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Original Research Article

Immunohistochemical Expression of SATB2 and Clinicopathological Correlation in Colorectal Adenocarcinoma

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Abstract

Special AT-rich sequence-binding protein 2(SATB2) is a peculiar marker in the diagnosis of colorectal carcinoma (CRC), SATB2 has been employed as a colorectal differentiation marker with the potential to be useful in distinguishing the origin of adenocarcinomas of unknown primary origin. Also SATB2 inhibit colorectal cancer progression and low expression of SATB2 protein has been associated with low survival outcome. The aim of the study was to assess the SATB2 immunohistochemical expression in CRC, and association with several clinicopathological characteristics. Immunohistochemical staining for SATB2 was done on 70 cases of colorectal adenocarcinoma that underwent colectomy. Their expressions were analysed as negative, intermediate and strong then correlated to clinico-pathological parameters in an attempt to obtain the most significant predictors of SATB2. SATB2 score was negative in 30 %of the cases, intermediate in 54.3% and strong in 15.7%. Strong SATB2 expression was significantly associated with a low tumor histological grade (P = 0.007), a low tumor invasiveness stage (P = 0.001), the absence of lymph node metastasis (P = 0.001), the absence of detected distant metastasis (P = 0.039), a low TNM stage (P = 0.001), a low modified Dukes stage (P = 0.001), the absence of lympho-vascular invasion (P value 0.001) and the absence of perineural invasion (P = 0.001).A High rate of SATB2 expression was associated with left colon tumors and adenocarcinoma histological type, but without a statistically significant correlation. In the cases analyzed, there was no significant association between SATB2 expression and age, sex, or tumor size. Strong SATB2 expression is associated with the accepted clinicopathological parameters favoring good prognosis in the colorectal cancer and may represent a potential therapeutic target.

Keywords: Colorectal carcinoma, Immunohistochemistry, SATB2.

INTRODUCTION

Colorectal cancer (CRC) represents the third as regard the incidence rate and the second one regarding the cause of cancer death in both sexes Worldwide (Bray et al., 2018). Developed countries have experienced the highest rate of CRC (Keum, 2017). However in Egypt, CRC represent the 7th most common cancer in both sexes (Metwally et al., 2018). CRC is a complex and heterogeneous disease that results from a complex

interaction of numerous predisposing factors, such as genetic factors and environmental variables including nutrition and lifestyle (Ioannou et al., 2015). In CRC, the Tumor-Nodes-Metastasis (T.N.M.) classification is the most accurate predictor of prognosis. TNM stage, on the other hand, is not a perfect technique because patients with the same disease stage can have quite varied clinical outcomes (Kwon et al., 2010). A full understanding of the underlying molecular pathways of CRC progression is essential to discover biomarkers and therapeutic targets for the diagnosis, prognosis, and treatment of CRC (Dowling et al., 2017).

Special AT-rich sequence binding protein (SATB2) is an epigenetic regulator and nuclear matrix-associated transcription factor (Gyorgy et al. 2008).It was discovered to be highly expressed in the epithelium of the lower gastrointestinal tract (including the appendix, colon, and rectum) as well as neoplastic epithelial cells of colorectal origin using tissue microarrays (Magnusson et al., 2011).SATB2 has been identified as a colorectal differentiation marker with potential applications in distinguishing primary ovarian mucinous adenocarcinomas from colorectal metastases and determining the primary origin of adenocarcinomas of unknown primary origin(Berg and Schaeffer 2017). SATB2 is disorganized in many cancers; SATB2 acts as a tumor suppressor gene in several tumors like clear cell renal cell carcinoma, laryngeal carcinoma, esophageal squamous cell carcinoma, gastric cancer, (Chung et al. 2010; T. R. Liu et al. 2012; Geng et al., 2015; Wu et al., 2016; Guo et al., 2015).

SATB2 inhibits colorectal cancer growth by inactivating mitogen/extracellular signal-regulated kinase 5 (MEK5)/extracellularly signal-regulated kinases (ERK5) signaling. It also inhibits the expression of c-MYC in CRC cells (Mansour et al., 2015, 2016). STAB2 prevents the epithelial mesenchymal transition (EMT) by enhancing E-cadherin expression, and lowering expression of both vimentin and N-cadherin in CRC cell lines (Gu et al., 2018). In CRC tissues, SATB2 levels were considerably lower than in healthy controls. As a result, it's possible that SATB2 has a tumor-suppressing role in CRC. Many studies have found that high SATB2 expression is an independent predictor of a better prognosis in colon cancer patients. Poor prognosis was more common in SATB2-negative colonic adenocarcinomas. SATB2-negative expression was also shown to be more commonly in tumors that had a mucinous or signet ring cell differentiation (Wang et al., 2009; Brocato and Costa, 2014; Eberhard et al., 2012; Ma Olevian et al., 2019). Moreover, it has been revealed that patients with metastatic CRC expressing high level of SATB2 have a better prognosis and treatment response than those with a low SATB2 expression (Mezheyeuski et al., 2020). So it is useful to assess SATB2 immunohistochemical expression in CRC, and association with several clinicopathological characteristics.

MATERIALS AND METHODS

Retrieval of Cases

70 formalin fixed, paraffin embedded tumor sections from colectomy specimens of patients with colorectal adenocarcinoma from Kasr El Ainy Hospital, Faculty of Medicine, Cairo University and multiple private laboratories, in the time period from December, 2019 till March, 2020. The specimens were anonymous for confidentiality and replaced by numbers.

