	低表达	高表达
癌组织	101	42	59	42	59
癌旁组织	79	55	24	52	27
χ^2值		14.022		10.438	
P值		<0.001		0.001	

表 2　FGL1 与 YAP1 在结直肠癌组织中的表达情况　(例)

Tab.2　Expression of FGL1 and YAP1 in colorectal cancer tissues　(case)

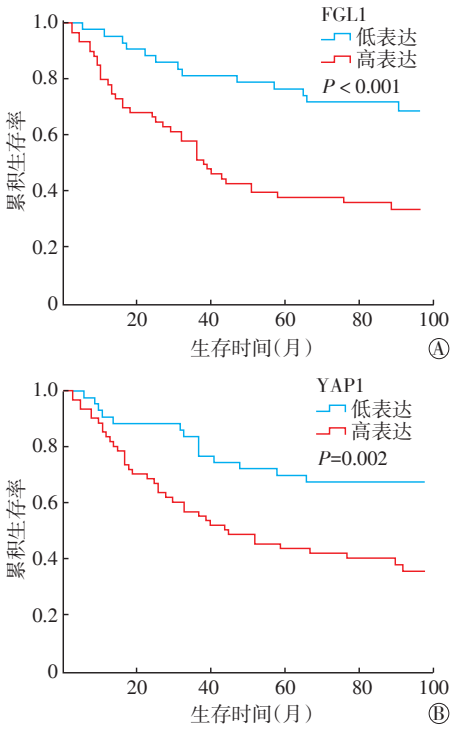
蛋白表达情况	YAP1 低表达	YAP1 高表达	合计
FGL1 低表达	23	19	42
FGL1 高表达	19	40	59
合计	42	59	101

表 3　结直肠癌组织中 FGL1、YAP1 表达与临床病理学参数的关系　[例(%)]

Tab.3　The relationship between the expressions of FGL1 and YAP1 in colorectal cancer tissues and clinicopathological parameters [case(%)]

临床病理特征	例数	FGL1		χ^2值	P值	YAP1		χ^2值	P值
		低表达(n=42)	高表达(n=59)			低表达(n=42)	高表达(n=59)		
年龄									
≥69 岁	50	20(40.00)	30(60.00)	0.102	0.749	22(44.00)	28(56.00)	0.238	0.626
<69 岁	51	22(43.14)	29(56.86)			20(39.22)	31(60.78)		
性别									
男	50	18(36.00)	32(64.00)	1.271	0.260	18(36.00)	32(64.00)	1.271	0.260
女	51	24(47.06)	27(52.94)			24(47.06)	27(52.94)		
病理分级									
中高分化	74	31(41.89)	43(58.11)	0.011	0.917	29(39.19)	45(60.81)	0.654	0.419
低分化	27	11(40.74)	16(59.26)			13(48.15)	14(51.85)		
肿瘤最大径									
≤5 cm	67	30(44.78)	37(55.22)	0.835	0.361	28(41.79)	39(58.21)	0.004	0.953
>5 cm	34	12(35.29)	22(64.71)			14(41.18)	20(58.82)		
浸润深度									
T1~T2	20	6(30.00)	14(70.00)	1.378	0.241	7(35.00)	13(65.00)	0.445	0.505
T3~T4	81	36(44.44)	45(55.56)			35(43.21)	46(56.79)		
淋巴结转移									
无	54	30(55.56)	24(44.44)	9.325	0.002	28(51.85)	26(48.15)	5.036	0.025
有	47	12(25.53)	35(74.47)			14(29.79)	33(70.21)		
TNM 分期									
Ⅰ~Ⅱ	54	30(55.56)	24(44.44)	9.325	0.002	28(51.85)	26(48.15)	5.036	0.025
Ⅲ~Ⅳ	47	12(25.53)	35(74.47)			14(29.79)	33(70.21)		

2.5　结直肠癌患者预后影响因素的 Cox 回归模型分析　Cox 回归模型进行多因素分析，结果显示，TNM 分期（*P*=0.001）、FGL1 表达（*P*=0.016）和 YAP1 表达（*P*=0.030）是影响结直肠癌患者预后的独立因素。见表 4。



注：A，FGL1 不同表达患者生存曲线；B，YAP1 不同表达患者生存曲线。

图 2　FGL1 及 YAP1 表达与结直肠癌患者的 Kaplan-Meier 曲线

Fig.2　Kaplan-Meier curves of FGL1 and YAP1 expressions in patients with colorectal cancer

表 4　影响结直肠癌患者预后的单因素及多因素分析

Tab.4　Univariate and multivariate analyses of factors influencing the prognosis of patients with colorectal cancer

因素	单因素分析		多因素分析	
	HR（95%*CI*）	*P* 值	*HR*（95%*CI*）	*P* 值
年龄	1.342（0.778~2.316）	0.290		
性别	1.070（0.621~1.843）	0.809		
病理分级	1.638（0.917~2.926）	0.095		
肿瘤最大径	1.225（0.696~2.155）	0.481		
浸润深度	0.745（0.390~1.422）	0.372		
TNM 分期	3.490（1.947~6.257）	<0.001	2.664（1.471~4.824）	0.001
FGL1 表达	3.017（1.605~5.669）	0.001	2.208（1.162~4.192）	0.016
YAP1 表达	2.525（1.365~4.668）	0.003	1.980（1.067~3.674）	0.030

