Immunohistochemical Expression of Debiquitinating Enzyme OTUB$_1$ in Colorectal Carcinoma

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Abstract

Background and Objective: Colorectal Carcinoma (CRC) is the most common malignancy of the gastrointestinal tract. The overall five-year survival for colon cancer and rectal cancer are 65% and 68%, respectively with liver metastasis being the leading cause of death. Despite the use of active targeted drugs for treatment of metastatic CRC in the past decade, cure rates remain low. Therefore, research on novel markers for earlier diagnosis and target therapy of CRC is of a great concern. OTUB$_1$ (OTU deubiquitinase, ubiquitin aldehyde binding 1) is a deubiquitinating enzyme (DUB) that belongs to the OTU (ovarian tumor) superfamily. The aim of this work is to study the immunohistochemical expression of OTUB$_1$ in CRC and its correlation with the available clinico-pathological variables.

Material and Methods: This retrospective study was conducted on a total number of 45 cases of CRC. All cases were retrieved from the archival files of the pathology labs of Ain Shams University Hospitals (from 2012-2016). Immunohistochemistry using rabbit polyclonal anti OTUB 1 antibody was performed.

Results: OTUB 1 was overexpressed in CRC tissues, and the expression level of OTUB$_1$ was correlated significantly with histologic grade ($p<0.001$), depth of invasion (pathological T) ($p=0.03$) and location of CRC ($p=0.002$). On the other hand, no significant correlation was found with age, gender, metastasis whether nodal or distant, TNM stage and size of tumor.

Conclusion: OTUB1 may have a possible role in tumor differentiation as well as local tumor invasion, thus could be useful in identification of biologically aggressive tumors in colonoscopic biopsies in addition to providing a basis for targeted therapy which could play a major role in the treatment of CRC.

Key Words: OTUB1 – Colorectal carcinoma – Immunohisto-chemistry.

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Introduction

COLORECTAL Cancer (CRC) is the most common malignancy of the gastrointestinal tract ranking the third most commonly diagnosed malignancy in men while the second most common cancer in women and the fourth leading cause of cancer death. More than two-thirds of all cases and about 60% of all deaths occurred in countries with a high or very high human development index [1]. CRC in Egypt, as most of developing countries, has lower incidence than that of western countries with sedentary lifestyle. In Egypt, it is the sixth most common cancer constituting about 4% of total cancers in both sexes [2].

From a molecular aspect, several genes have been implicated in bladder carcinogenesis, mostly oncogenes (i.e. k-ras) and tumor suppressor genes (i.e. APC, p53, SMAD4), whose alterations lead to genetic instability and eventually to full development of histologically apparent colorectal tumors [3].

DUBs are cysteine proteases that catalyze the removal of Ubiquitin (UB) from Ub-modified proteins and responsible for the processing of nascent translated linked Ub precursors. OTUB$_1$ is a cysteine protease that hydrolyses the isopeptide bond between ubiquitin and the target molecule [4]. OTUB$_1$ has recently emerged as a unique atypical DUB that binds and inhibits several classes of E2s, thus in this way inhibits DNA repair [5]. Recent studies found that DUBs are crucial in regulating a variety of cellular pathways, including cell growth and proliferation as well as apoptosis, thus are key molecular determinants of aberrant cancer proteome [5,6,8,9].

The overexpression of OTUB$_1$ has been found in many human cancers such as in prostate, color-

ectal, breast, gastric and lung cancers that are associated with poor survival, high metastatic potential, and chemotherapeutic drug resistance [10].

To date, there is a paucity of data in the relationship between OTUB $_1$ and colorectal carcinoma. The aim of the present study is to assess the immunohistochemical expression of OTUB $_1$ in cases of CRC and to correlate it with various clinico-pathological parameters.

Material and Methods

Tissue collection:

The current study was conducted on 45 cases of colorectal carcinoma. Cases were retrieved from archives of the Pathology Department, Ain-Shams University Hospital during the period from January 2012 to December 2016. They were obtained by radical colectomy. The surgical and histopathology reports were reviewed to determine age, sex of the patients as well as the histologic type of CRC. In addition, 10 cases of non-neoplastic colonic lesions were obtained by colonoscopic biopsies included as a control.