Inclusion criteria included; radical colectomy specimens of adenocarcinoma NOS (not otherwise specified) histological subtype with available clinical data and accessible tissue blocks. Exclusion criteria included colonoscopy biopsies, in which the stage cannot be assessed, and cases received preoperative chemo-therapy or radiotherapy.

While the pathological tumor size of 5 cm is an independent predictive factor for local recurrence in rectal adenocarcinoma. The size of the tumor was calculated as the length of the longest dimension with a cut off value of 5 cm (Chen et al. 2017). The data in the final pathology reports were used to determine the tumor extension into the colonic wall and the lymph node status.

Histopathological Examination

Each paraffin block was re-cut by a rotatory microtome at 4 µm thickness then mounted on glass slides and stained by hematoxylin and eosin (H&E) for routine histopa-thological examination and mounted on charged slides for immunostaining.

SATB2 Immunohistochemical Staining and Evaluation

The serial sections that were prepared from the paraffin blocks and mounted on charged slides were submitted for immunostaining against SATB2. Antigen retrieval was performed with (Ventana) Cell *Conditioning* Solution (CC1) at PH 9. Sections were stained with anti- SATB2 antibody (Rabbit Monoclonal Primary Antibody; clone EP 281, obtained from Cell Marque Corporation, Rocklin, California (USA)). Immunohistochemical staining was performed in an automated staining instrument (Ventana, Bench Mark ULTRA). The antibody was detected using a (Ventana) ultra-View Universal DAB Detection Kit, and hematoxylin was used as a counterstain.

All procedures performed in the current study were approved by Helwan Research Ethics Committee (June 2019) in accordance with the 1964 Helsinki declaration and its later amendments.

Table 1. Pathological characteristics of the studied cases

Pathological characteristics		Number (%)
Age group	<60ys	33(47.1%)
	≥60ys	37 (52.9%)
Size group	<5cm	18 (25.7%)
	≥5cm	52 (74.3%)
Sex	Female	37 (52.9%)
	Male	33 (47.1%)
Tumor Site	Right	26 (37.1%)
	Left	44 (62.9%)
Tumor histological type	Adenocarcinoma	53 (75.7 %)
	Mucoid carcinoma	17 (24.3 %)
Histopathological grade	Low grade	43 (61.4%)
	High grade	27 (38.6%)
Extent of primary tumor (T)	T1	0 (0%)
	T2	4 (5.7%)
	T3	26 (37.1%)
	T4	40 (57.1%)
Lymph node Status (N)	N0	28 (40.0%)
	N1	19 (27.1%)
	N2	23 (32.9%)
Prescence of detected distant metastasis (M)	Not detected	61 (87.1%)
	Present	9 (12.9%)
Lympho-vascular invasion	Absent	28 (40.0%)
	Present	42 (60%)
Perineural invasion	Absent	56 (80.0%)
	Present	14 (20.0%)
TNM Stage Group	I	4 (5.7%)
	II	23 (32.8%)
	III	34 (48.6%)
	IV	9 (12.9)
Modified Duke's stage	B1	4 (5.7%)
	B2	23 (32.8%)
	C2	34 (48.6%)
	D	9 (12.9%)

Statistical Analysis

Data were coded and entered using the IBM SPSS Statistics version 20. (Armonk, NY: IBM Corp) (Kirkpatrick and Brooke 2015). Qualitative data were described using number and percent. Quantitative data were described using range (minimum and maximum), mean, standard deviation, median and IQR (interquartile range). Significance of the obtained results was judged at the 5% level.

The used tests were; Chi-square test for categorical variables, to compare between different groups. Monte Carlo test for Correction for chi-square when more than 20% of the cells have expected count less than 5. F-test (ANOVA) for normally distributed quantitative variables, to compare between more than two groups. Kruskal Wallis test for abnormally distributed quantitative variables, to compare between more than two studied groups.

RESULTS

This study included 70 cases of CRC. The mean age in this study was 58.89 years (22-83 years). 47.1 % of the cases were < 60 years and 52.9% were ≥ 60 years. There was slight female predominance (52.9%). 62.9% of the cases were left sided and 37.1% were right sided. The median tumor size in this study was 6.10 cm. 25.7% of the cases are < 5 cm and 74.3% are ≥5 cm. The most common histological type in the present study was adenocarcinoma (75.7%), while mucoid carcinoma was only 24.3%. According to the grade of differentiation, 61.4% of the cases were low grade and 38.6% were high grade. Most of the cases were T4 representing (57.1%). Most of the cases were N0 representing (40%).Only 12.9% of the cases showed detected distant metastasis. Stage grouping of TNM was applied, where stage III was the most common (48.6%). According to modified Dukes'

