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Original article

Evaluation of Special AT-Rich Sequence-Binding Protein 2 (SATB2) Expression in Colonic Carcinoma: Immunohistochemical Study

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Abstract

Background: Globally, colorectal cancer poses a significant oncologic challenge, with colonic carcinoma ranking as the third most prevalent cancer worldwide. In Egypt, it represents a noteworthy portion of both male and female cancer cases. The prognosis for colonic carcinoma remains poor due to the lack of early symptoms, emphasizing the need for effective biomarkers to predict prognosis and guide treatment strategies. **This study aimed to** evaluate SATB2 expression in colonic carcinoma by immunohistochemistry and assess correlation between SATB2 protein and clinicopathological parameters of colonic carcinoma. **Methods:** This retrospective study was carried out upon 50 cases of colonic adenocarcinoma obtained from the pathology department and early cancer detection unit at Benha Faculty of Medicine during the period of 2017 to 2021. Cases were selected on basis of availability of demographic data (age, sex) and clinicopathological data (Tumor site, tumor size, depth of invasion, lymph node status, grade, TNM stage, lympho-vascular invasion and presence of distant metastasis). **Results**: There was a highly significant inverse statistical correlation between SATB2 expression and tumor grade, depth of tumor invasion, lymph node metastasis, distant metastasis and tumor stage (P value <0.01). Also, there was a significant inverse statistical correlation between SATB2 expression and presence of lympho-vascular invasion (P value <0.05). **Conclusion:** SATB2 expression in colonic cancer aligns with key prognostic factors, making it a potential predictor of prognosis. Furthermore, SATB2 expression inversely correlates with tumor aggressiveness, suggesting it may indicate a favorable prognosis, while loss of SATB2 expression may imply a poorer prognosis in colonic cancer.

Keywords: Special AT-Rich; Sequence-Binding Protein 2 (SATB2); Colonic Carcinoma; Immunohistochemical.

Introduction

Globally, gastrointestinal (GI) cancer presents a major oncologic problem **(1)**.Colonic carcinoma is the third most common cancer worldwide after lung and breast cancers with two-thirds of all colorectal cancers occurring in the more developed regions of the world **(2)**. Colonic carcinoma affects men and women of all racial and ethnic groups and is most often found in those aged 50 years or older **(3).**Colonic carcinoma is the 7th commonest cancer in Egypt, representing 3.47% of male cancers and 3% of female cancers **(4**). The prognosis of patients with colonic carcinoma remains poor because of the absence of obvious symptoms at the early stage. An early and accurate diagnosis would greatly improve the treatment for Colonic carcinoma **(5)**. Therefore, more effective biomarkers are needed for people to predict colonic carcinoma prognosis and to perform treatment stratification **(6).** The matrix attachment region–binding transcription factor family consists of transcription factors binding to AT-rich regions in the nuclear matrix (matrix attachment regions).

These transcription factors are capable of altering chromatin structure over large distances and affecting multiple genes **(7).** SATB2 is part of the family of matrix attachment region binding transcription factors, and has developmental roles in craniofacial, neural, and osteoblastic differentiation.

Recently, SATB2 has been shown to be highly expressed in the epithelium of the lower gastrointestinal tract, with a relatively narrow expression profile in malignancies, including colorectal/appendiceal adenocarcinomas, tumors of osteoblastic differentiation, and renal/urothelial carcinomas. SATB2 has gained interest as a relatively specific marker of colorectal differentiation, with potential applications including determining origin of adenocarcinomas of unknown primary and distinguishing primary ovarian mucinous adenocarcinomas from colorectal metastases **(8).**

The purpose of this study was to evaluate SATB2 expression in colonic carcinoma by immunohistochemistry and assess correlation between SATB2 protein and clinicopathological parameters of colonic carcinoma.

Patients and methods

This retrospective study was carried out upon 50 cases of colonic adenocarcinoma at the Pathology Department and Early Cancer Detection Unit at Benha Faculty of Medicine, during the period of 2017 to 2021.

Inclusion criteria: Cases were selected on basis of availability of demographic data (age, sex) and clinicopathological data (Tumor site, tumor size, depth of tumor invasion, grade, stage, lymph node status, presence of lympho-vascular invasion and presence of distant metastasis).

Exclusion criteria: Cases with no available paraffin blocks or clinicopathological data- were excluded from the current study.

Histopathological Analysis:
Formalin fixed /paraffin embedded blocks were cut at 4 μm thickness and stained using hematoxylin and eosin stain. Two observers reviewed the microscopic sections from all the cases.

