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Original Article

Expression and significance of cystine transporter SLC7A11/xCT in early colorectal cancer specimens from endoscopic submucosal dissection

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Abstract

The SLC7A11/xCT cystine transporter is intricately linked with ferroptosis. By mediating intracellular cystine flux, it regulates oxidative stress within neoplastic cells, thereby curtailing ferroptosis and influencing the emergence of colorectal cancer. This study aimed to gauge the SLC7A11/xCT expression across various tumorigenic stages in early colorectal adenocarcinoma tissues, shedding light on its specific role in the genesis of these early malignancies. Sixty specimens that underwent endoscopic submucosal dissection (ESD) resection with pathologic diagnosis of colorectal adenocarcinoma were collected. SLC7A11/xCT expression was pinpointed using immunohistochemistry, and correlations with the patients' clinical-pathological features were drawn. Additionally, a comprehensive bioinformatics assessment was undertaken to discern differential SLC7A11/xCT expressions across a spectrum of cancers. Immunohistochemical assessments unveiled a pronounced cytoplasmic SLC7A11/xCT expression, manifesting as a brownish-yellow hue, particularly in nascent colorectal cancer samples. Its expression was discernibly correlated with both patient gender and adenocarcinoma differentiation grade ($P<0.05$). Nevertheless, factors such as patient age, tumor localization, infiltration depth, diameter, adjacent adenoma histology, its major axis, and dysplasia degree bore no statistical significance with SLC7A11/xCT levels ($P>0.05$). Bioinformatics insights pointed to an upregulated SLC7A11/xCT expression across diverse malignancies, inclusive of colon adenocarcinoma, esophageal cancer, acute myeloid leukemia, lung squamous cell carcinoma, colorectal cancer, and endometrial cancer ($P<0.05$). Elevated SLC7A11/xCT expression marks early colorectal adenocarcinoma, with the intensity of this expression being intertwined with the patient's gender and the tumor's differentiation grade. It is postulated that colorectal cancer cells might amplify SLC7A11/xCT to stymie ferroptosis, thus fostering neoplastic proliferation, metastasis, and cellular stemness.

Keywords: Early colorectal cancer, SLC7A11/xCT, Colorectal adenoma, Ferroptosis.

1. Introduction

Colorectal cancer (CRC) stands as a predominant malignancy within the digestive system, with a conspicuous presence in older individuals [1,2]. CRC typically embarks on a trajectory from adenoma to dysplasia, advancing to carcinoma and ultimately metastasis. Originating from aberrant crypt foci, it matures to benign adenomatous polyps and gradually metamorphoses into sporadic CRC over roughly a decade or a tad longer [3]. As such, delving into the molecular shifts accompanying pre-cancerous colorectal adenomas and their transformation into tumors offers invaluable insights for early detection and tailored therapeutic strategies.

The solute carrier family 7 member 11 (SLC7A11), colloquially termed xCT, functions as a sodium-independent, chloride-dependent anionic L-cystine/L-glutamate exchanger on cellular surfaces. It orchestrates an array of cellular dynamics, spanning from redox equilibrium and metabolic adaptability to immune functions and ferroptosis regulation. Within the tumor milieu, cystine predominantly infiltrates cells via SLC7A11/xCT, becoming a linchpin in glutathione biosynthesis. This nexus underpins tumor cells' fortified defense against ferroptosis, fostering both tumor initiation and progression [4]. Elevated SLC7A11/xCT expressions are evident across an array of malignancies, including but not limited to lymphomas, leukemias, squamous cell carcinomas, breast neoplasms, glioblastomas, and pancreatic ductal adenocarcinomas [5]. Surprisingly, its implication in CRC evolution remains uncharted. In this investigation, employing immunohistochemistry, we delineated SLC7A11/xCT expressions in adenocarcinoma and neighboring adenoma tissues from 60 patients diagnosed with early-stage colorectal adenocarcinoma. Our objective centers on discerning the nuanced roles of SLC7A11/xCT in the genesis and progression of early colorectal adenocarcinoma, aiming to enrich the diagnostic and therapeutic landscape for this malignancy.

2. Materials and methods

Study Subjects: Sixty specimens who underwent endoscopic submucosal dissection (ESD) resection and were pathologically diagnosed as early colorectal adenocarci-

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noma from January 01, 2018, to December 2022 in the Zibo Frist Hospital were selected. Inclusion criteria: All were diagnosed for the first time, and postoperative histopathological examination confirmed them as primary colorectal adenocarcinoma. They had not received any relevant treatments such as chemotherapy, immunotherapy, etc., prior to the surgery. Moreover, the pathological slices indicated that all basal margins were negative, ensuring that it was stage T1 colorectal cancer.

