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Expression and Clinical Significance of PKM2 and SERBP1 in Colorectal Cancer

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Abstract: *Objective*: To investigate the expression of pyruvate kinase M2 (PKM2) and RNA binding proteins 1 (SERBP1) in colorectal cancer (CRC) and their clinical significance. *Methods*: A total of 101 cases of colorectal adenocarcinoma tissues and their corresponding adjacent tissues were collected from our hospital from December 2020 to December 2023. The immunohistochemical Elivision method was used to detect the expression of PKM2 and SERBP1 in CRC and corresponding adjacent tissues. The experimental data were analyzed using statistical software SPSS 27.0. *Results:* The expression rates of PKM2 and SERBP1 in CRC were higher than those in adjacent tissues. The expression of PKM2 was positively correlated with lymph node metastasis and TNM stage. The expression of SERBP1 was positively correlated with the degree of differentiation, lymph node metastasis, and TNM stage of CRC. *Conclusion:* PKM2 and SERBP1 may promote the occurrence and tumor progression of CRC, but further experimental research is still needed.

Keywords: PKM2; SERBP1; Colorectal cancer

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1. Introduction

Colorectal cancer (CRC) is a common malignant tumor with high heterogeneity and genetic instability. According to global cancer statistics, in 2022, more than 1.9 million people were diagnosed with colorectal cancer (including anal cancer) and 904,000 deaths occurred, accounting for nearly one-tenth of cancer cases and deaths. Overall, colorectal cancer ranks third in global incidence and second in mortality [1]. The occurrence of colorectal cancer involves multiple pathophysiological mechanisms, including abnormal cell proliferation, cell differentiation, resistance to apoptosis, invasion of adjacent structures by tumor cells, distant metastasis, etc., exhibiting a high degree of heterogeneity.

Abnormally active glycolysis is a significant characteristic of tumor cells [2]. Pyruvate kinase (PK) catalyzes the conversion of phosphoenolpyruvate (PEP) to pyruvate, representing the final rate-limiting step in the glycolytic

cascade. There are four PK isoforms: L, R, M1, and M2, each expressed in specific tissues. The M2 isoform, a splicing variant of M1, is expressed during embryonic development and tumorigenesis. Pyruvate kinase M2 (PKM2) can switch between a tetrameric form with high affinity for its substrate PEP and a dimeric form with low affinity for PEP. PKM2 primarily exists in two forms: a highly active tetrameric form and a less active dimeric form. The tetrameric PKM2 exhibits high affinity for its substrate phosphoenolpyruvate, demonstrating strong enzymatic catalytic ability. It often forms complexes with other glycolysis-related enzymes, facilitating the production of pyruvate and adenosine triphosphate. Tetrameric PKM2 is predominantly found in differentiated tissues and normally proliferating cells. Conversely, dimeric PKM2 is commonly present in tumor cells, displaying low affinity for its substrate and promoting the accumulation of glycolytic intermediates such as phosphoenol compounds within tumor cells. Intracellular glucose is utilized for the synthesis of nucleic acids, phospholipids, and amino acids, playing a crucial role in tumor cell proliferation [3]. PKM2 is the predominant form of pyruvate kinase in tumor tissues, exhibiting high expression in various tumor tissues and cell lines. Experimental studies both in vitro and in vivo have demonstrated that PKM2 promotes the proliferation and growth of tumor cells [4]. Elevated levels of PKM2 have been observed in serum samples from patients with gastric cancer, pancreatic cancer, cervical cancer, among others, suggesting its potential as a novel tumor marker. When combined with appropriate traditional tumor markers for detection, PKM2 can enhance the sensitivity of tumor detection.