Interpretation and assessment:

Colorectal adenocarcinoma cases were graded according to **Ueno et al.,(9).** Pathological tumor-node-metastasis (TNM) staging was determined according to the criteria of the American Joint Committee on Cancer (**AJCC, 8th edition) (10)** .

Immunohistochemical study:
Slides were immune stained according to manufacturer's instructions with SATB2 rabbit monoclonal antibody (**Chongqing biopsies co., Cat No YMA1178, China)** at a dilution of 1:50, at room temperature, overnight. Immunodetection was carried out using a standard labeled streptavidin-biotin system (**Genemed, CA 94080, USA, South San Francisco).** Antigen retrieval was done by using 10 mmol/L citrate monohydrate buffer (pH 6.0) and heating for 15 minutes in the microwave. The chromogen diaminobenzene (DAB, Envision TM Flex /HRP-Dako, REF K 8000) used was freshly prepared. The counter satin was Mayer's hematoxylin.

Negative & positive controls:

- Sections from normal colonic mucosa were used as a positive control for SATB2.
- For negative control the primary antibody was omitted from the staining procedure.

Immunohistochemical assessment:

SATB2 (monoclonal Anti-SATB2 antibody). expression was detected as nuclear brown stain in tumor cells. Five random fields were selected and analyzed. The final immunostaining score reported was the average of two observers. The annotation process included a semiquantitative, categorical estimation of the fraction (%) of tumor cell nuclei positive for SATB2 regardless of intensity (nuclear fraction [NF]), which was scored 0 for less than 1%, 1 for 2% to 25%, 2 for 26% to 75%, and 3 for more than 75%. For the purpose of statistical analyses, SATB2 nuclear staining was further dichotomized into negative tumors (score 0) and positive tumors (scores 1–3) **(28).**
The Ethics committee of faculty of medicine, Benha University, Egypt approved this study code (M. S. 10-11-2019).

Statistical analysis

Results were analyzed using SPSS (version 16) statistical package for Microsoft windows as follow: P value >0.05 is non-significant (NS), P<0.05 is significant (S) and P≤ 0.001 is highly significant (HS).

Results

Microscopic examination of colorectal adenocarcinoma cases revealed that 10 cases (20%) were grade I, 27 cases (54%) were grade II, and 13 cases (26%) were grade III.

There was an insignificant relationship between tumor grade and tumor site in studied cases (P value>0.05). There was an insignificant relationship between tumor grade and tumor size in studied cases (P value>0.05).

There was an insignificant correlation between tumor grade and depth of tumor invasion (P value >0.05). There was a significant direct statistical correlation between tumor grade and lymph node metastasis in studied cases (P value< 0.05).

There was a highly significant direct statistical correlation between tumor grade and presence of lympho-vascular invasion in studied cases (P value < 0.01). There was a highly significant direct statistical correlation between tumor grade and tumor stage in studied cases (P value < 0.01).

Immunohistochemical results:

Out of 50 cases colorectal adenocarcinoma, 13 cases (26%) were negative for SATB2 expression (Score 0) and 37 cases (74%) were positive for SATB2 expression ;12 cases (24%) showed score (1+), 15 cases (30%) showed score (2+), 10 cases (20%) showed score (3+), **Figure (1**).

There wasn't significant statistical relationship between SATB2 expression and tumor site in studied cases (P value >0.05). There was an insignificant statistical relationship between SATB2 expression and tumor size in studied cases (P value >0.05).

There was a highly significant inverse statistical correlation between SATB2 expression and tumor grade (P value <0.01), **Table (1**).

There was a highly significant inverse statistical correlation between SATB2 expression and depth of tumor invasion (T) (P value <0.01), **Table (1**).

There was a highly significant inverse statistical correlation between SATB2 expression and lymph node metastasis (N) (P value <0.01), **Table (1).**

There was a significant inverse statistical correlation between SATB2 expression and presence of lympho-vascular invasion (P value <0.05), **Table (1).**

There was a highly significant inverse statistical correlation between SATB2 expression and tumor stage in studied cases (P value <0.01), **Table (1).**

Table (1): Correlation between SATB2 score clinico-pathological parameters in studied cases