Exclusion criteria: Patients who had previously undergone chemotherapy or biological therapy, or those with recurrent tumors or other malignant tumors.

The pathological staging of the patients was determined after two pathology experts separately reviewed the pathology slides. Only when their findings were consistent would the patient be considered for inclusion in the study. The staging criteria followed the UICC/AJCC Colorectal Cancer TNM staging standards (8th edition, 2017). The study protocol was approved by the Ethics Committee of Zibo First Hospital.

2.1. Methods

2.1.1. Immunohistochemistry

The specimens were retrieved from the pathology department, fixed in a 4% formaldehyde solution, embedded in paraffin, and then sectioned continuously into 4 um thick slices. After routine deparaffinization in xylene and rehydration through graded ethanol, antigen retrieval was performed using EDTA antigen retrieval buffer (from Bosen Biotechnology Co., Ltd., Shenzhen, China) and microwaved. Endogenous peroxidase was blocked with a 3% hydrogen peroxide solution and incubated at room temperature for 25 minutes. This was followed by blocking with 10% rabbit serum (from Boster Company, Wuhan, China) at room temperature for 30 minutes. Rabbit anti-human SLC7A11/xCT polyclonal antibody (from Abcam, diluted at 1:200, Cambridge, MA, USA) was added and incubated in a wet box overnight at 4°C. Secondary antibodies (sheep anti-rabbit, from Solarbio, diluted at 1:200, Beijing, China) were applied over the tissues and incubated at room temperature for 50 minutes. Freshly prepared DAB was applied and incubated at room temperature until color developed, followed by rinsing with tap water to stop the reaction. Hematoxylin (from Bosen Biotechnology Co., Ltd., Shenzhen, China) was used for counterstaining for approximately 3 minutes, followed by dehydration and mounting. For negative controls in this study, the primary antibody was replaced with PBS, and strongly positive stained gastric cancer specimens were used as positive controls for SLC7A11/xCT staining.

2.1.2. Criteria for positive results

Referencing the methods of Pan et al. [6], a semi-quantitative scoring method was employed. Specifically, under the microscope, three unfolded fields were randomly selected and scored separately based on the percentage of positively stained cells (PP) and staining intensity (SI). PP Scoring (Total 0-4 points): This is based on the ratio of positively stained cells to the total number of cells in each field. If ≤5% cells were positive, 0 points were given; >5% but ≤25% earned 1 point; >25% but ≤50% earned 2 points; >50% but ≤75% earned 3 points; and >75% earned 4 points. SI Scoring (Total 0-3 points): This was determined by staining intensity, with no color scoring 0 points, pale yellow 1 point, brown-yellow 2 points, and brown 3 points. The final Immunoreactive Score (IRS) was calculated as IRS = PP × SI. A score of 0 was denoted as (-), 1-4 as (+), 5-8 as (++), and 9-12 as (+++).

2.1.3. Analysis of SLC7A11/xCT expression across various cancers in the TCGA database

The Cancer Genome Atlas (TCGA) database is currently the largest repository of cancer genetic information (https://cancergenome.nih.gov/). It encompasses genomic transcriptional profiles, copy number variations, single nucleotide polymorphisms, and associated clinical data. Data pertaining to 31 tumor-related datasets were downloaded from the TCGA database for subsequent differential expression analysis. R 3.5.3 software was employed for statistical data analysis and visualization of graphs.

2.2. Statistical analysis

Statistical analyses were conducted using Statistic Package for Social Science (SPSS) 26.0 software (IBM, Armonk, NY, USA). Quantitative data were represented as mean ± standard deviation and intergroup comparisons were made using the t-test. Qualitative data were represented as proportions or rates, and the Chi-square test (X^2 test) was used for intergroup comparisons. The correlation between two variables was analyzed using the Spearman test. A P-value of less than 0.05 indicated statistically significant differences.

3. Results

3.1. Clinical and pathological features analysis of colorectal adenocarcinoma patients

Among the 60 patients with colorectal adenocarcinoma who underwent ESD, there were 44 males and 16 females, with a male-to-female ratio of 2.75:1. The average age of these patients was 66 ± 9 years, with the youngest being 42 years old and the oldest 85 years old. Lesions in the colon were more prevalent than those in the rectum, with 26 cases located in the rectum and 34 in the colon. The right half of the colon was the most common site for colon cancer. The degree of adenocarcinoma differentiation was predominantly high, accounting for 48 cases, and there were 12 cases with moderate differentiation. Most adenocarcinomas, 55 cases, had invasive depths confined within the mucosa, while 5 cases infiltrated the submucosa. Half of the adenocarcinomas had a diameter <0.2 cm, and the other half ≥0.2 cm.