Haematoxylin and Eosin stained slides were examined for the confirmation of the diagnosis. Examination of the tumor was done for pathologic typing and grading following recommendations of the World Health Organization [11]. In addition, depth of invasion (T), nodal status (N), distant metastasis (M) (was obtained from Oncology files) and staging were assessed according to the American Joint Committee on Cancer [12].

Immunohistochemistry:

Four micrometer sections of formalin-fixed paraffin-embedded tissue samples of he studied cases were prepared. All sections were incubated with 3% hydrogen peroxide for 15min to block endogenous peroxidase activity at first. The antigen retrieval was performed by high pressure method for 3min in citrate buffer (pH 6). Immunohistochemical (IHC) staining was performed using the primary antibody which was rabbit polyclonal antibody, Anti-OTUB $_1$ (ab 198214) concentrate antibody (Abcam, Cambridge, UK), was applied at the dilution of 1:100 for 2h at room temperature. After rinsing, staining was performed with Reagent A and Reagent B subsequently. The color was developed by reacting with Diaminobenzidine (DAB). Sections were then counterstained with hematoxylin, dehydrated, cleared and cover slipped. The positive staining was demonstrated by the presence of obvious brown or yellow particles on a low-power objective. The human breast tissue was used as positive control according to the manufactures instructions.

Interpretation of immunohistochemical staining:

Positive immunoexpression was defined as cases showing cytoplasmic staining pattern of tumor cells. OTUB $_1$ Immunoreactivity Score (IRS) was calculated by the multiply of two values: (A) Staining intensity: No immunoreactivity was scored as 0, weak immunostaining was 1, moderate immunostaining was 2, and strong immunostaining was 3; (B) Percentage of positive tumor cells: 0-5% was 0, 6-25% was 1, 26-75% was 2, and 75-100% was 3. The final score of 0-3 was categorized as low expression, and 4-9 was categorized as high expression [4].

Statistical analysis:

The collected data was revised, coded, tabulated and introduced to a PC using Statistical package for Social science (SPSS 15.0.1 for windows; SPSS Inc, Chicago, IL, 2001). Data were expressed as mean ($\pm$SD) for quantitative parametric measures in addition to both number and percentage for categorized data. Chi-square (χ^2) test was done to study the association between more than one variable as between OTUB $_1$ expression and different clinico-pathological parameters of the studied cases. Student *t*-test was used to assess the statistical significance of the difference between two study group means. Fisher's exact test: Was used to examine the relationship between two qualitative variables when the expected count is less than 5 in more than 20% of cells. $p \leq 0.05$ was considered the cut off value of significant. Differences were considered highly significant when $p \leq 0.001$.

Results

Clinicopathological results:

In the present study, the mean age of patients was 50.64 ± 12.27 years and female to male ratio was 1.36:1. The pathological features regarding the cases of CRC such as tumor depth, lymph node status, distant metastasis, stage and histologic grading are shown in (Table 1). Most of cases (26 cases; 57.8%) were low grade and infiltrating into subserosa or perirectal tissue (T $_3$), metastasis to 1-3 lymph nodes (N $_1$) was detected in 20 cases (44.4%), distant metastasis was present in 19 cases (42.2%), and stage III and IV were the commonest stages (36 cases; 80%).

Immunohistochemical results:

OTUB $_1$ expression was mainly detected in the cell cytoplasm. Non-neoplastic colonic lesions

showed negative staining and few showed weak focal staining. Immunohistochemical expression of $OTUB_1$ is summarized in (Table 2). High $OTUB_1$ expression was found in 57.8% of the studies cases while low $OTUB_1$ expression was found in 42.2% of cases (Table 2), Graph (1).

High OTUB 1 expression was statistically associated with high grade tumors ($p<0.001$), depth T ($p=0.03$) and location of CRC ($p=0.002$).

69.2% of cases with high $OTUB_1$ expression were associated with high grade tumors Graph (2). Mean $OTUB_1$ expression in high grade tumors (7.21) was significantly higher than that of low grade tumors (2.77) Graph (3). Most of high grade tumors expressed the marker with score ›_6 with sensitivity (84.2%) and specificity (73.1%) Graph (4). 88.5% of cases with high OTUB1 expression were associated with greater tumor depth T_3 and T_4 Graph (5).