RNA binding proteins 1 (SERBP1) is an arginine-methylated mRNA-binding protein and serves as an important intracellular RNA-binding partner. It was initially described as binding to the 3'-untranslated region (3'-UTR) of type 1 plasminogen activator inhibitor (PAI-1) mRNA, thereby regulating its stability [5]. RNA-binding proteins (RBPs) play crucial roles in coordinating post-transcriptional regulation and modulating many aspects of tumorigenesis, participating in nearly all aspects of RNA metabolism, from transcription to RNA degradation [6]. SERBP1 has been recognized as a significant regulator in various cancers, influencing mRNA degradation and the formation of RNA-protein complexes, thereby affecting mRNA stability and controlling the mRNA levels of target genes [7]. SERBP1 plays a vital role in many tumor cells. It is overexpressed in ovarian cancer epidermal cells and is significantly associated with the progression and grading (FIGO) of ovarian cancer, suggesting its important biological function in tumor invasion and metastasis [8]. In breast cancer, the expression of SERBP1 is significantly associated with a favorable prognosis [9]. Further research indicates that overexpression of SERBP1 in the HEK293T cell line can induce changes in genes related to cell proliferation, apoptosis, and the cell cycle [10]. In prostate cancer, miR-26a-5p promotes cell migration, invasion, and proliferation by negatively regulating SERBP1 expression [11]. A recent study also demonstrated that in pancreatic cancer, lncRNA-PVT1 acts as a molecular sponge to adsorb miR-448, thereby regulating the expression of its target SERBP1 and promoting proliferation and metastasis at the cellular level [12]. It has been reported that SERBP1 is a ribosome-associated protein involved in protein translation. Therefore, we can clearly conclude that SERBP1, as an RBP, plays a significant regulatory role in gene translation and tumor progression [13]. However, the regulatory mechanisms and pathways of SERBP1 remain largely unknown. Currently, there is limited research on the expression of PKM2 and SERBP1 in colorectal cancer, a disease with persistently high incidence and mortality rates that is difficult to cure. Therefore, further in-depth research on colorectal cancer is necessary, particularly in the search for new and effective targeted therapeutic approaches. This paper aims to discuss the expression of SERBP1 and PKM2 in colorectal cancer and their clinical significance, hoping to provide new research ideas for the treatment of colorectal cancer.

2. Materials and methods

2.1. General information

This experiment collated and collected 101 cases of colorectal adenocarcinoma diagnosed by the pathology department of our hospital from December 2020 to December 2023. After screening, all cases had been excluded for other diseases affecting survival time, and none had received any relevant treatment other than surgery. Paraffin-embedded tissue specimens from the selected cases were chosen, with the control group consisting of corresponding normal tissues adjacent to the cancer in the selected cases.

2.2. Clinical and pathological characteristics

Among the 101 CRC cases, there were 55 males and 46 females; 52 cases were ≤ 67 years old, and 49 cases were > 67 years old; 16 cases had mucinous adenocarcinoma components, while 85 cases did not; 15 cases were poorly differentiated, and 86 cases were moderately to well differentiated; 43 cases had no lymph node metastasis, while 58 cases did; 22 cases were in stages T1 and T2, and 79 cases were in stages T3 and T4; 3 cases exhibited microsatellite instability (MSI), and 98 cases were microsatellite stable (MSS) (**Table 1**).

Table 1. Clinical and pathological characteristics of patients

Clinical Pathological Feature	Frequency (n)	Percentage (%)
Gender		
Male	55	54.46
Female	46	45.54
Age (years)		
≤ 67	52	51.49
> 67	49	48.51
Mucinous Adenocarcinoma		
Yes	16	15.84
No	85	84.16
Differentiation Grade		
Low	15	14.85
Moderate/High	86	85.15
Lymph Node Metastasis		
No	43	42.57
Yes	58	57.43
T Stage		
T1 + T2	22	21.78
T3 + T4	79	78.22
MSI Status		
MSI	3	2.97
MSS	98	97.03

2.3. Methods

All surgical specimens were fixed with 4% neutral formaldehyde solution, routinely dehydrated, paraffin-embedded, and sectioned continuously at a thickness of 4 μm. The sections were stained with HE and observed under a light microscope. Immunohistochemistry was performed using the EnVision two-step method. The antibodies PKM2 and SERBP1 used were purchased from Wuhan Sanying Biotechnology Co., Ltd. The experimental process was carried out strictly in accordance with the reagent instructions, with PBS used as a blank control instead of the primary antibody.

2.4. Evaluation criteria and results of immunohistochemistry

Both PKM2 and SERBP1 proteins are expressed in the cytoplasm (**Figure 1**). Scoring based on the proportion of positive cells: a score of 0 is assigned if the number of positive cells is less than 5%; a score of 1 is assigned if it is 5% or more; a score of 2 is assigned if it is 25% or more; a score of 3 is assigned if it is 50% or more; and a score of 4 is assigned if it is 75% or more. Scoring based on staining intensity: negative (0 points) indicates the absence of brown granules; weakly positive (1 point) indicates scattered, pale, or fine brown granules; moderately positive (2 points) indicates the presence of large brownish-yellow granules; and strongly positive (3 points) indicates a dense distribution of brownish-yellow granules. The final score for each specimen is calculated by multiplying the proportion of stained cells by the staining intensity: a score of 0 indicates negative (–), scores from 1 to 4 indicate weakly positive (+), scores from 5 to 8 indicate moderately positive (2+), and scores greater than 8 indicate strongly positive (3+).

