Archives of Razi Institute, Vol. 77, No. 6 (2022) 2049-2057

DOI: 10.22092/ARI.2022.358611.2261

Original Article

The Impact of CD37 Ectoenzyme Expression in Benign and Malignant Colorectal Tumors

Falih Soliman, N[1 *], Jasim Mohamad, B[1]

1. Department of Biology, Collage of Science, University of Baghdad, Baghdad, Iraq

Received 7 May 2022; Accepted 8 June 2022
Corresponding Author: sukaina.2t@yahoo.com

Abstract

The depth of invasion of colorectal cancer through the bowel wall provided the basis for pathological staging. The establishment of prognostic markers for CRC is important in the search for potential targets for therapeutic intervention. The cell surface nucleotidase (CD73) is an enzyme involved in tumor progression and metastasis. Its main function is to convert adenosine monophosphate (AMP) to adenosine. Preclinical studies suggest that CD73 can be targeted for cancer treatment. This study was designed to investigate the prognostic value of CD73 in malignant and benign colorectal tumors among Iraqi patients and its correlation with clinicopathological features using the immunohistochemistry (IHC) technique. In the current study, 60 cases of formalin-fixed paraffin-embedded (FFPE) tissues of colorectal tumors were collected from the Teaching Laboratories of Baghdad Medical City Teaching Hospital, Baghdad – Iraq & private labs in Baghdad. Of them, 52 were malignant, and 8 of benign cases. In addition, 10 cases of the non-pathological significance of colorectal tissues were used as a control group. This study's results revealed significant differences (P=0.001) in the expression of CD73 between malignant tumors and benign and non-significant pathology groups. The highest expression of CD73 was detected in 76.9% of malignant cases, while in the benign group, only 12.5% of cases showed weak positive expression for this marker. Furthermore, significant differences had been reported in CD73 expression with patients' age groups for malignant (P=0.0335), tumor side (P=0.0409), and tumor grade & stage (P=≤0.01). No significant differences had been seen between CD73 expression with tumor diameter and patients' gender.

Keywords: CD37, ectoenzyme, colorectal tumors, Iraqi patients

1. Introduction

Colorectal cancer (CRC) is the most common malignancy in the gastrointestinal tract and is the fourth leading reason behind cancer-associated death world (1). According to the Iraqi cancer registry, CRC ranked seventh among the most common ten cancer cases reported (2). The importance of CRC comes from the fact that despite its high incidence, it is an entirely treatable disease if caught early (3). The significant challenge to the management of CRC is early detection worldwide, which makes this treatment option to be administered so late after tumor metastasis. If tumors are detected early enough, and polyps are surgically resected, they may reduce the incidence and death rate of CRC (4). CRC has a poor prognosis, and there is an essential need for new diagnostic and prognostic biomarkers to avoid CRC-related deaths (5). Biomarkers play a vital role in the management of CRC. Indeed, they will reveal the predisposition for the disease and detect the disease at an early stage. They are also helpful in monitoring the efficacy of treatment, neo-adjuvant therapy, follow-up, and disease recurrence. They can also help to pick out the foremost appropriate chemotherapeutic drug across a broad spectrum of patients (6). Recently, targeted and biological therapeutics have made substantial advances

in metastatic CRC treatment and have prolonged overall survival and disease-free survival of patients, with fewer adverse effects than conventional chemotherapy. Since these therapeutics act on specific target proteins, they are restricted to certain individuals consistent with their molecular profiles. Therefore, more specific biomarkers, which determine the biological nature and behavior of colorectal cancer, are required to benefit more patients (7). Among them, Ecto-5'-nucleotidase (CD73), a glycosylated 70 kDa protein bounding to the external surface of the plasma membrane through a glycosyl phosphatidyl inositol (GPI) anchor, is overexpressed in a diversity of tumors, including breast cancer, ovarian cancer, and renal cell cancer (8). CD73 is also a regulatory molecule associated with cancer metastatic and invasive properties. This enzyme plays a crucial part in extracellular purinergic signaling by generating adenosine from AMP (9). Adenosine is an immunosuppressive molecule associated with tumor immune escape over its ability to reduce anti-tumor immune effectors' functions (10). This study aimed to Assess the expression of CD73 ectoenzyme in malignant and benign colorectal tumors, Investigate its correlation with disease prognosis and clinicopathological features (age, tumor site & size, node involvement, tumor stage & grade) using an IHC assay.