No statistically significant relationship was detected as regards age ($p=0.93$), gender ($p=0.99$), lymph node metastasis ($p=0.36$), distant metastasis ($p=0.22$), TNM stage ($p=0.12$), size of tumor ($p=0.5$) (Table 3).
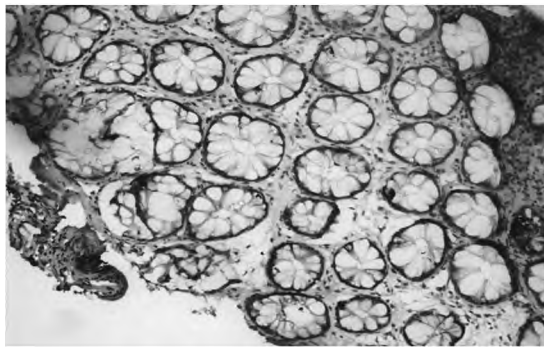

Fig. (1): $OTUB_1$ staining of non-neoplastic colonic mucosa shows negative staining (IHC X200).
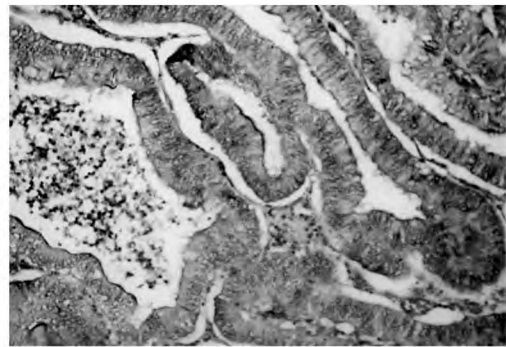

Fig. (2): A case of low grade colonic adenocarcinoma shows low expression of $OTUB_1$ (IHC X200).
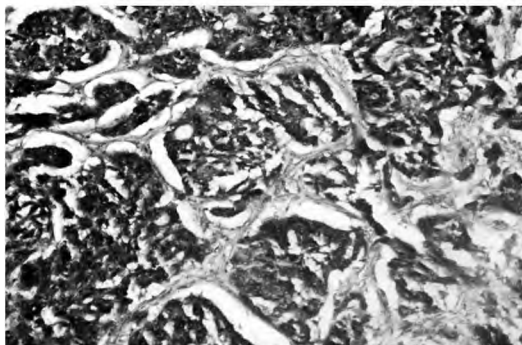

Fig. (3): A case of high grade colonic adenocarcinoma shows high expression of $OTUB_1$ (IHC X200).
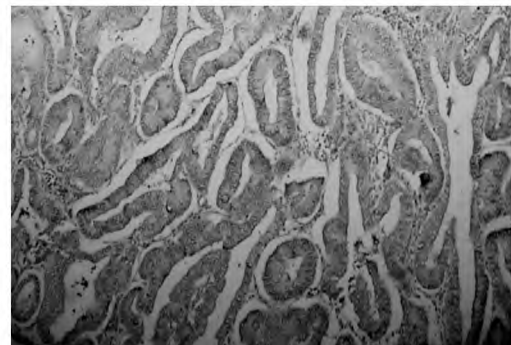

Fig. (4): A case of low grade colonic adenocarcinoma invades submucosa (T_1) shows low expression of $OTUB_1$ (IHC X100).
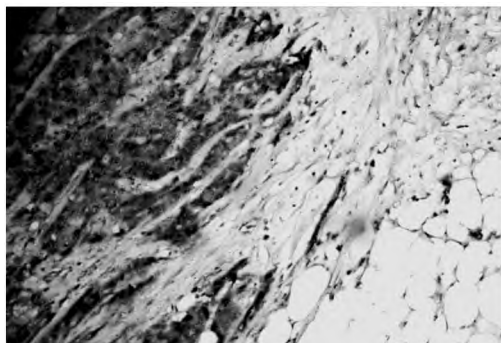