Parameters		**SATB2 Score**			
		0	+1	+2	+3
Grade	I	1 (7.6%)	1 (8.3%)	2 (13.3%)	6 (60%)
	II	5 (38.5%)	6 (50%)	12 (80%)	4 (40%)
	III	7 (53.8%)	5 (41.7)	1 (6.7%)	0 (0%)
Depth of Tumor invasion (T)	T1	1 (7.7%)	0 (0%)	1 (6.7%)	5 (50%)
	T2	1 (7.7%)	6 (50%)	6 (40%)	4 (40%)
	T3	4 (30.8%)	3 (25%)	8 (53.3%)	1 (10%)
	T4	7 (53.8%)	3 (25%)	0 (0%)	0 (0%)
Lymph node metastasis	N0	3 (33.1%)	6 (50%)	9 (60%)	9 (90%)
	N1	2 (15.4%)	5 (41.7%)	6 (40%)	1 (10%)
	N2	8 (61.5%)	1 (8.3%)	0 (0%)	0 (0%)
Distant metastasis	M0	8 (61.5%)	9 (75%)	14 (93.3 %)	9 (90%)
	M1	5 (38.5%)	3 (25%)	1 (6.7%)	1 (10%)
Lympho-vascular invasion	Absent	4 (30.8%)	4 (33.3%)	10 (66.7%)	9 (90%)
	present	9 (69.2%)	8 (66.7%)	5 (33.3%)	1 (10%)
Stage	I	1 (6.7%)	2 (16.7%)	3 (20%)	4 (40%)
	II	1 (20%)	4 (33.3%)	5 (33.3%)	6 (60%)
	III	5 (33.3%)	3 (25%)	6 (40%)	0 (0%)
	IV	6 (40%)	3 (25%)	1 (6.7%)	0 (0%)