2. Materials and Methods

A total of 60 cases of colonic biopsies (total colectomy and excisional biopsies) in the form of paraffin-embedded tissue blocks were collected from archive files between the years (2015-2021) of the Department of Pathology of teaching laboratories of Baghdad Medical City Teaching Hospital and private labs, Baghdad–Iraq. Tissue samples from Iraqi patients involved 52 cases of malignant tumors, 8 cases of benign tumors, and 10 cases of colorectal tissue without significant pathology as a control. Clinical information, including age, tumor site, size, pathological grade, and stage, were collected from the patient's data reports.

2.1. Immunohistochemistry (IHC)

The immunohistochemistry (IHC) staining procedure for CD73 was carried out according to (Abcam) protocol instructions, under a standard interaction term for temperature 25^{o}C and PH=7.4 in a humidity chamber. Firstly, sections were deparaffinized in xylene and rehydrated in decreasing ethanol concentration. Then, Slides were then immersed in the antigen retrieval solution and pressure cooked for 30 minutes. Next, slides were incubated in a hydrogen peroxide block for 10min. Then, the block was added to the tissue sections and incubated for 10 minutes.CD73 Primary antibodies (abcam133582) were diluted to 1:100 using primary Ab diluent, added to the tissue sections, and incubated for 30 minutes at room temperature. After washing the slides, the secondary antibodies Goat Anti-Rabbit HRP Conjugate (abcam236469) were added and incubated for 15 minutes at room temperature in the humidity chamber. Then, slides were incubated with diaminobenzidine (DAB) for 5 to 10 minutes until the brown color appeared and washed in PBS twice each for 5 min. Slides were then counterstained by hematoxylin for 10 seconds and then washed with distilled water. Finally, slides were dehydrated, cleared, mounted, and coverslipped for overview.

2.2. Scoring System of IHC

Staining was scored semi-quantitatively for CD73. CD73 expression levels were graded on a scale of 0 to 3 based on cytoplasmic and membrane staining intensity and the proportion of positive tumor cells by an expert pathologist. The staining was graded as 0 if no-cancer cells were reactive, 1 if staining was weakly positive in 2/3 of cancer cells, or strongly positive in >1/3 of cancer cells, and 3 if staining was weakly positive in most cancer cells, or strongly positive in >2/3 of cancer cells. Immunohistochemical staining for CD73 in colorectal cancer tissue was classified as unfavorable (grade 0) or positive (grade 1 to 3).

2.3. Statistical Analyses

Data analysis was carried out using the available statistical package of SPSS-26 (Statistical Packages for

Social Sciences- version 26); computer software was used for this purpose. Data were presented in simple measures of frequency, percentage, mean, standard deviation, and range (minimum-maximum values). The significance of the difference of different percentages (qualitative data) was tested using the Pearson Chi-square test (χ 2 -test), applying Yate's correction or Fisher Exact test whenever applicable. Statistical significance was considered whenever the *P*-value was equal to or less than 0.05 ($P \leq 0.05$).

3. Results

The positive expression of CD73 was seen as brown cytoplasmic and cell membrane staining in tumor cells. Results showed that CD73 ectonucleotidase was positively expressed in 76.9% of malignant cases and 12.5% of benign samples, as well as in 10% of normal colorectal tissues (Table 1 and Figure 1).