Fig. (5): A case of high grade colonic adenocarcinoma infiltrating up to serosal fat (T_3) shows high expression of $OTUB_1$ (IHC X200).
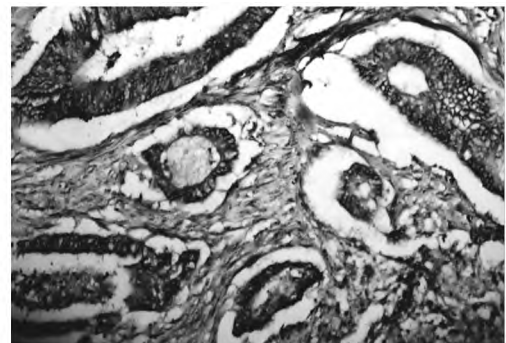

Fig. (6): A case of low grade colonic adenocarcinoma invades urinary bladder (T_4) shows high expression of $OTUB_1$ (IHC X200).

Table (1): Clinicopathological parameters.

	N Minimum	Maximum	Mean	SD
Age 45	23.00	70.00	50.64	12.27

	Count	Percentage
Gender:		
Males	19	42.2
Females	26	57.8
Total	45	100.0

	Count	Minimum	Maximum	Mean	SD
Tumor sixe (cm)	45	2.00	13.00	4.69	2.43

Site	Count	Percentage
Right sided	19	42.22
Left sided	26	57.78
Total number	45	100

	Count	%
Grading:		
Low	26	57.8
High	19	42.2
Depth:		
T_1	2	4.4
T_2	8	17.8
T_3	26	57.8
T4	9	20.0
LN:		
N_0	14	31.2
N_1	20	44.4
N2	11	24.4
Metastasis:		
M_0	26	57.8
M1	19	42.2
Stage:		
I	5	11.1
II	4	8.9
III	18	40.0
IV	18	40.0
Total number	45	100

Table (2): Distribution of OTUB₁ expression in the studied cases.

	N	Minimum	Maximum	Mean	SD
Score	45	0.00	9.00	4.64	3.45

	Count	Percentage
OTUB₁ grade:		
Low	19	42.2
High	26	57.8
Total	45	100.0

Table (3): Relation between OTUB₁ expression and clinico-pathologic data.

	OTUB1				t^*	p-value
	Low		High			
	Mean	SD	Mean	SD		
Age	50.84	13.12	50.50	11.87	0.09	0.93

	OTUB1				x^2*	p-value
	Low		High			
	Count	Percentage	Count	Percentage		
Gender:						
Male	8	42.1	11	42.3	0.00	0.99
Female	11	57.9	15	57.7		

	OTUB1				x^2*	p-value
	Low		High			
	Count	Percentage	Count	Percentage		
Size:						
<5	13	68.4	16	61.5	0.23	0.63
>5	6	31.6	10	38.5		

	OTUB1				x^2*	p-value
	Low		High			
	Count	Per‑centage	Count	Per‑centage		
Site:						
Left sided	16	84.22	10	38.46	10.10	.002
Right sided	3	15.78	16	61.54		

	OTUB1				x^2*	p-value
	Low		High			
	Count	Percentage	Count	Percentage		
Grading:						
Low	18	94.7	8	30.8	18.41	<0.001
High	1	5.3	18	69.2		

	OTUB1		t^*	p-value
	Mean	SD		
Grading:				
Low	2.77	2.76	5.52	<0.001
High	7.21	2.53		

	OTUB1				x^2*	p-value
	Low		High			
	Count	%	Count	%		
Depth:						
T_1	2	10.5	0	0.0	5.15	0.03
T_2	5	26.3	3	11.5	Fisher	
T_3	10	52.6	16	61.5	exact	
T4	2	10.5	7	26.9		
Depth:						
T1/T2	7	36.8	3	11.5	4.07	0.04
T3/T4	12	63.2	23	88.5		

Table (3): Count.