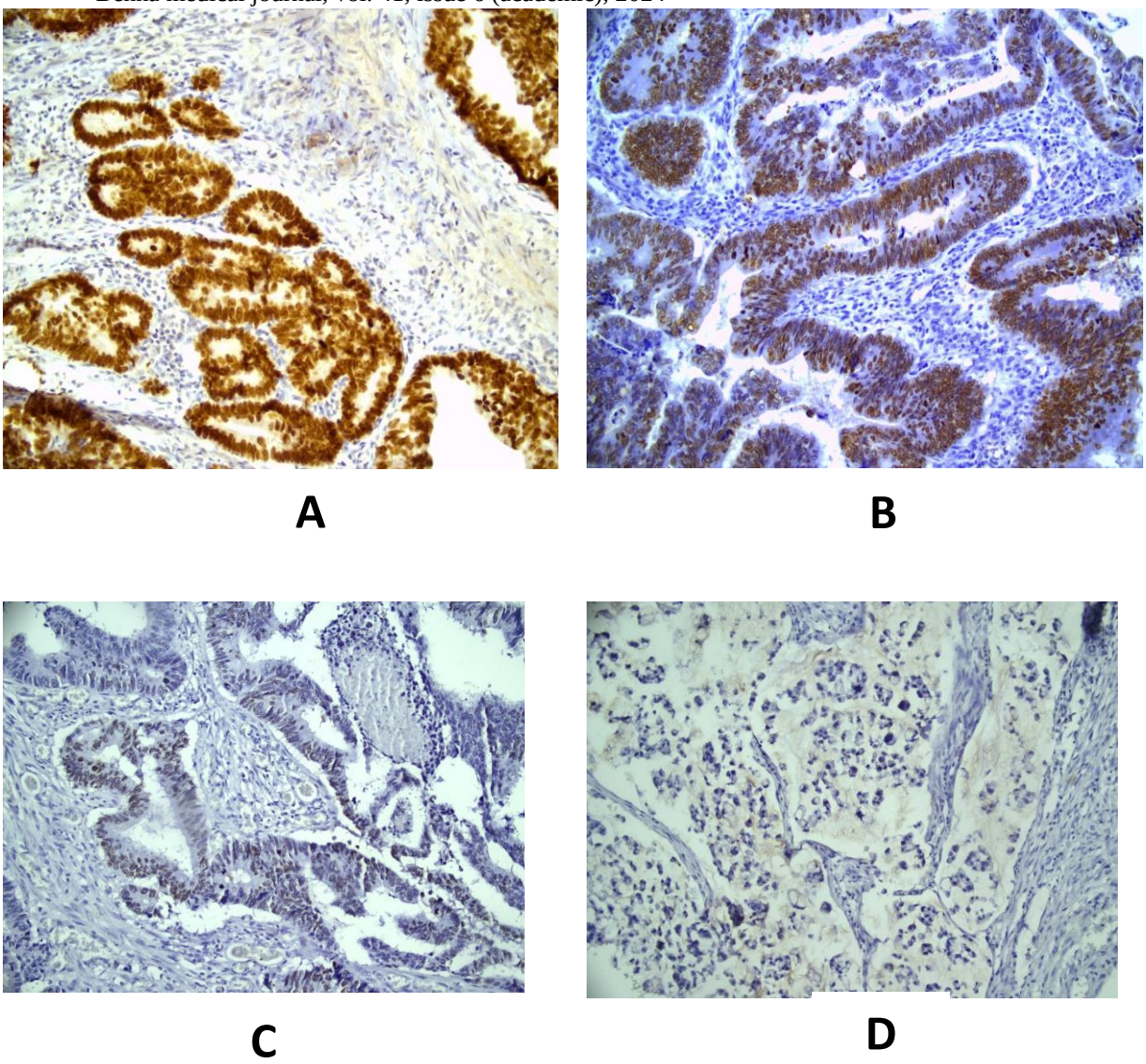

Figure (1) A: Well differentiated colonic adenocarcinoma show strong nuclear staining, score 3 (SATB2, X200).
B: Moderately differentiated colonic adenocarcinoma show moderate nuclear staining, score 2 (SATB2, X200).
C: Moderately differentiated colonic adenocarcinoma show weak nuclear staining, score1(SATB2, X200).
D: Poorly differentiated colonic adenocarcinoma show absent staining, score 0(SATB2, X200).

Discussion

Colorectal carcinoma (CRC) is the third most prevalent neoplasm in the world; around one million new cases are diagnosed annually **(1).**

This retrospective study was carried upon 50 cases of colorectal adenocarcinoma, 54% of cases were males and 46% of cases were females with male to female ratio 1.1:1. The age of studied cases ranged from 19 to 70 years old with mean age 55 years old, they were distributed into two age

groups as follow: 24% of cases were <50 years old and 76%were ≥50 years**.** These findings were similar to those reported by a research stated that the mean patient's age in their study was (55.9 ± 3.9) years **(11).**

Studied cases ranged in size from 3cm to 20 cm in the largest dimension, with mean size 5 cm, 40% of cases were <5 cm, while 60% of cases were ≥5 cm.

Also, a study revealed that 130 cases of colorectal carcinoma with mean size 5 cm found that 48 % of cases were <5 cm while 52% were >=5 cm in greatest dimension **(12).**

According to tumor site, our findings were close to a study done on 56 cases of CRC in Egypt, in which 56% of cases were located in right colon while 44% of cases were in left colon **(13).**

In our study, microscopic examination revealed that 20% of cases were grade I, 54% were grade II and 26%were grade III.

The current finding agreed with two studies who found that the commonest grade was grade II, followed by grade III, then grade I **(31,32).** On the other hand, other study found that the commonest grade was grade I, followed by grade II, then grade III **(30)** and also one study reported that grade III was the commonest histopathological grade of CRC **(29).**

The variations mentioned regarding the predominant histopathological grade may be explained by a substantial degree of interobserver variability and that morphological grading is applied only on conventional adenocarcinomas and other morphologic variants carry their own prognostic significance (22).

Regarding observed Lymph node metastases our findings also agreed with the finding of a study stated that most of their studied cases showed involved lymph nodes **(14, 15).**

Regarding distant metastases (M1), our results were in contrast with other studies reported distant metastasis in 28.4% and 6.1% of their cases respectively **(15,30).** This can be explained by different number of cases studied in different works and different histologic types of cases involved with different tumor grades.

Concerning lympho-vascular invasion (LVI), our results were more or less similar to that reported by one study who stated presence of vascular invasion in 43.2% of their studied cases **(15).** Two studie**s** reported vascular invasion in only 13.3 % and 22.9% of their cases respectively, which are lower than the rate of vascular invasion in our study **(33, 30).**

As regard TNM staging according to AJCC (2018), our results were similar to other studies reported that the most diagnosed tumor stage was stage II constituting 38.3%, 41.9% and 44.1% of their cases respectively**(16, 30, 14).** Other study reported that the most diagnosed tumor stage was stage III constituting 39.6% of their cases **(34).**

Regarding the depth of tumor invasion (T), 18% were T1, 32% were T2, 30% were T3 and 20% were T4. Two studies reported that T3 was the most diagnosed T category of their cases, followed by T4, while T1 was the least

(35, 36). This may be attributed to different number of cases studied and different methods of interpretation.

SATB2(Special AT-rich sequence-binding protein) is a recently described transcriptional regulator, encoded on chromosome 2q32-33, which is involved in osteoblastic, cortical neuron differentiation and in skeletal development **(17).**

In the current study SATB2 was detected as nuclear brown stain, 26% were negative for SATB2 expression (Score 0) and 74% were positive for SATB2 expression ;24% showed score (1+), 30% showed score (2+), 20% showed score (3+).