Table 1. Scoring of CD73 expression for colorectal tissue sample

CD73 expression score	Adenocarcinoma n (%)	Adenoma n (%)	No pathology N (%)	*P*-value
Score 0	12 (23.1)	7 (87.5)	9 (90.0)	0.001*
Score 1	12 (23.1)	1 (12.5)	1 (10.0)	
Score 2	13 (25.0)	----	----	
Score 3	15 (28.8)	----	----	

*Significant differences between proportions using Chi-square test at 0.05 level

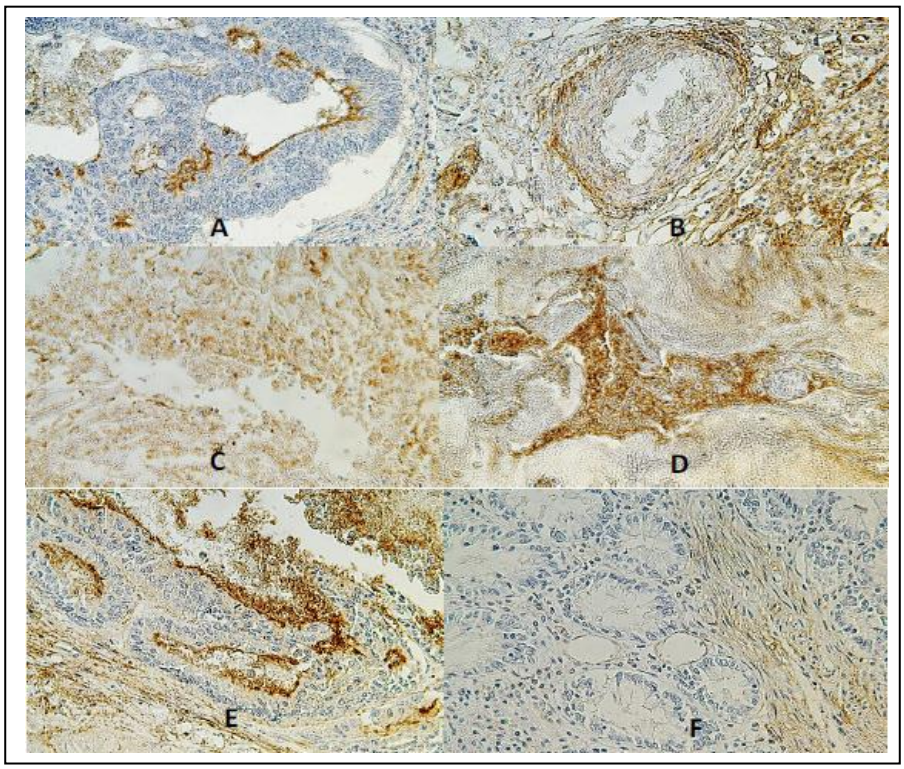

Figure 1. Immunohistochemical assessment of CD73
A) Weak cytoplasmic expression of CD73 in moderately differentiated adenocarcinoma, (400×). B) Moderate cytoplasmic expression of CD73 in moderately differentiated adenocarcinoma, (400×). C) Strong cytoplasmic expression of CD73 in poorly differentiated adenocarcinoma, (400×). D) Strong cytoplasmic expression of CD73 in well-differentiated adenocarcinoma, (400×). E) Strong cytoplasmic expression of CD73 in moderately differentiated adenocarcinoma, (400×). F) Normal colon tissue showing weak cytoplasmic expression of CD73 (400×)

3.1. Association of CD73 Expression with Clinicopathological Features

3.1.1. Association of CD73 Expression with Age

Results showed significant differences (P=0.0335) in the expression of CD73 among age categories in the adenocarcinoma group but not within benign. The highest CD73 expressions (score 3) were seen in the adenocarcinoma group <55years old comprising 35.0%, as demonstrated in table 2.

3.1.2. Association of CD73 Expression with Gender

Results showed no significant differences in CD73 expression between males and females in the study groups (Table 3).

3.1.3. Association of CD3 Expression with Tumor Site

Results revealed significant differences (P=0.0409) between the expression of CD73 and the location of the tumor in adenocarcinoma cases, the highest CD73 expression (score 3) was seen in right-sided colon comprising 39.0% (Table 4).

3.1.4. Association of CD73 Expression with Tumor Diameter

The present study revealed that the expression of CD73 did not significantly correlate with tumor diameter (Table 5).