The immunohistochemical results demonstrated that the expression of SLC7A11/xCT was localized in the cytoplasm, with positive staining presenting as brown-yellow. High expression was observed in early-stage colorectal

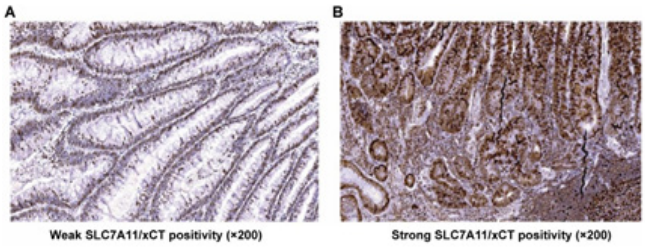

Fig. 1. Representative images of the expression of SLC7A11/xCT in early-stage colorectal cancer samples as detected by immunohistochemistry.

cancer specimens. Through immunohistochemical assessment, we evaluated the intensity of SLC7A11/xCT expression in the samples. Patients were divided into a group with strong SLC7A11/xCT positivity and a group with weak SLC7A11/xCT positivity (representative images can be seen in Figure 1). The differences in the clinical and pathological parameters between the two groups of early-stage colorectal adenocarcinoma patients were compared using the Chi-square test.

The results indicated a significant correlation between the expression levels of SLC7A11/xCT and both the gender of the patients and the degree of adenocarcinoma differentiation (P<0.05, see Table 1). However, there was no apparent correlation between the expression levels of SLC7A11/xCT and the patients' age, location of the adenocarcinoma, depth of adenocarcinoma infiltration, and diameter of the adenocarcinoma (all P>0.05, see Table 1).

3.2. Expression of SLC7A11/xCT in peri-tumoral adenomas

The occurrence and development of cancer are closely related to peri-tumoral adenomas. In the 60 early-stage colorectal cancer specimens, the presence of peri-tumoral adenomas was observed in all cases. Tubulovillous adenomas were the most common pathological type of peri-tumoral adenoma, followed by tubular adenomas. Two-thirds of the adenomas had a long diameter exceeding 2 cm, with the largest peri-tumoral adenoma reaching 7 cm and the smallest being 0.5 cm. Most peri-tumoral adenomas were accompanied by varying degrees of dysplasia; 80% of peri-tumoral adenomas showed mild to moderate dysplasia, while approximately 20% exhibited severe dysplasia. We also investigated the correlation between the expression of SLC7A11/xCT and the pathological features of peri-tumoral adenomas. The positive expression rates of SLC7A11/xCT in different types of adenomas adjacent to early-stage colorectal cancer, such as tubulovillous adenomas, tubular adenomas, villous adenomas, and other types, were 70.0%, 86.7%, 100%, and 53.8%, respectively. The positive rate of SLC7A11/xCT in peri-tumoral adenoma tissues with severe dysplasia was 80%, which is higher than in those with mild to moderate dysplasia (55%). However, the chi-square test results showed that there was no significant correlation between the expression levels of SLC7A11/xCT and the histological type, long diameter, and dysplastic degree of the peri-tumoral adenomas (all

Table 1. Clinical and pathological features of early-stage colorectal adenocarcinoma patients

Clinical Pathological Parameters	Classification	n	SLC7A11/ xCT Strongly Positive	SLC7A11/ xCT Weakly Positive	X^2-Value	P-Value
Gender	Male	44	28	16	5.240	0.025
	Female	16	15	1		
Age	<60 years	15	10	5	0.246	0.743
	≥60 years	45	33	12		
Adenocarcinoma Location	Ascending colon	15	7	8	7.116	0.117
	Transverse colon	2	1	1		
	Descending colon	5	4	1		
	Sigmoid colon	12	10	2		
	Rectum	26	21	5		
Adenocarcinoma Differentiation	Well-differentiated	37	21	16	5.007	0.041
	Moderately-well differentiated	10	10	0		
	Moderately differentiated	2	1	1		
Adenocarcinoma Infiltration Depth	Not to the muscularis mucosae	39	24	15	1.299	0.508
	Muscularis mucosae	6	5	1		
	Submucosa	5	4	1		
Adenocarcinoma Diameter	<0.5 cm	30	18	12	4.022	0.084
	≥0.5 cm	30	25	5		

Table 2. Correlation between SLC7A11/xCT expression and pathological features of peri-tumoral adenomas in early-stage colorectal adenocarcinoma.