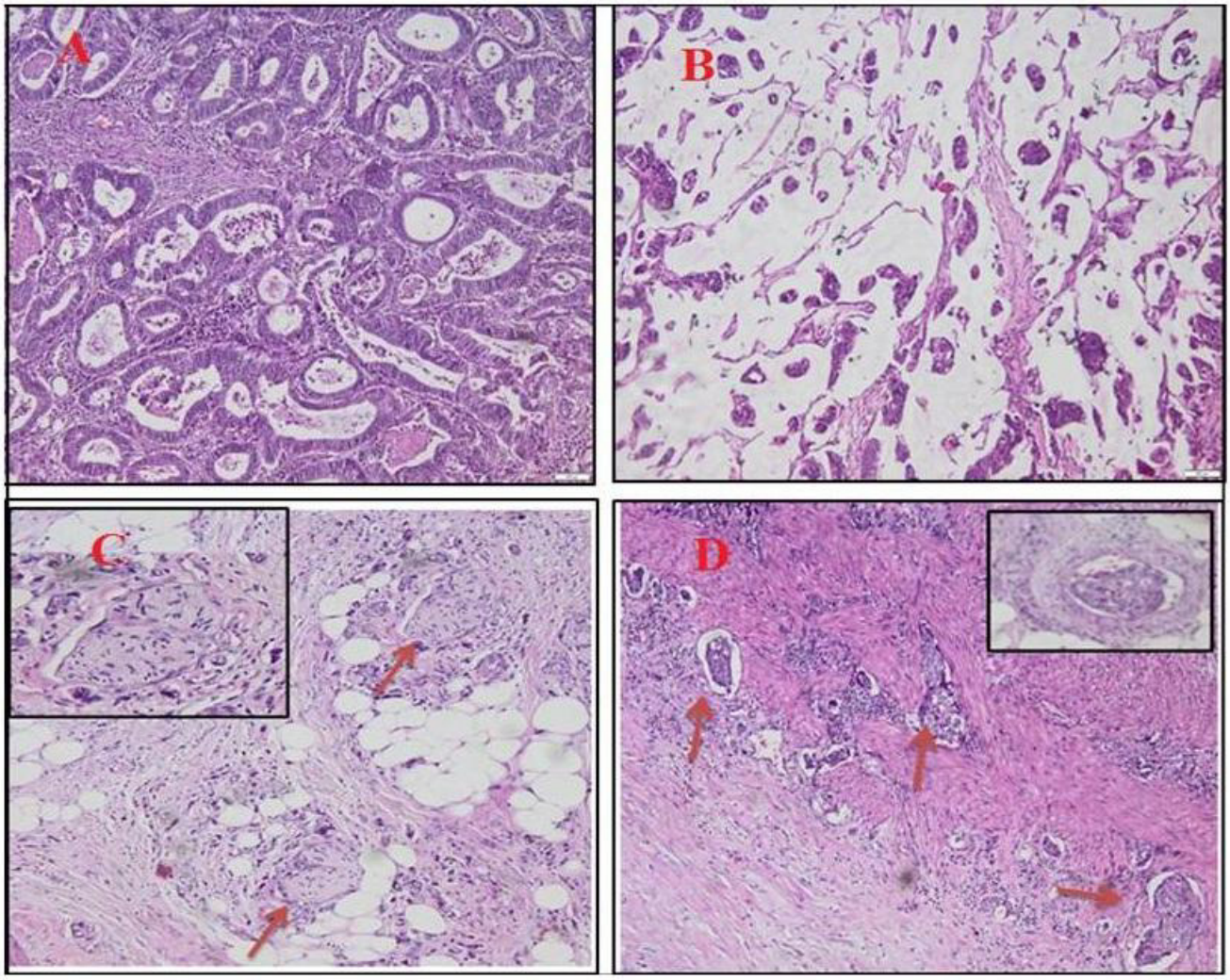

Figure 1. (A): A photograph of a low grade adenocarcinoma formed of variable sized and irregular shaped glands lined by malignant epithelial cells showing low grade anaplasia surrounded by moderate desmoplastic stromal reaction (H&E X100 original magnification). **(B):** A photograph of a mucinous adenocarcinoma formed of malignant glands with extracellular mucin lakes (H&E X 100). **(C):** A photograph of an invasive adenocarcinoma with perineural invasion by malignant glands (arrows) (H&E X 100), The inset demonstrates perineural invasion by malignant glands (H&E X 200). **(D):** A photograph of an invasive adenocarcinoma with multiple lympho-vascular emboli (arrows) (H&E X 100). The inset demonstrates lympho-vascular emboli (H&E X 200).