3.1.5. Association of CD73 Expression with Tumor Grade and Stage

Results showed highly significant differences ($P \leq 0.01$) in the expression of CD73 in different stages and grades of the tumor. The strong expression of CD73 was seen in 31.4% of cases with moderate tumor grade and 27.2% of cases with a well-differentiated grade, while the strong expression of this marker was seen in only 17.0% of poorly differentiated cases. Concerning tumor stage, the highest proportion of strong expression of CD73 was observed in stage IIA of the disease comprising 25.0% (7 cases) of the total (Tables 6 and 7).

Table 2. Association between CD73 IHC expression and age

CD73 expression score	Adenocarcinoma		Adenoma	
	< 55-year n (%)	> 55-year n (%)	< 55-year n (%)	>55 year n (%)
Score 0	5 (27.0)	7 (20.0)	6 (100)	1 (50)
Score 1	3 (16.0)	9 (26.5)	0	1 (50)
Score 2	4 (22.0)	9 (26.5)	0	0
Score 3	7 (35.0)	8 (27.4)	0	0
χ^2 (P-value)	* (0.0335)		0.422	

*Significant differences between proportions using Chi-square test at 0.05 level

Table 3. Association between CD73 IHC expression and gender

CD73 expression score	Adenocarcinoma		Adenoma	
	Male n (%)	Female n (%)	Male n (%)	Female n (%)
Score 0	4 (16.0)	8 (29.5)	5 (83.3)	2 (83.3)
Score 1	7 (28.0)	6 (22.2)	1 (16.7)	0
Score 2	9 (36.0)	4 (14.9)	0	0
Score 3	6 (24.0)	9 (33.4)	0	0
χ^2 (P-value)	0.285		(0.422)	

*Significant differences between proportions using Chi-square test at 0.05 level

Table 4. Association between CD73 IHC expression and tumor site

CD73 expression score	Adenocarcinoma		Adenoma	
	Right n (%)	Left n (%)	Right n (%)	Left n (%)
Score 0	4 (20.0)	8 (25.8)	3 (100)	4 (80)
Score 1	4 (20.0)	8 (25.8)	0	1 (20)
Score 2	5 (21.0)	9 (29.0)	0	0
Score 3	8 (39.0)	7 (19.4)	0	0
χ^2 (*P*-value)	* (0.0409)		(0.661)	

*Significant differences between proportions using Chi-square test at 0.05 level

Table 5. Association between CD73 IHC expression and tumor diameter

CD73 expression score	Adenocarcinoma			Adenoma		
	<5 cm n (%)	5-10 cm n (%)	>10 cm n (%)	<5 cm n (%)	5-10 cm n (%)	>10 cm n (%)
Score 0	9 (25.7)	2 (15.3)	1 (25.0)	2 (16.0)	5 (29.6)	----
Score 1	4 (13.3)	6 (46.0)	2 (50.0)	1 (36.0)	----	----
Score 2	11 (29.6)	2 (8.0)	1 (25.0)	----	----	----
Score 3	11 (31.4)	4 (30.7)	----	----	----	----
P-value	0.298			(0.422)		

*Significant differences between proportions using Chi-square test at 0.05 level

Table 6. Association of CD73 expression with tumor grade

CD73 expression score	Tumor grade		
	Well-differentiated n (%)	Moderate differentiated n (%)	Poor differentiated n (%)
Score 0	4 (36.3)	7 (20.1)	1 (17.0)
Score 1	1 (9.1)	8 (22.8)	3 (50.0)
Score 2	3 (27.2)	9 (25.7)	1 (17.0)
Score 3	3 (27.2)	11 (31.4)	1 (17.0)
Total	11 (100)	35 (100)	6 (100)
P-value	** ≤ 0.01		

Table 7. Association of CD73 expression with tumor stage

CD73 expression score	Tumor stage					
	I n (%)	IA n (%)	IB n (%)	IIA n (%)	IIB n (%)	IIIB n (%)
Score 0	1 (50.0)	0	1 (100)	7 (25.0)	3 (30.0)	0
Score 1	1 (50.0)	0	0	6 (21.4)	2 (20.0)	3 (60.0)
Score 2	0	1 (100)	0	8 (28.6)	3 (30.0)	1 (20.0)
Score 3	0	0	0	7 (25.0)	2 (20.0)	1 (20.0)
P value	** ≤ 0.01					