Pathological Parameters of Peri-tumoral Adenoma	Classification	Total (cases)	SLC7A11/ xCTStrong Positive (cases)	SLC7A11/xCT Weak Positive (cases)	X^2-value	P-value
Histological Type of Adenoma	Tubulovillous Adenoma	30	21	9	4.020	0.241
	Tubular Adenoma	15	13	2		
	Villous Adenoma	2	2	0		
	Other Types	13	7	6		
Adenoma Long Diameter	<2 cm	20	11	9	4.104	0.067
	≥2 cm	40	32	8		
Dysplasia Degree of Adenoma	Severe	12	7	5	1.313	0.293
	Mild to Moderate	48	36	12		

P>0.05, see Table 2).

3.3. Differential expression of SLC7A11/xCT in pan-cancer

By analyzing the TCGA database, the differential expression of SLC7A11/xCT in 31 types of tumor tissues was studied. The results showed that compared with normal tissues, the expression of SLC7A11/xCT was increased in several tumors including colon adenocarcinoma (COAD), esophageal carcinoma (ESCA), acute myeloid leukemia (LAML), lung squamous cell carcinoma (LUSC), rectum adenocarcinoma (READ), and uterine corpus endometrial carcinoma (UCEC). The differences were statistically significant (P<0.05, see Figure 2).

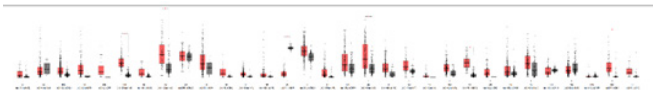

Fig. 2. Differential expression of SLC7A11/xCT in 31 types of pan-cancer.

4. Discussion

The onset of colorectal cancer (CRC) commences with early-stage CRC, where cancerous cells are confined to the mucosal and submucosal regions. While advanced stages of CRC present a somber picture with a mere 5-year survival rate of less than 20%, early-stage CRC paints a more optimistic scenario, with survival rates nearing 90% over a 5-year duration [7]. The treatment strategy of choice for this stage pivots around endoscopic radical resection, with a particular emphasis on endoscopic submucosal dissection (ESD) [8]. With the ascent in public health awareness combined with strides in molecular biology methodologies, the detection rate of early-stage CRC has notably amplified.

In our research, a cohort of 60 early-stage CRC patients undergoing endoscopic submucosal dissection was studied. An in-depth analysis of the clinical-pathological characteristics of their CRC and neighboring adenomatous tissues revealed a pronounced male predominance in early-stage CRC incidence, with a ratio of 2.75:1. This mirrors the broader trend of higher CRC incidence in males [9]. Potential drivers for this gender disparity could include heightened smoking tendencies among males, along with irregular lifestyle patterns and other contributory risk elements. It's noteworthy that the majority of the afflicted were aged above 60, with only two instances of precocious colorectal adenocarcinoma (under 50 years). This age distribution resonates with the extended natural trajectory of CRC evolution. Yet, it's imperative to acknowledge the ongoing demographic shift in CRC, with the median age at diagnosis descending from 72 in the 2001-2002 bracket to 66 during 2015-2016. Concurrently, the incidence of early-onset CRC is exhibiting a concerning rise [10].

The locational predisposition of early-stage CRC lesions is notably biased towards the left side, constituting over 70% of such instances. When juxtaposed with adenomas, the tubulovillous adenoma stands out as the most recurrent pathological subtype, representing half of these combined cases. Given these observations, there's a pressing need to amplify CRC screening endeavors, particularly in the senior male population. Meanwhile, the younger cohorts, especially those presenting with elevated risk factors, ought to remain alert and be encouraged to undergo regular screenings. Within these screening procedures, heightened scrutiny should be dedicated to alterations in the left segment of the colon, with emphasis on the rectum and sigmoid colon areas. Upon diagnosis of tubulovillous adenoma, preemptive measures are crucial to preclude its progression into colorectal adenocarcinoma.