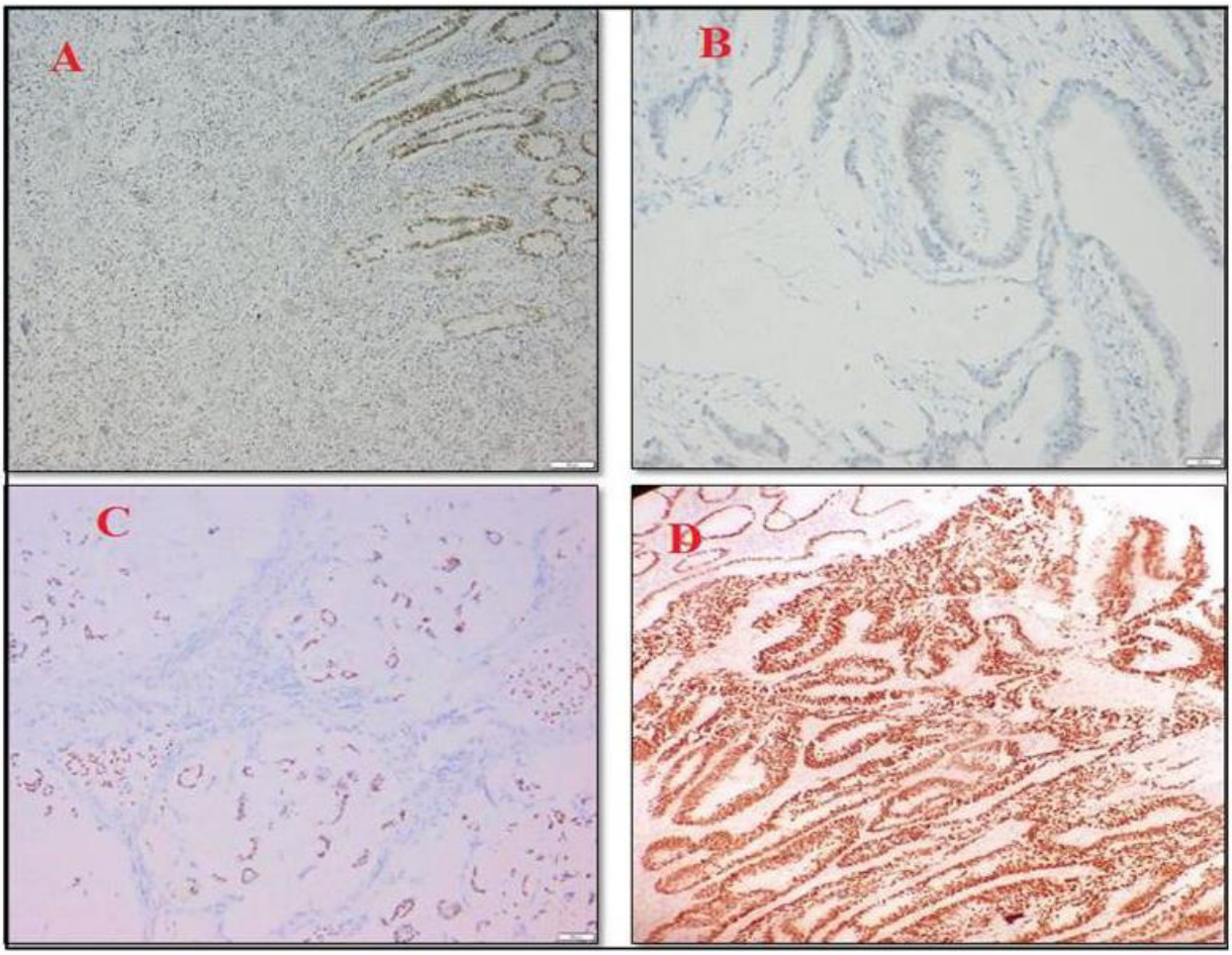

Figure 2. SATB2 IHC Expression (A): A photograph of a high grade adenocarcinoma showing absent SATB2 expression with positive internal control staining of normal colorectal mucosa (X100).**(B):** A photograph of a low grade adenocarcinoma with a weak positive nuclear SATB2 staining (X 200). **(C):**A photograph of a mucinous adenocarcinoma with a moderate positive nuclear SATB2 staining(X 100). **(D):** Low grade adenocarcinoma with a strong positive nuclear SATB2 expression compared with a positive internal control staining of a normal colorectal mucosa (X 100).

Table 2. Correlation of SATB2 expression with various pathological characteristics among the studied case

		Negative	Intermediate	Strong	P value
Age	**<60**	11(52.4%)	16 (42.1%)	6 (54.5%)	0.650
	≥60	10(47.6%)	22 (57.9%)	5 (45.5%)	
Size	**<5**	4 (19.0%)	12 (31.6%)	2 (18.2%)	0.472
	≥5	17(81.0%)	26 (68.4%)	9 (81.8%)	
Sex	Male	10(47.6%)	16 (42.1%)	7 (63.6%)	0.452
	Female	11(52.4%)	22 (57.9%)	4 (36.4%)	
Site	Right	9 (42.9%)	14 (36.8%)	3 (27.3%)	0.686
	Left	12(57.1%)	24 (63.2%)	8 (72.7%)	
Histological grade	Low grade	9 (42.9%)	23 (60.5%)	11(100%)	0.007*
	High grade	12(57.1%)	15 (39.5%)	0 (0.0%)	
Histological type	Adenocarcinoma	13(61.9%)	29 (76.3%)	11(100%)	0.057
	Mucoid carcinoma	8 (38.1%)	9 (23.7%)	0 (0%)	
Extent of primary tumor (T)	T2	0 (0.0%)	2 (5.3%)	2 (18.2%)	<0.001*
	T3	3 (14.3%)	15 (39.5%)	8 (72.7%)	
	T4	18 (85.7%)	21 (55.3%)	1 (9.1%)	
Lymph node status (N)	N0	3 (14.3%)	14 (36.8%)	11 (100%)	<0.001*
	N1	7 (33.3%)	12 (31.6%)	0 (0%)	
	N2	11(52.4%)	12 (31.6%)	0 (0%)	
Prescence of detected distant metastasis (M)	Not detected	15 (71.4%)	35 (92.1%)	11(100%)	0.039*
	Present	6 (28.6%)	3 (7.9%)	0 (0%)	
Lympho-vascular Invasion	Absent	2 (9.5%)	15 (39.5%)	11 (100%)	<0.001*
	Present	19 (90.5%)	23 (60.5%)	0 (0%)	
Perineural Invasion	Absent	11(52.4%)	34 (89.5%)	11 (100%)	=0.001*
	Present	10 (47.6%)	4 (10.5%)	0 (0%)	
Stage group	I	0 (0%)	2 (5.3%)	2 (18.2%)	<0.001*
	II	4 (19.0%)	10 (26.3%)	9 (81.8%)	
	III	11(52.4%)	23 (60.5%)	0 (0%)	
	IV	6 (28.6%)	3 (7.9%)	0 (0%)	
Modified Duke's	B1	0 (0%)	2 (5.3%)	2 (18.2%)	<0.00*
	B2	4 (19.0%)	10 (26.3%)	9 (81.8%)	
	C2	11(52.4%)	23 (26.3%)	0 (0%)	
	D	6 (28.6%)	3 (7.9%)	0 (0%)	

*Significance < 0.05

classification, group C2 accounted for the highest percentage (48.6%) (Table (1), Figure 1(A, B)) Perineural invasion and Lympho-vascular invasion were detected in 20% and 60% of the cases respectively. Regarding SATB2 expression, it was negative score in 21 cases (30%) (Figure 2 A), intermediate score in 38 cases (54.3%) (Figures 2(B, C)), and strong score in 11 cases (15.7%) (Figure 2 D).