To our knowledge, this study is the first done in Iraq to investigate the expression of CD73 ectoenzyme in colorectal tumors by IHC and assessment the association between the expressions of this marker with some clinicopathological variables. As a starting point to discuss the role of CD73 in CRC, it is important to establish that the final step in converting pro-inflammatory extracellular ATP to immunosuppressive adenosine is catalyzed by the rate-limiting membrane-bound and soluble ectonucleotidase CD73, and constitutes an important negative-feedback mechanism that prevents excessive immune responses. Recent evidence support that many solid tumors usurp this pathway as an immune escape mechanism (8). Accumulating extracellular adenosine through activation of 5′ectonucleotidase (CD73) and subsequent signaling through adenosine receptors is a common mechanism for tumors escaping tumor immune surveillance (11). As a result, inhibition of CD73 could be a therapeutic adjuvant to improve cancer immunotherapy (12). CD73 expression and activity seem modulated upon many therapies; co-targeting CD73 with other therapeutic reagents is a rational strategy. CD73 inhibition, in general, is expected to boost immune response to keep the tumor cells in control (13). Remarkably, CD73 appeared as a potential prognostic biomarker and a promising target to counteract the immunosuppressive tumor microenvironment and favor anti-tumor immune response (14). Previous studies have shown that CD73 on tumor cells can mediate proliferation and migration apart from its enzymatic activity and that blocking CD73 can suppress tumor growth. As well, CD73 has been shown to contribute to the angiogenesis process via its enzymatic and non-enzymatic functions. These findings suggest that CD73 blockade may suppress the growth of tumor metastases through mechanisms unrelated to immunity (15).

The results of the current study demonstrated that CD73 was positively expressed in colorectal cancer, articulating about 76.9% in malignant cases. Moreover, there were significant differences between CD73 expression and colorectal tumor type (P=0.001). This outcome comes in agreement with Jiang, Xu (16), who stated in his meta-analysis study that the median CD73 expression level in tumor tissues was significantly higher than that in normal tissues in most kinds of cancers, including bladder, brain, invasive lobular breast, esophageal, gastric, pancreatic cancer, rectal mucinous, renal cell, large lung cell, oral cavity squamous cell carcinoma, melanoma, and lung adenocarcinoma.

Early studies assessing CD73 in CRC were part of more considerable efforts examining enzymatic patterns of critical enzymes involved with purine metabolism and salvage, including ADA, alkaline phosphatase, hypoxanthine-guanine phosphoribosyltransferase (17). Wu, He (18) study showed that CD73 expression was significantly greater in CRC tissues than in normal colorectal tissues. Another study showed that CD73 expression was significantly higher in CRC cells with high malignant potential than in CRC cells with low malignant potential (7).

In this study, the adenocarcinoma group showed high positive expression of CD73 in 76.9% of cases, which is compatible with Wang, Zhang (19), who stated that CD73 was highly expressed in adenocarcinoma tumors rather than other types. Moreover, this study showed negative CD73 expression in 90% of normal colorectal tissues. This finding agreed with previous study findings, which showed that solid tumors contain a higher level of extracellular ADO than the surrounding normal tissues (20).

Concerning the association of CD73 expression with some clinicopathological features of them the age, it was highly expressed in adenocarcinoma group patients with age of <55 by 35.0%. While for patients older than 55 years, the expression was 27.4%, and there were highly significant differences between CD73 expression and age compared to the adenoma group had no significant differences with CD73 expression. A meta-analysis study by Jiang, Xu (16) showed no significant correlation between CD73 expression and

age in several types of cancer of the CRC, which is in contrast with this study's findings. Our result also disagrees with Messaoudi, Cousineau (8), who revealed no significant correlation between CD73 expression and age, and with Tsukui, Horie (15), who stated in their study on a murine model that the CD73 expression level did not show a significant correlation with clinical or pathological findings including age. Also, in a study with different types of cancer, there were no significant differences between CD73 and age in breast cancer (21). Another study on salivary gland tumor patients showed no significant association between CD73 expression and clinicopathological variables such as age, gender, and tumor size (22).