	OTUB1				χ^2*	p-value
	Low		High			
	Count	%	Count	%		
LN:						
N0	8	42.1	6	23.1	2.55	0.49
N1	6	31.6	14	53.8		
N2	5	26.3	6	23.1		
LN:						
LN_0	8	42.1	6	23.1	1.86	0.17
LN1/LN2	11	57.9	20	76.9		

	OTUB1				χ^2*	p-value
	Low		High			
	Count	%	Count	%		
Metastasis:						
M_0	13	68.4	13	50.0	1.53	0.22
M_1	6	31.6	13	50.0		

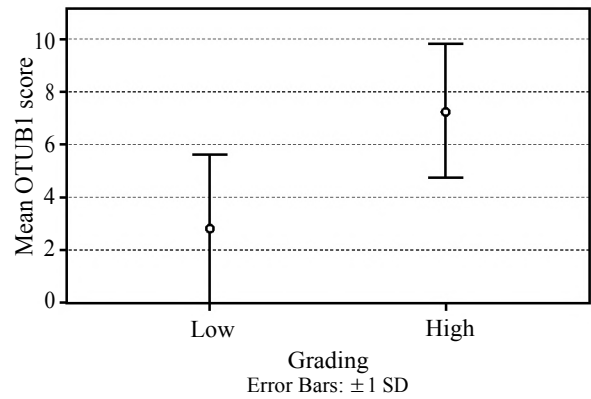|	OTUB1				χ^2*	p-value
	Low		High			
	Count	%	Count	%		
Stage:						
I	4	21.1	1	3.8	5.11	0.09
II	1	5.3	3	11.5	Fisher	
III	9	47.4	9	34.6	exact	
IV	5	26.3	13	50.0		
Stage:						
I or II	5	26.3	4	15.4	0.82	0.37
III or IV	14	73.7	22	84.6		

*: Student *t*-test.   *: Chi square test.
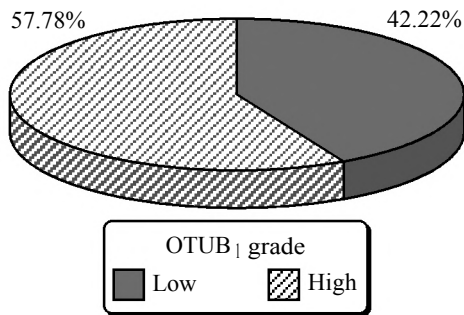
Graph (1): Distribution of OTUB₁ expression in the studied cases.
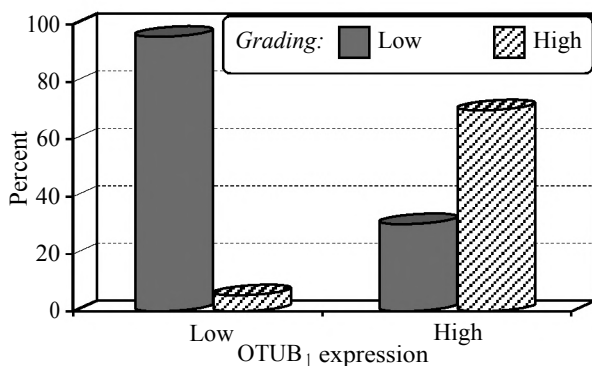
Graph (2): Immunohistochemical expression of OTUB₁ and histopathological grading of tumor.

Graph (3): Mean of OTUB1 score and histopathological grading ± 1 SD. Mean OTUB1 expression in low grade tumors was 2.77±1 SD while was 7.21 ±1 SD in high grade tumors.
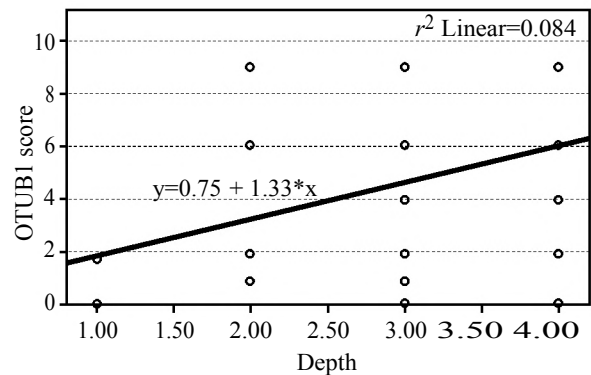