A strong SATB2 expression showed a statistically significant correlation with a low tumor histological grade (P-value = 0.007), a low tumor invasiveness stage (P-value <0.001), an absence of lymph node metastasis (P-value <0.001), an absence of detected distant metastasis (P-value = 0.039), a low overall pathologic stage group (P-value <0.001), a low modified Dukes' stage (P-value < 0.001), an absence of lymphovascular invasion (P-value <0.001) and an absence of perineural invasion (P-value = 0.001). A higher rate of SATB2 expression was noticed with left colon tumors and adenocarcinoma histological type, but yet with no statistically significant correlation. Correlation of SATB2 expression with various pathological characteristics among the studied cases is summarized in Table (2).

DISCUSSION

Worldwide, CRC is one of the most common mortalities in cancer of both sexes (Bray et al., 2018). This could be elucidated by the late diagnosis of CRC and so the prognosis of patients with CRC remains poor (Ballester, Rashtak, and Boardman 2016; Vermeer et al., 2017).

The most important prognostic factor in CRC is the tumor stage upon diagnosis. However, it is not a completely adequate method because patients with disease at the same stage may have different clinical outcomes. As a result, many efforts have been made to find molecular markers and therapeutic targets for the diagnosis, prognosis and treatment of CRC and to identify patients with high-risk disease (Dowling et al.,

2017; Eberhard et al., 2012).

SATB2 is a DNA-binding protein, and is involved in regulation of transcription and chromatin remodeling. SATB2 protein is specifically expressed in the nuclei of epithelial cells in the lower GI tract. Also SATB2 is expressed in a subset of lymphoid cells, germ cells in the testis, and certain neurons in the central nervous system (Magnusson et al., 2011).

It has been revealed that SATB2 is a highly sensitive and a specific immunohistochemical marker to confirm or rule out tumors of colorectal origin (Dragomir et al., 2014). Moreover, it was found that downregulated expression of SATB2 is associated with metastasis and poor prognosis both in an animal model of CRC and in a prospective patient cohort(S. Wang et al., 2009; Eberhard et al., 2012). The tumor suppressive role of SATB2 could be due to many factors. These factors include inactivation of c-Myc and MEK5/ERK5 signaling (Mansour et al., 2015, 2016). Also, SATB2 suppresses the EMT by increasing E-cadherin expression, whereas decreasing expression of both vimentin and N-cadherin. SATB2 may serve as molecular targets in CRC treatment to suppress the metastasis and weaken the EMT (Y. Q. Wang et al., 2019; Kara et al., 2015; Gu et al., 2018).

In the present study, the score of SATB2 positivity didn't reveal a statistically significant association with the mean age of the cases (p value = 0.691). Similarly, Ma, Olevian et al., 2019. and Mezheyeuski et al., 2020 studies reported an insignificant correlation with the mean age (P value = 0.5 and 0.146 respectively) (Ma, Olevian, et al., 2019; Mezheyeuski et al., 2020). Also there was a statistically insignificant relation between SATB2 expression and the age group (p value = 0.650). Similarly, Liu et al. 2019 and Yang et al. 2018 studies reported an insignificant correlation with the age group (P-value = 0.397 and 0.275 respectively) (Yang et al., 2018; Liu et al., 2019).

The sex of the cases of this study was not significantly correlated with SATB2 expression (p value = 0.452) which was in an agreement with that was reported in Mezheyeuski et al. 2020, Yang et al. 2018, and Ma Henn et al., 2019 studies.(p value = 0.317, 0.1 and 0.414 respectively) (Yang et al., 2018; Ma, Henn et al., 2019; Mezheyeuski et al., 2020).

The relation between the tumor size and SATB2 expression was statistically insignificant (p value = 0.472) (Liu et al., 2019). This was in line with the findings of Liu et al. (2019) study (p value = 0.397) while Yang et al. (2018) study showed a statistically significant relation between SATB2 expression and tumour size (p value = 0.028) (Yang et al., 2018).

The site of the primary tumor was not significantly correlated with SATB2 expression (p value = 0.686). However, this study showed a high rate of SATB2 expression in the left colon tumors, but did not reach the level of statistical significance. This result yet with statistically significant difference was reported by Ma, et al., 2019. And Mezheyeuski et al., 2020 studies (p value =0.01 and < 0.001 respectively) (Mezheyeuski et al., 2020; Ma, Olevian, et al., 2019). Another study showed no significant relation (p value = 0.804) (Liu et al., 2019).

The current study cases showed a negative, an intermediate and a high SATB2 scores (30.0%, 54.3% and 15.7% respectively). These approximate the results of Eberhard et al., 2012 study but with different percentages; 28.8% of the cases were negative, 49.1% were intermediate and 22% were strong (Eberhard et al., 2012).

In the present study, there were statistically significant correlations between strong SATB2 expression and some of the clinicopathological parameters; a low tumor histological grade, a low tumor invasiveness (T), an absence of lymph node metastasis (N), an absence of detected distant metastasis (M), a low TNM pathologic stage, a low modified Dukes' classification, and absence of lympho-vascular invasion and a perineural invasion, while there were statistically insignificant correlations between SATB2 expression with age, sex, tumor size, primary site of the tumor and tumor histological type.