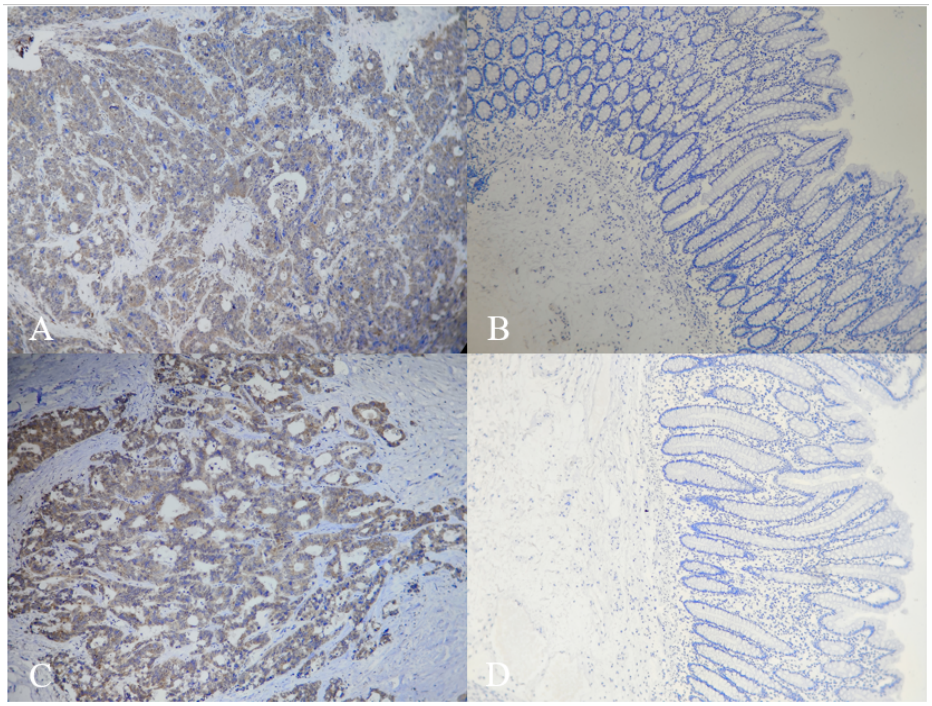

Figure 1. Expression of PKM2 and SERBP1 in CRC and adjacent tissues (immunohistochemical staining × 100). (A) Positive expression of PKM2 in CRC, with positive localization in the cytoplasm.(B) Negative expression of PKM2 in adjacent tissues.(C) Positive expression of SERBP1 in CRC, with positive localization in the cytoplasm. (D) Negative expression of SERBP1 in adjacent tissues.

2.5. Statistical analysis of data

All data in this study were analyzed using SPSS 27.0 software. The chi-square test was used to determine the relationship between clinicopathological parameters and PKM2 and SERBP1. A p-value less than 0.05 was considered statistically significant.

3. Results

3.1. Expression of PKM2 and SERBP1 in CRC and corresponding adjacent normal tissues

Among the 101 CRC specimens, 65 cases (65/101) exhibited positive PKM2 expression, with a positive expression rate of 75.25%. In contrast, 43 cases (43/101) of the corresponding adjacent normal tissues showed positive expression, with a positive expression rate of 42.57%. The difference in expression between the two groups was statistically significant ($\chi^2 = 9.630$, $P \approx 0.002$) (**Table 1**).

Among the 101 CRC specimens, 60 cases (60/101) demonstrated positive SERBP1 expression, with a positive expression rate of 59.41%. Conversely, 46 cases (46/101) of the corresponding adjacent normal tissues exhibited positive expression, with a positive expression rate of 45.54%. The difference in expression between the two groups was statistically significant ($\chi^2 = 3.891$, $P \approx 0.049$) (**Table 2**).

Table 2. Expression of PKM2 and SERBP1 in cancerous and adjacent normal tissues

Group	PKM2				SERBP1			
	Negative (n)	Positive (n)	χ^2	*P*-value	Negative (n)	Positive (n)	χ^2	*P*-value
Cancer Tissue	36	65	9.630	0.002	41	60	3.891	0.049
Paracancerous Tissue	58	43	—	—	55	46	—	—

3.2. Relationship between PKM2 and SERBP1 expression and clinicopathological features in CRC

Immunohistochemical results revealed that in CRC specimens, PKM2 expression was positively correlated with lymph node metastasis and TNM staging, with statistical significance ($P < 0.001$, $P = 0.036$). It was not associated with gender, age, mucinous adenocarcinoma status, degree of differentiation, or MSI status. SERBP1 expression was positively correlated with the degree of differentiation, lymph node metastasis, and TNM staging in CRC specimens, with statistical significance ($P = 0.004$, $P < 0.001$, $P = 0.013$). It was not related to gender, age, mucinous adenocarcinoma status, or MSI status (**Table 3**).