Diagonal segments are produced by ties
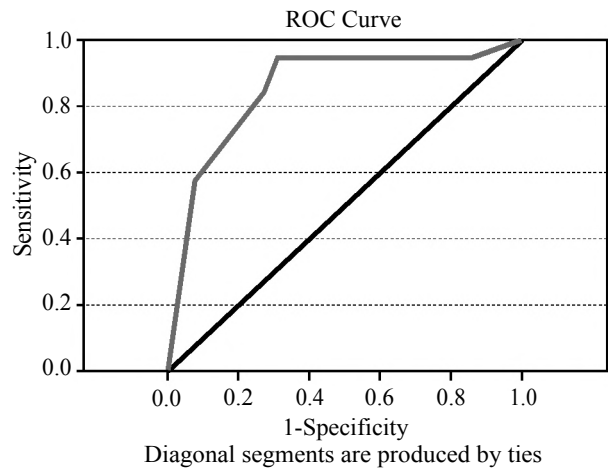
Area under the curve
Test result variable (s): OTUB₁ score

Area	Std. error	Sig.	95% confidence interval	
			Lower Bound	Upper Bound
0.853	0.062	<0.001	0.733	0.974

Graph (4): Validity of OTUB₁ expression in low and high grades of tumor.

Graph (5): Correlation between OTUB₁ expression and depth of tumor.

Discussion

OTUB $_1$ gene is located in human chromosome 11 q 13.1, and its protein has an OTU domain of 130 amino acids, which are highly conserved from yeast to mammals [13]. OTUB $_1$ has recently emerged as a unique atypical DUB that inhibits DNA repair without reflecting DUB activity per se [5].

A limited number of studies have provided conflicting results regarding the functions of OTUB $_1$ as OTUB $_1$ might have a tumor suppressor function by inducing p53 dependent apoptosis and inhibited cell growth [14]. However OTUB $_1$ also played crucial roles in transforming growth factor-β (TGF-β mediated) gene transcription and cellular migration by stabilizing SMAD 2/3 which drives cell invasion in somatic cells, suggesting that it might be involved in tumor migration [7].

In this study, higher expression level in CRC tissues was obviously noted compared to the non-neoplastic colonic mucosa. Thereby, OTUB $_1$ seems to play a role in tumor initiation: This is supported by [9] who reported a positive correlation between OTUB $_1$ and nuclear β-catenin expression which increases from early adenoma to carcinomas [15].

In this work, high OTUB $_1$ staining was detected in twenty six of CRC cases representing (57.8%), and low OTUB $_1$ expression was observed in nineteen of CRC patients constituting (42.2%). This is compatible with what was reported by Liu et al., who observed high OTUB $_1$ expression in (62%) of cases and low OTUB $_1$ expression in (38%) [4], and Ni et al., also reported that high OTUB $_1$ expression in (61%) of cases and low OTUB $_1$ expression in (39%) [16].

There was no significant relationship between the OTUB $_1$ expression and demographic data such as age and gender in our study. These results are compatible with Liu et al., Zhou et al., and Ni et al., [4,9,16].

No statistically significant correlation between OTUB $_1$ expression and size of CRC in our study. Our results were in accordance with that of Zhou et al., and Ni et al., in CRC and Hepatocellular Carcinoma (HCC), respectively [9,16].

In our study there was statistically significant correlation between right and left colon as higher OTUB $_1$ expression was observed in right sided of colon as compared to left sided. Zhou et al., [9] reported that there was no statistically significant

correlation between the site of CRC whether colonic or rectal carcinoma and the expression of OTUB $_1$.

The present study showed that OTUB $_1$ expression significantly correlated with tumor differentiation, indicating that OTUB $_1$ is an advert factor of prognosis. The frequency of OTUB $_1$ overexpression was 30.8% and 69.2%, respectively, in low grade and high grade cancer tissues. These results are in accordance with Liu et al., and Ni et al., who reported positive correlation of OTUB $_1$ expression and degree of differentiation in CRC and HCC, respectively [4,16].

On the contrary, Weng et al., reported that there was no significant correlation between OTUB $_1$ expression and degree of differentiation in invasive gastric carcinoma [17].