These results were in an agreement with previous studies (Ma, Olevian et al., 2019; Eberhard et al., 2012; S. Wang et al., 2009; F. Liu et al., 2019; Mezheyeuski et al., 2020; Ma, Henn et al., 2019).

There was a high rate of SATB2 expression in the adenocarcinoma histological type. However, it wasn't statistically significant in the current study (P value = 0.057). This result could be attributed to the predominance of adenocarcinoma variant 75% of the cases and the study had 2 variants only. Similarly, Gu et al. (2018) study showed an insignificant relation (p value = 0.244) (Gu et al., 2018).

The low tumor histological grade was statistically significantly correlated with strong SATB2 expression in the current study (P value = 0.007), which was in agreement with results of Ma, D. Olevian et al., 2019. And Mezheyeuski et al., 2020 studies (P value <0.001 in both) (Ma, Olevian et al., 2019; Mezheyeuski et al., 2020) and Liu et al., 2019 study (p value = 0.002) (Liu et al., 2019). Furthermore the strong SATB2 expression was statistically significant with absence of lymphovascular invasion (P value <0.001), and absence of perineural invasion (P value = 0.001). These results were consistent with the results of Eberhard et al., 2012 and Ma, Olevian et al., 2019 studies (Eberhard et al., 2012; Ma, Olevian et al., 2019).

The strong SATB2 expression was statistically significant with a low T stage (P value <0.001), an absence of lymph node metastasis (P value <0.001), and an absence of detected distant metastasis (P value = 0.039). These results were consistent with the results of Eberhard et al., 2012 and Yang et al., 2018 studies (Eberhard et al., 2012; Yang et al., 2018).

Regarding AJCC staging system, the present study showed that the strong SATB2 expression was

statistically significant with the low tumor stage (P value <0.001), which is in agreement with previous studies. This result confirms the fact that SATB2 could play a tumor-suppressing role in CRC and considered as a strong independent factor of good prognosis (Brocato and Costa 2014; Wang et al., 2009; Ma, Olevian et al., 2019; Eberhard et al., 2012; Yang et al., 2018). Similarly, strong SATB2 expression was significantly association with low modified dukes stage (P value <0.001), which is in agreement with the results of Wang et al. 2009 study (p value =0.025) (Wang et al., 2009).

Despite the fact that the current study and comparable ones, reported more or less close figures of SATB2 expression positivity. However, different sample sizes, variable grades and pathologic stages enrolled in these studies might explain the contradictory results regarding correlations between SATB2 expressions in the colorectal adenocarcinoma with the other clinico-pathological parameters.

CONCLUSION

SATB2 negative tumors more often displayed adverse histologic features including mucinous adenocarcinoma (0% strong SATB2 score), high tumor grade (0% strong SATB2 score), high tumor invasiveness (T4) (9.1% strong SATB2 score), high lymph node stage (N2) (0% strong SATB2 score), presence of detected distant metastasis (M) (0% strong SATB2 score), high TNM pathologic stage; stage IV (0% strong SATB2 score), high modified Dukes' classification stage; stage D(0% strong SATB2 score) and presence of lymphovascular invasion (0% strong SATB2 score) and presence of perineural invasion (0% strong SATB2 score). This suggests considering high rate of SATB2 expression is associated with known favorable clinicopathological parameters in colorectal adenocarcinoma.

Authors Contribution

1. Conceptualization: SAE, DFM, NAS
2. Data curation: SAE
3. Formal analysis: NAS
4. Funding acquisition: SAE
5. Investigation: SAE, DFM
6. Methodology: SAE
7. Project administration: SAE
8. Resources: SAE
9. Software: NAS
10. Supervision: NAS, DFM, MMS
11. Validation: NAS,MMS
12. Visualization: DFM,NAS
13. Writing – original draft: SAE
14. Writing – review & editing: NAS, DFM
15. Approval of final manuscript: all authors

CONCLUSION

Strong SATB2 expression is associated with known favorable clinicopathological parameters in colorectal cancer and may represent a potential therapeutic target.

Conflict of Interest

The authors declare no conflict of interest.

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REFERENCES

Ballester, Veroushka, Shahrooz Rashtak, and Lisa Boardman (2016). "Clinical and Molecular Features of Young-Onset Colorectal Cancer." World J. Gastroenterol. 22 (5): 1736–44. https://doi.org/10.3748/wjg.v22.i5.1736.

Berg Kyra B, David FS (2017). "SATB2 as an Immunohistochemical Marker for Colorectal Adenocarcinoma a Concise Review of Benefits and Pitfalls." Archives of Pathology and Laboratory Medicine 141 (10): 1428–33. https://doi.org/10.5858/arpa.2016-0243-RS.

Bray, Freddie, Jacques Ferlay, Isabelle Soerjomataram, Rebecca L. Siegel, Lindsey A. Torre, and Ahmedin Jemal. (2018). "Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries." CA: A Cancer J. Clinic. 68 (6): 394–424. https://doi.org/10.3322/caac.21492.

Brocato J, Max C (2014). "SATB1 and 2 in Colorectal Cancer." Carcinogenesis 36 (2): 186–91. https://doi.org/10.1093/carcin/bgu322.

Chen, Chien Hsin, Mao Chih Hsieh, Ping Kun Hsiao, En Kwang Lin, Yen Jung Lu, and Szu Yuan Wu. 2017. "A Critical Reappraisal for the Value of Tumor Size as a Prognostic Variable in Rectal Adenocarcinoma." J. Cancer 8 (10): 1927–34. https://doi.org/10.7150/JCA.17930.