On the other hand, in this study, the correlation of gender and diameter of tumor for both adenocarcinoma and adenoma colorectal tumors showed no significant differences with CD73 expression. These findings are in accordance with a study by Bertoni, Bracco (23), who reported no association between CD73 and the diameter of tumors in papillary thyroid cancer. While in a study on breast cancer patients, it was found that tumor-infiltrating NK cells upregulated CD73 expression, and the frequency of these CD73-positive NK cells was correlated with larger tumor diameter (24). Even though in pancreatic ductal adenocarcinoma, high expression of CD73 was associated with increased tumor diameter (17).

This study observed a significant correlation between CD73 expression and tumor site. This result disagrees with Messaoudi, Cousineau (8), who showed no correlation between CD73 expression and tumor site. Another study by Wu, He (18) study showed no significant association between CD73 expression and tumor location.

Another finding in this task is that the expression of CD73 was elevated in adenocarcinoma tumors with moderate gradings. This finding is supported by Wu, He (18) study and Messaoudi, Cousineau (8). They showed that CD73 expression was significantly associated with tumor grade. At the same time, Tsukui, Horie (15) stated in their study on a murine model that CD73 expression level did not significantly correlate with clinical or pathological findings. Similarly, Zhong, Yang (25) declared that there was no association between CD73 and tumor grade in pancreatic cancer. Theoretically, cancer cells with high CD73 expression possessed higher aggressiveness and invasiveness (16). Babat, Polat (26) emphasized that the patients with higher grades lived shorter than the ones with lower grades (overall survival=21 and 59.8 months, respectively). In a point of view, the CD73-adenosinergic pathway enhances tumor progress not only by regulating the tumor cells' angiogenesis and proliferation but as well promoting the tumor to form a suppressive environment by inhibiting CD8+ T cells, NK cells function, and increasing the generation of myeloid-derived suppressor cells (19).

Furthermore, this study observed a significant correlation between CD73 expression and tumor stage. Most cases with different colorectal tumor stages showed convergingly positive CD73 reactivity. Hence, high CD73 expression was likely to be associated with poor prognosis in the current study. Likewise, another study by Wu, He (18) showed that high CD73 expression was correlated with the clinical stage. Zhang, Song (27) also indicated that higher stromal CD73 expression was favorable and linked to early tumor stages. Hu, Meng (28) recorded a significant association between CD73 and tumor stage in gastric cancer. Even though in breast cancer, CD73 expression was significantly associated with tumor stage (29). Contrarily to this study's findings, another study disagreed and showed that CD73 expression was significantly higher in colorectal cancer cells with high malignant potential than in colorectal cancer cells with low malignant potential (7). Tsukui, Horie (15) also showed in their study on a murine model that there is no significant correlation with clinical or pathological findings. Correspondingly, Jiang, Xu (16) showed that high CD73 expression was not correlated with the clinical stage. In another type of cancer, no correlation

was observed between CD73 and clinical stage in head and neck squamous cell carcinomas (30). Also, bladder cancer was not associated with the tumor stage (31). The difference in results may be due to the histological tissue types utilized in investigating CD73 expression (32). These results indicated that distinct histological types of cancers would have distinct CD73 expressions.

Authors' Contribution

Study concept and design: N. F. S.
Acquisition of data: N. F. S. and B. J. M.
Analysis and interpretation of data: B. J. M.
Drafting of the manuscript: B. J. M.
Critical revision of the manuscript for important intellectual content: N. F. S.
Statistical analysis: B. J. M.
Administrative, technical, and material support: N. F. S.

Ethics

The study protocol were approved by the ethics committee of the University of Baghdad, Baghdad, Iraq

Conflict of Interest

The authors declare that they have no conflict of interest.

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