CRC arises from a complex cascade where diverse genetic anomalies stimulate the initiation and progression of colorectal tumors, all while being modulated by environmental and lifestyle-associated risk factors [11]. Recently, the realm of metabolic reprogramming has taken center stage in scientific investigations. Alterations in certain metabolic pathways may play pivotal roles in the onset of CRC and its transition from adenoma to malignancy [12]. Given the heightened metabolic demands of tumor cells and their dependence on exogenous amino acids, the metabolism of amino acids takes on significant physiological and pathological roles within tumoral contexts [13]. These amino acids are quintessential, providing crucial building blocks for nucleotides that aid tumor cell proliferation, invasion, and immune evasion. Moreover, they are essential for activating immune cells and enhancing their tumor-suppressive activities within the tumor environment [14].

Within this metabolic context, cysteine stands out for its multifaceted roles, crucial in protein synthesis, post-translational modifications, and the maintenance of redox balance. Given the elevated antioxidant needs of tumor cells and the inadequacy of cysteine derived from biosynthetic pathways or protein breakdown, most tumor cells lean heavily on nutrient transport mechanisms to glean cysteine from the extracellular milieu [15]. Central to this is the transporter SLC7A11/xCT, which operates as a cysteine/glutamate exchanger. It mediates cysteine uptake and concurrently releases glutamate, thereby facilitating the synthesis of glutathione. This action serves as a fortress against oxidative assaults, preserving cellular redox stability. Such protective strategies act as deterrents against the onset of ferroptosis induced by lipid peroxidation [16].

Amid a wealth of studies examining the role of SLC7A11/xCT in colorectal cancer (CRC), information concerning early colorectal adenocarcinomas remains sparse. Through transcriptomic data analysis, Kaya et al. [17] discerned a heightened expression of SLC7A11/xCT in the bloodstreams of CRC patients. In a separate study, Zhang et al. [18] reported an amplified expression of SLC7A11/xCT in specific cell lines: the DLD-1 human colorectal adenocarcinoma epithelial cell line and the HCT116 human colon cancer cell line. Significantly, this augmented expression seemingly attenuated the induction of ferroptosis in these cancer cells when exposed to the benzopyrene derivative IMCA. Han et al. [19] found that bolstering SLC7A11/xCT expression could at least partially offset the effects of apoptosis and ferroptosis induced by the compound Pt3R5G, derived from black goji, especially in the less differentiated RKO colon cancer cell line. Sun et al. [20] made an intriguing observation that, in metastatic colon cancer cells, the suppression of SLC7A11/xCT ramped up ferroptosis, leading to a significant decline in the colonization and growth of liver metastasis. On a similar note, Tang et al. [21] identified robust SLC7A11/xCT expression in tissue samples from CRC patients post-operatively. Reducing SLC7A11/xCT

expression markedly impeded the proliferation, migration, and inherent stemness of specific colon cancer cell lines, namely HCT116 and HCT15. Supporting these in-vitro findings, animal models underscored that the inhibition of xCT drastically hampered the potential for lung metastasis in colon cancer, potentially mediated through the MELK/AKT/mTOR signaling pathway.

These findings insinuate that, in nascent colorectal adenocarcinomas or even surrounding peri-cancer adenomas, the SLC7A11/xCT molecule may facilitate tumorigenesis and tumor evolution by countering lipid peroxidation and reducing cell ferroptosis. Though our analysis did not uncover a linkage between cellular atypia in peri-cancer adenomas and SLC7A11/xCT molecule expression, an intensified examination centered on ferroptosis-associated molecules and lipid peroxidation measures is essential.

In conclusion, the SLC7A11/xCT molecule manifests a marked expression in initial stages of colorectal adenocarcinomas. Notably, the intensity of SLC7A11/xCT expression seems to be intricately tied to both the patient's gender and the adenocarcinoma's differentiation level. One plausible mechanism suggests that colorectal cancer cells elevate SLC7A11/xCT expression to counteract lipid peroxidation, sustain oxidative stress equilibrium, mitigate ferroptosis, and consequently bolster tumor cell proliferation, metastasis, and stemness. This heightened expression of the SLC7A11/xCT molecule might emerge as an incipient event in the development of colorectal cancer. Thus, targeting SLC7A11/xCT expression and the accompanying ferroptosis offers a promising therapeutic avenue. Nevertheless, the exact mechanisms warrant more detailed exploration.

Ethical compliance

This study was approved by the ethics committee of Zibo Frist Hospital.

Conflict of interest

The authors have no potential conflicts of interest to report relevant to this article.

Author contributions

XZ, CW and XK designed the study and performed the experiments, XZ, CW and ZY collected the data, XK and ZY analyzed the data, XZ, CW and XK prepared the manuscript. All authors read and approved the final manuscript.

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