3　讨　论

结直肠癌在 2022 年全球恶性肿瘤中发病率排名第三，同时死亡率排名第二[10]，在中国恶性肿瘤的发病率和死亡率排名中位居第二和第四[11]。随着对健康饮食结构和结直肠癌筛查的重视程度提高，结直肠癌的发病率和死亡率均有所降低，但整体情况仍较为严峻，大部分患者在确诊时已是中晚期[12]。因此，需要寻找可以有效评估患者预后和提供新治疗靶点的相关分子，帮助提高结直肠癌诊断效率，延长结直肠癌患者生存期。

LAG3 是一种重要的免疫检查点分子，是免疫球蛋白超家族成员，主要在活化的 T 细胞、调节性 T 细胞（regulatory T cells，Treg）、B 细胞和自然杀伤（natural killer，NK）细胞等免疫细胞表面表达[13]。FGL1 与 LAG3 的结合独立于主要组织相容性复合体（major histocompatibility complex，MHC）-Ⅱ/淋巴细胞激活基因 3（lymphocyte-activation gene 3，LAG3）结合，FGL1 可通过其纤维蛋白原样结构域与 LAG3 的 D1 和 D2 结构域相互作用激活 LAG3，抑制 T 细胞功能，从而促进肿瘤进展[3]。程序性死亡受体 1（programmed death-1，PD-1）和其配体 PD-L1 的发现是肿瘤免疫治疗领域的里程碑事件，也是近年来肿瘤免疫疗法研究的热点，FGL1/LAG3 与 PD-1/PD-L1 免疫抑制通路独立存在，两者在 T 细胞功能抑制和促进肿瘤免疫逃逸方面存在协同作用，这也增强了 FGL1 的研究价值[14]。Zhou 等[15]发现 FGL1 在胃腺癌中显著表达，并且通过激活 Notch 信号通路抑制 $CD8^+$ T 细胞活化，从而导致胃腺癌肿瘤细胞免疫逃逸。有研究发现 FGL1 在非小细胞肺癌组织中表达明显高于相邻正常组织，FGL1 过表达可促进非小细胞肺癌的增殖、迁移和侵袭，并且与非小细胞肺癌患者的不良预后密切相关[16]。然而目前关于 FGL1 在结直肠癌中的作用鲜有报道。本研究发现，FGL1 在结直肠癌中表达显著高于癌旁组织，这提示 FGL1 可能与结直肠癌的发生发展密切相关。进一步分析发现，TNM 分期为Ⅲ~Ⅳ期、淋巴结转移与 FGL1 表达升高有关，提示 FGL1 在结直肠癌中促进肿瘤进展。此外，Kaplan-Meier 生存分析显示，FGL1 高表达组患者总生存率显著低于低表达组，同时 Cox 单因素及多因素分析均提示 FGL1 可能为结直肠癌患者不良预后的预测因素，提示 FGL1 有成为结直肠癌患者预后评估标志物的潜力。

Hippo 通路是一个高度保守的激酶级联系统，其核心功能是调控细胞增殖、分化、凋亡以及器官大小和再生[17]。YAP1 活性受到 Hippo 通路的严格调控，并在细胞增殖、分化、器官发育及组织稳态中发挥关键作用。在生理状态下，Hippo 通路通过激酶级联反应（如 MST1/2 和 LATS1/2）磷酸化 YAP1，导致其滞留在细胞质中被降解或失活；当 Hippo 通路被抑制时，YAP1 去磷酸化同时转移至细胞核，与转录增强相关

结构域蛋白(transcriptional enhanced associate domain, TEAD)等转录因子结合,激活下游靶基因,从而促进细胞增殖和存活[9]。YAP1 与男性发育不良候选基因 1、家族序列相似性 118 成员 B 和转录因子增强子 3 等基因可以产生基因融合现象,YAP1 融合蛋白保留了 TEAD 结合域,但由于持续性核定位和丢失 S397 残基抵抗 Hippo 通路的负调控,持续驱动肿瘤增殖,此类融合已在脑膜瘤、上皮样血管内皮肉瘤、宫颈鳞状细胞癌等肿瘤中发现[18]。本研究通过 IHC 发现 YAP1 在结直肠癌中高表达,提示 YAP1 在结直肠癌中同样发挥致癌作用,这与舒莉珊等[19]研究结果一致。YAP1 表达与淋巴结转移、临床分期有关,提示 YAP1 可能促进结直肠癌的淋巴结转移,与结直肠癌发展与转移有关。此外 Kaplan-Meier 生存分析显示,YAP1 高表达组患者生存期较低表达组差。提示 YAP1 高表达对结直肠癌患者预后产生影响,检测 YAP1 可以协助评估结直肠癌患者疾病进展及预后。目前研究推测 Kirsten 大鼠肉瘤病毒癌基因同源物(Kirsten ratsarcoma viral oncogene homolog, KRAS)突变的肺腺癌中,KRAS 激活细胞外调节蛋白激酶(extracellular regulatory protein kinase, ERK)1/2 信号通路,导致 SET 结构域蛋白 1A(SET domain containing 1A, SETD1A)甲基转移酶的磷酸化和稳定化。SET1A 进一步介导 YAP1 的甲基化修饰,促使 YAP1 在核内滞留并增强其转录活性,激活 FGL1 的转录表达,从而促进 KRAS 突变的肺腺癌进展[20]。因此笔者推测 YAP1 通过类似转录调控机制驱动结直肠癌中 FGL1 的表达,两者协同促进肿瘤免疫逃逸和恶性进展。未来的研究应聚焦于解析 YAP1-FGL1 的动态交互网络及其与微环境的关联,以开发更精准的治疗策略。

综上所述,FGL1 和 YAP1 高表达提示结直肠癌的不良预后。因此,FGL1 和 YAP1 有望成为预测结直肠癌预后的标志物,以及为免疫抑制疗法提供新的思路。

利益冲突　无

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