Chung, Jacky, Joanne Lau, Lynn S. Cheng, R. Ian Grant, Fiona Robinson, Troy Ketela, Patricia P. Reis, et al. 2010. "SATB2 Augments Δnp63α in Head and Neck Squamous Cell Carcinoma." EMBO Reports 11 (10): 777–83. https://doi.org/10.1038/embor.2010.125.

Dowling, Catríona M., Sheri L. Hayes, James J. Phelan, Mary Clare Cathcart, Stephen P. Finn, Brian Mehigan, Paul McCormick, John C. Coffey, Jacintha O'Sullivan, and Patrick A. Kiely. 2017. "Expression of Protein Kinase C Gamma Promotes Cell Migration

in Colon Cancer." Oncotarget 8 (42): 72096–107. https://doi.org/10.18632/oncotarget.18916.

Dragomir, Anca, Meike De Wit, Christine Johansson, Mathias Uhlen, and Fredrik Ponteń. 2014. "The Role of SATB2 as a Diagnostic Marker for Tumors of Colorectal Origin: Results of a Pathology-Based Clinical Prospective Study." American Journal of Clinical Pathology 141 (5): 630–38. https://doi.org/10.1309/AJCPWW2URZ9JKQJU.

Eberhard, J., A. Gaber, S. Wangefjord, B. Nodin, M. Uhlén, K. Ericson Lindquist, and K. Jirström. 2012. "A Cohort Study of the Prognostic and Treatment Predictive Value of SATB2 Expression in Colorectal Cancer." British Journal of Cancer 106 (5): 931–38. https://doi.org/10.1038/bjc.2012.34.

Geng, Guo Jun, Ning Li, Yan Jun Mi, Xiu Yi Yu, Xian Yang Luo, Jing Gao, Qi Cong Luo, Jing Dun Xie, Xian En Fa, and Jie Jiang. 2015. "Prognostic Value of SATB2 Expression in Patients with Esophageal Squamous Cell Carcinoma." International Journal of Clinical and Experimental Pathology 8 (1): 423–31. /pmc/articles/PMC4348808/.

Gu, Jingfeng, Guiqi Wang, Haixia Liu, and Chaohui Xiong. 2018. "SATB2 Targeted by Methylated MiR-34c-5p Suppresses Proliferation and Metastasis Attenuating the Epithelial-Mesenchymal Transition in Colorectal Cancer." Cell Proliferation 51 (4). https://doi.org/10.1111/cpr.12455.

Guo, Changcheng, Dabo Xiong, Xudong Yao, Wenyu Gu, Haimin Zhang, Bin Yang, Bo Peng, Min Liu, and Junhua Zheng. 2015. "Decreased SATB2 Expression Is Associated with Metastasis and Poor Prognosis in Human Clear Cell Renal Cell Carcinoma." Int. J. Clin. Experimental Pathol. 8 (4): 3710–18. /pmc/articles/PMC4466939/.

Gyorgy, Andrea B., Marianna Szemes, Camino De Juan Romero, Victor Tarabykin, and Denes V. Agoston. 2008. "SATB2 Interacts with Chromatin-Remodeling Molecules in Differentiating Cortical Neurons." European Journal of Neuroscience 27 (4): 865–73. https://doi.org/10.1111/j.1460-9568.2008.06061.x.

Ioannou, Maria, Efrosyni Paraskeva, Korina Baxevanidou, George Simos, Roidoula Papamichali, Constantina Papacharalambous, Maria Samara, and George Koukoulis. 2015. "HIF-1α in Colorectal Carcinoma: Review of the Literature." J. B.U.ON. 2015. https://pubmed.ncbi.nlm.nih.gov/26214618/.

Kara, Murat, Onder Yumrutas, Onder Ozcan, Ozgur Ilhan Celik, Esra Bozgeyik, Ibrahim Bozgeyik, and Sener Tasdemir. 2015. "Differential Expressions of Cancer-Associated Genes and Their Regulatory MiRNAs in Colorectal Carcinoma." Gene 567 (1): 81–86. https://doi.org/10.1016/j.gene.2015.04.065.

Keum N, Giovannucci EL. 2017. Epidemiology of Colorectal Cancer. In: Pathology and Epidemiology of Cancer. Springer.

Kirkpatrick, Lee A., and C. Feeney Brooke. 2015. A Simple Guide to IBM SPSS Statistics. Cengage Learning. https://www.worldcat.org/title/simple-guide-to-ibm-spss-statistics-for-version-200/oclc/793220809.

Kwon, Hyuk Chan, Sung Hyun Kim, Sung Yong Oh, Suee Lee, Kyung A. Kwon, Hong Jo Choi, Ki Jae Park, Hyo Jin Kim, and Mee Sook Roh. 2010. "Clinicopathological Significance of P53, Hypoxia-Inducible Factor 1α, and Vascular Endothelial Growth Factor Expression in Colorectal Cancer." Anticancer Research 30 (10): 4163–68. https://doi.org/10.1200/jco.2010.28.15_suppl.3609.

Liu, Fangfang, Zhidong Gao, Danhua Shen, Haiou Zhao, Chao Wang, Yingjiang Ye, Yingteng Ma, and Fangzhou Kong. 2019. "Significance of SATB2 Expression in Colon Cancer and Its Differential Diagnosis in Digestive Tract Adenocarcinoma and Ovarian Primary and Metastatic Carcinoma." Pathology Research and Practice 215 (7): 152430. https://doi.org/10.1016/j.prp.2019.04.022.