Table 3. Relationship between the expression of PKM2 and SERBP1 and clinicopathological characteristics in colorectal cancer

Group	PKM2				SERBP1			
	Negative	Positive	χ^2	*P*-value	Negative	Positive	χ^2	*P*-value
Gender			0.027	0.869			3.443	0.064
Male	20	35			22	43		
Female	16	30			19	17		

Table 3 (Continued)

Group	PKM2				SERBP1			
	Negative	Positive	χ^2	*P*-value	Negative	Positive	χ^2	*P*-value
Age (years)			2.075	0.150			0.330	0.566
≤ 67	22	30			19	33		
> 67	14	35			12	27		
Mucinous Adenocarcinoma			2.365	0.124			0.074	0.784
Yes	3	13			6	10		
No	33	52			35	50		
Differentiation Grade			0.041	0.840			8.409	0.004
Low	5	10			1	14		
Moderate/High	31	55			40	46		
Lymph Node Metastasis			49.079	< 0.001			64.148	< 0.001
No	32	11			37	6		
Yes	4	54			4	54		
T Stage			4.381	0.036			6.193	0.013
T1+T2	12	10			14	8		
T3+T4	24	55			27	52		
MSI Status			0.007	0.932			2.113	0.146
MSI	1	2			0	3		
MSS	35	63			41	57		

4. Discussion

Colorectal cancer ranks third in global incidence and second in mortality. Currently, surgical resection is the primary treatment approach, while adjuvant therapies such as radiotherapy, chemotherapy, targeted therapy, and immunotherapy are available for patients who are not candidates for surgery. Due to the high degree of tumor heterogeneity, the application of a uniform treatment strategy to different patients results in significant variations in treatment outcomes among individuals. Some patients with colorectal cancer are diagnosed at an advanced stage of the disease, and approximately 30% of early-stage colorectal cancers can metastasize, with a 5-year survival rate of around 60% for colorectal cancer patients. Therefore, identifying biological factors associated with the invasion, metastasis, and prognosis of colorectal cancer, as well as seeking new therapeutic targets, is of paramount importance.

Tumorigenesis is closely associated with glycolysis. Normal cells primarily obtain energy required for growth and proliferation through aerobic oxidation of glucose, with glycolysis occurring only under hypoxic conditions. In contrast, malignant tumor cells primarily rely on glycolysis for energy (even under aerobic conditions), consuming large amounts of glucose and producing lactic acid, a phenomenon known as the Warburg effect [14]. The conversion of glucose to lactic acid is a key characteristic that enables many cancer cells to promote rapid

growth. PKM2 is a classic glycolytic enzyme, and increased expression of PKM2 promotes lactic acid production in cancer cells [15]. PKM2 regulates its activity by switching between the low-activity dimer and high-activity tetramer states, thereby allowing cellular metabolism to shift between glycolysis and mitochondrial respiration, respectively [16]. Current literature reports that PKM2 is closely associated with the development of many tumors. This experimental study found that PKM2 expression is higher in colorectal cancer (CRC) than in adjacent normal tissues, and that PKM2 expression is statistically significantly correlated with lymph node metastasis and TNM staging, suggesting that PKM2 promotes the development of colorectal cancer, consistent with reports in the literature. RNA-binding proteins (RBPs) are crucial binding partners for intracellular RNA. Without RBPs,

RNA cannot perform any physiological functions. RBPs dynamically interact with RNA to form various complexes, such as ribonucleoprotein particles (RNPs) [6]. RBPs regulate cell fate through interactions with RNA and play a significant role in post-transcriptional gene regulation [17]. RBPs are involved in almost all aspects of RNA metabolism, from transcription to RNA degradation [18]. SERBP1, an arginine-methylated mRNA-binding protein, is an important binding partner for intracellular RNA. SERBP1 influences tumor proliferation and apoptosis through multiple mechanisms, suggesting its potential involvement in cancer cell metabolism. Studies have reported elevated levels of SERBP1 in various cancers, including acute lymphoblastic leukemia, breast cancer, ovarian cancer, glioblastoma, and squamous lung cell carcinoma [19]. The results of this experiment indicate that the expression of SERBP1 in colorectal cancer (CRC) is higher than that in adjacent normal tissues. Furthermore, the expression of SERBP1 is associated with the degree of differentiation, lymph node metastasis, and TNM staging of CRC, consistent with findings reported in the literature, suggesting that SERBP1 is involved in the occurrence and development of CRC.

5. Conclusion

In summary, among the 101 cases in this study, PKM2 and SERBP1 were upregulated in CRC, indicating a possible relationship between PKM2 and SERBP1 and the occurrence of CRC. The expression of PKM2 is positively correlated with lymph node metastasis and TNM staging in CRC, while the expression of SERBP1 is positively correlated with the degree of differentiation, lymph node metastasis, and TNM staging in CRC, with statistically significant differences. Therefore, we hypothesize that PKM2 and SERBP1 may play a role in promoting the development of CRC, but further experimental research is needed.

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Disclosure statement

The authors declare no conflict of interest.

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