Our results revealed that the expression level of OTUB $_1$ was significantly associated with tumor invasive, as OTUB $_1$ overexpression in T_1/T_2 was 11.5% while in T_3/T_4 was 88.5%. Similar results were obtained by Zhou et al., Weng et al., and Baietti et al., who reported positive correlation between the OTUB $_1$ expression and depth in CRC, invasive gastric carcinoma and extension in lung carcinoma, respectively [9,10,17]. Consistent with these results, Liu et al., reported that the expression of USP22 (another DUBs member) was highly correlated with the depth in CRC [4].

In this study, OTUB $_1$ expression was not correlated with lymph node metastasis. On the contrary studies obtained by Liu et al., and Zhou et al., reported significant difference [4,9]. It may be attributed to the difference in the sample size between our study and these two previous studies.

Regarding distant metastasis, Zhou et al., and Ni et al., reported a positive correlation between OTUB $_1$ expression and distant metastasis in CRC and HCC, respectively [9,16]. Zhou et al., demonstrated that OTUB $_1$ could promote metastasis through inhibition or loss of E-cadherin in CRC cell lines [9].

On the other hand, no statistically significant association between OTUB $_1$ expression and distant metastasis in our work. This is compatible with Liu et al., Wang et al., and Weng et al., who also reported no significant correlation between OTUB $_1$ expression and distant metastasis in CRC, ovarian and gastric carcinoma, respectively [4,17,18]. Thus, we propose that although OTUB $_1$ might be involved in local tumor progression and dedifferentiation. It seems that it might not have a direct role in metastasis whether nodal or distant.

In this study no statistically significant association between OTUB1 expression and the TNM staging, this is compatible with Zhou et al., who found that OTUB1 expression was not associated with stage II, III CRC patients [9]. Karunarathna et al., also reported no significant association between OTUB₁ expression and breast cancer staging [19].

On the other hand, Weng et al., and Ni et al., reported significant association between OTUB₁ expression and staging in gastric carcinoma and HCC, respectively [16,17].

Such controversy highlights the need of further studies on larger scale to elucidate the relation OTUB₁ and each of nodal metastasis, distant metastasis and tumor stage. This, in turn, may help to determine whether or not OTUB₁ could serve as a biomarker of metastasis and consequently advanced stage.

In conclusion, the present study demonstrated that OTUB₁ is overexpressed in CRC, and its expression level is related with some clinico-pathologic parameters. The result indicated OTUB₁ may be responsible for the tumor development especially in the right sided CRC and invasion. High OTUB₁ expression in CRC cases especially with a score ≥6 could be useful in identification of biologically aggressive tumors in colonoscopic biopsies. OTUB₁ could be an attractive target for the development of new strategies in the diagnosis and treatment of CRC in order to reduce local invasiveness pre-operatively.

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الظهور الهيستولوجى الكيميائى المناعى للإنزيم المسئول عن إزاله وإعادة تدوير جزيئات اليوبيوكويتين OTUB$_1$ فى حالات سرطان القولون والمستقيم

يعتبر سرطان القولون من آكثر الآورام السرطانية شيوعا ليمثل آكثر من ٩٪ من جميع حالات السرطان، وترتفع معدلات الإصابة بين الذكور عن الإناث وتقوم العوامل الوراثية والبيئية بالآليه المرضيه لسرطان القولون حيث آن ٢٠٪ من الحالات لهم تاريخ مرضى فى العائلة مع مشاركة بعض إنزيم يعمل على OTUB$_1$. المتلازمات الوراثية مثل متلازمة جاردنر كذلك النظام الغذائى ونمط الحياة إزالة وتحول اليوبيكويتين هو يظهر بصورة حرة بالآنسجة البشرية، وتهدف هذه الدراسة إلى دراسة الظهور الهيستولوجى المناعى للإنزيم فى الحالات المصابة بسرطان القولون حيث تمت دراسة الإنزيم على ٤٥ عينة من الآنسجة المصابة بسرطان القولون و١٠ عينات من الآنسجة غير مصابة بالسرطان كمجموعة ضابطة للدراسة وآتى ظهور الإنزيم بالآنسجة السرطانية متأثرا بعمق توغل الخلايا السرطانية ومكان الورم والدرجة الهيستولوجية للورم ليكون للإنزيم دور محتمل فى التعرف على عدائية النسيج السرطانى وإختيار نظام العلاج للحالات المصابة.