In the present study, there was no significant statistical relationship between SATB2 expression and age, gender and tumor site of studied cases (P value >0.05). Other studies reported that no significant association between SATB2 expression and age, sex according to **(21, 23, 24, 26).**

According to tumor site this study disagreed with previous studies in which the incidence of SATB2 negativity in left-sided tumors range from 57%-82% and 18-43% in right-sided tumors **(26, 37).**

The prognostic significance of the differential expression of SATB2 in the right and left-sided cancers should be considered and further studies are required to find out the actual biological properties of these tumors with respect to side.

In the current study, there was a highly significant inverse statistical correlation between SATB2 expression and tumor grade (P value <0.01).

One study reported that a significant association with the parameter grade. Lower grade was associated with higher intensity and higher number of SATB2-positive cells **(23).** Other studies observed significant associations with the grade **(21)**.

One study reported that most of the mucinous adenocarcinomas and all the cases of signet ring adenocarcinoma in their study were SATB2 negative and this was consistent with other results **(27, 25, 37, 20).**

In contrast, the studies done by **Zhang et al (24)** and **Wang et al (26)** did not confirm any significant associations between SATB2 expression and grade. This may be attributed to different number of cases studied, different antibody clones, protocols and scoring methods used.

There was a highly significant inverse statistical correlation between SATB2 expression and tumor stage in studied cases (P value <0.01).

One study observed a significant relationship between the intensity of immunoreaction and the parameter stage where stage IV was associated with strong intensity **(23).**

The study published by **Wang et al (26)** revealed that significant associations between SATB2 expression and stage.

The study done by **Eberhard et al (21)** showed significant associations with T and N stage**.**

One study reported that decreased expression of SATB2 was associated with a higher stage which also showed statistical significance **(27).** This was also shown in the previous studies done by **(25, 37, 20).**

In contrast, other study did not confirm any significant associations between SATB2 expression and stage **(24).**

There was a significant inverse statistical correlation between SATB2 expression and presence of lympho-vascular invasion (P value <0.05).

The study published by **Cígváero et al (23)** revealed that the vascular invasion significantly associated with the percentage of positive cells.

Other study observed significant associations with vascular invasion **(21).**

Decreased expression of SATB2 was associated with lympho-vascular invasion which also showed statistical significance. This was also shown in the previous studies **(27, 37, 20).**

There was a highly significant inverse statistical relationship between SATB2 expression and lymph node metastasis (N) (P value <0.01)

Furthermore, the study published by **Cígváero et al (23)** demonstrated that the lymph node status significantly associated with intensity. Negative lymph nodes were associated with higher intensity.

One study reported significant associations between SATB2 expression and lymph node metastasis **(26).**

There was a significant inverse statistical correlation between SATB2expression and distant metastasis in studied cases (M) (P value <0.05). One study showed an inverse association between SATB2 expression and the presence of metastasis **(27)**, which is associated with an unfavorable outcome in patients. Similar results were also seen in the studies **(25**, **26**, **37).**

There are several theories on the mechanism by which SATB2 affects tumor growth and spreading, including SATB2-mediated chromatin rearrangement and differential expression of microRNAs, both of which could affect the expression of genes important for migration and invasion **(18)**. A metastasis-suppressor microRNA, miRNA-31, binds directly to SATB2-mRNA and blocks its translation into SATB2 protein. This correlated with poor prognosis in patients with CRC **(19)**. SATB2 has a tumor suppressive function in in vitro models, where its expression inhibited the formation of invadopodia, actin-rich protrusions of the plasma membrane that are associated with degradation of the extracellular matrix and reduced invasiveness of cancer cells in a migration assay **(**18).

SATB2 overexpression is associated with reduced phosphorylation of ERK5, a mitogen-activated protein kinase that promotes aggressive behavior of tumors cells, including formation of invadopodia (1**8)**. A study reported an association between reduced SATB2 expression and more malignant phenotypes has been observed in several cancer types. There is thus overwhelming evidence that SATB2 is directly involved in mechanisms of tumor aggressiveness **(**20).

Conclusion

SATB2 expression in colonic cancer aligns with key prognostic factors, making it a potential predictor of prognosis. Furthermore, SATB2 expression inversely correlates with tumor aggressiveness, suggesting it

may indicate a favorable prognosis, while loss of SATB2 expression may imply a poorer prognosis in colonic cancer.

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