Liu, Tian Run, Li Hua Xu, An Kui Yang, Qian Zhong, Ming Song, Man Zhi Li, Li Juan Hu, et al. 2012. "Decreased Expression of SATB2: A Novel Independent Prognostic Marker of Worse Outcome in Laryngeal Carcinoma Patients." PLoS ONE 7 (7). https://doi.org/10.1371/journal.pone.0040704.

Ma, Changqing, Patrick Henn, Caitlyn Miller, Cameron Herbst, Douglas J. Hartman, and Reetesh K. Pai. 2019. "Loss of SATB2 Expression Is a Biomarker of Inflammatory Bowel Disease-Associated Colorectal Dysplasia and Adenocarcinoma." Ame. J. Surg. Pathol. 43 (10): 1314–22. https://doi.org/10.1097/PAS.0000000000001330.

Ma, Changqing, Dane Olevian, Caitlyn Miller, Cameron Herbst, Priya Jayachandran, Margaret M. Kozak, Daniel T. Chang, and Reetesh K. Pai. 2019. "SATB2 and CDX2 Are Prognostic Biomarkers in DNA Mismatch Repair Protein Deficient Colon Cancer." Modern Pathology 32 (8): 1217–31. https://doi.org/10.1038/s41379-019-0265-1.

Magnusson, Kristina, Meike De Wit, Donal J. Brennan, Louis B. Johnson, Sharon F. McGee, Emma Lundberg, Kirsha Naicker, et al. 2011. "SATB2 in Combination with Cytokeratin 20 Identifies over 95% of All Colorectal Carcinomas." Ame. J. Surg. Pathol. 35 (7): 937–48. https://doi.org/10.1097/ PAS.0b013e31821c3dae.

Mansour, Mohammed A., Toshinori Hyodo, Khondker Ayesha Akter, Toshio Kokuryo, Keisuke Uehara, Masato Nagino, and Takeshi Senga. 2016. "SATB1 and SATB2 Play Opposing Roles in C-Myc Expression and Progression of Colorectal Cancer." Oncotarget 7 (4): 4993–5006. https://doi.org/10.18632/oncotarget.6651.

Mansour, Mohammed A., Toshinori Hyodo, Satoko Ito, Kenji Kurita, Toshio Kokuryo, Keisuke Uehara, Masato Nagino, Masahide Takahashi, Michinari Hamaguchi, and Takeshi Senga. 2015. "SATB2 Suppresses the Progression of Colorectal Cancer Cells via Inactivation of MEK5/ERK5 Signaling." FEBS Journal 282 (8): 1394–1405. https://doi.org/10.1111/febs.13227.

Metwally, Islam H., Mosab Shetiwy, Amr F. Elalfy, Amr Abouzid, Saleh S. Saleh, and Mohamed Hamdy. 2018. "Epidemiology and Survival of Colon Cancer among Egyptians: A Retrospective Study." Journal of Coloproctology 38 (1): 24–29. https://doi.org/10.1016/j.jcol.2017.09.418.

Mezheyeuski, Artur, Fredrik Ponten, Per Henrik Edqvist, Magnus Sundström, Ulf Thunberg, Camilla Qvortrup, Per Pfeiffer, Halfdan Sorbye, Bengt Glimelius, and Anca Dragomir. 2020. "Metastatic Colorectal Carcinomas with High SATB2 Expression Are Associated with Better Prognosis and Response to Chemotherapy: A Population-Based Scandinavian Study." Acta Oncologica 59 (3): 284–90. https://doi.org/10.1080/0284186X.2019.1691258.

Vermeer, N. C.A., H. S. Snijders, F. A. Holman, G. J. Liefers, E. Bastiaannet, C. J.H. van de Velde, and K. C.M.J. Peeters. 2017. "Colorectal Cancer Screening: Systematic Review of Screen-Related Morbidity and Mortality." Cancer Treatment Reviews 54 (March): 87–98. https://doi.org/10.1016/j.ctrv.2017.02.002.

Wang, Shuang, Jun Zhou, Xiao Yan Wang, Jun Mei Hao, Juan Zhi Chen, Xiang Mei Zhang, He Jin, et al. 2009. "Down-Regulated Expression of SATB2 Is Associated with Metastasis and Poor Prognosis in Colorectal Cancer." Journal of Pathology 219 (1): 114–22. https://doi.org/10.1002/path.2575.

Wang, Yi Qing, Dong Mei Jiang, Sha Sha Hu, Li Zhao, Lan Wang, Min Hui Yang, Mei Ling Ai, et al. 2019. "SATB2-AS1 Suppresses Colorectal Carcinoma Aggressiveness by Inhibiting SATB2-Dependent Snail Transcription and Epithelial–Mesenchymal Transition." Cancer Research 79 (14): 3542–56. https://doi.org/10.1158/0008-5472.CAN-18-2900.

Wu, Liucheng, Jiansi Chen, Yuzhou Qin, Xianwei Mo, Minwei Huang, Haiming Ru, Yang Yang, Jungang Liu, and Yuan Lin. 2016. "SATB2 Suppresses Gastric Cancer Cell Proliferation and Migration." Tumor Biology 37 (4): 4597–4602. https://doi.org/10.1007/s13277-015-4282-5.

Yang, Daqing, Rizeng Li, Jianfu Xia, Wencai Li, and Hong Zhou. 2018. "MiR-3666 Suppresses Cellular Proliferation and Invasion in Colorectal Cancer by Targeting SATB2." Molecular Medicine Reports 18 (6): 4847–54. https://doi.org/10.3892/mmr.2018.9540.