Clinicopathologic Significance of SATB1 and DJ-1 Proteins Expression in Cervical Carcinoma

Ashraf Ishak Fawzy Tiwadros1* and Mohamed Mohamed Mohamed Khalafalla2

1Pathology Department, Faculty of Medicine, Minia University, El Minia, Egypt
2Obstetrics and gynecology Department, Faculty of Medicine, Menofia University, Menofia, Egypt

ABSTRACT

Background: Special AT-rich sequence binding protein 1 (SATB1) and DJ-1 proteins play a crucial role in tumorigenesis and tumor progression in many human malignancies. Limited data is available in literature about their role in cervical carcinomas.

Aims: The present study was designed to investigate the immunohistochemical expression of SATB1 and DJ-1 proteins in cervical carcinoma and their relationships to clinicopathologic variables.

Material and Methods: Tissue sections from 100 cervical lesions distributed as 60 cases of cervical carcinoma, 30 cases of squamous intraepithelial lesion (SIL) and 10 cases with normal cervical tissue were evaluated for SATB1 and DJ-1 proteins expression by immunohistochemistry.

Results: SATB1 expression was detected in 41.7% of cervical carcinomas versus 20% and 6.7% of HSIL and LSIL, respectively (p = 0.019). A significant positive correlation between SATB1 expression to lymph node metastasis (p = 0.004) and pTNM (p = 0.028) was noted. DJ-1 expression was detected in 68.3% versus 33.3% and 13.3% of HSIL and LSIL, respectively (p = 0.001). A significant positive association between DJ-1 expression and lymph node metastasis (p = 0.037) was noted. Normal cervical tissue was negative for SATB1 and DJ-1 expression. A significant positive association between SATB1 and DJ-1 immunoreactivity was detected in investigated cervical carcinomas (p = 0.027).

Conclusions: SATB1 and DJ-1 are shown to be promising potential prognostic biomarkers in cervical carcinoma since their overexpression is correlated with advanced clinicopathologic variables including lymph node metastasis. SATB1 and DJ-1 can be promising therapeutic targets for cervical cancer.

Keywords: Cervical Carcinoma, SATB1, DJ-1, Immunohistochemistry, Clinicopathologic Variables.

Introduction

Cervical cancer is the fourth most commonly diagnosed cancer in women worldwide and the fourth leading cause of cancer-related mortality. The majority of cervical cancer deaths occur in developing countries due to tumor diagnosis at advanced stages.[1] Squamous cell carcinoma is the most frequent histologic subtype, accounting for ~90% of cervical cancer cases.[2] Several molecular mechanisms underlie the progression of cervical cancer; hence understanding these mechanisms is an important target in predicting the prognosis and controlling the progression of such cancer.

Special AT-rich sequence binding protein 1 (SATB1) is a tissue-specific nuclear matrix binding protein that was originally described as T cell enriched transcription factor that regulates many genes involved in T cell development and differentiation.[3-4] SATB1 gene is located on the third chromosome (3p23) in humans. [4] SATB1 functions as a global chromatin organizer involved in regulation of large number of genes by selectively tethering their regulatory regions and via formation of a characteristic cage-like structure around the heterochromatic regions.[4,5] Under normal physiological conditions, SATB1 is highly expressed in the thymus and its expression is virtually undetectable in other tissues except for low levels in testis, fetal brain, and osteoblasts.[3] Recent studies in the last few years have shown overexpression of SATB1 in a variety of malignant tumors including cutaneous malignant melanoma, breast, gastric, colorectal and laryngeal carcinomas where it is linked to tumor progression and metastasis.[6]

DJ-1(PARK7) is an oncogene mapped at chromosome 1p36.2–p36.3, a locus known to be hot spot of chromosome aberrations in several cancers. [7] DJ-1 protein is widely expressed in various human tissues, with high expression levels in testis, kidney, pancreas, heart and skeletal muscle. [8] It is involved in diverse biologic processes such as cell migration, cell adhesion, apoptosis, chemotaxis, transcriptional regulation, antioxidant stress function, mitochondrial regulation and fertilization. [9,9] DJ-1 protein overexpression has been reported in a variety of malignant
tumors including breast, prostate, ovarian, hepatocellular, pancreatic, renal and non-small cell lung carcinomas.\textsuperscript{[7,9,10]} Very limited data is available in the literature regarding both SATB1 and DJ-1 expression in cervical cancer. Also present are conflicting reports about subcellular localization of DJ-1 protein expression detected by immunohistochemistry.

The present study was designed to investigate the immunohistochemical expression of SATB1 and DJ-1 proteins in cervical carcinoma, their relationships to clinicopathologic variables as well as to each other. Also targeted was highlighting biomarkers expression in cervical squamous intraepithelial lesion (SIL) as well as normal cervical tissue.

Materials and Methods

Study Design: The present study was carried out on paraffin blocks of formalin-fixed tissue sections of 100 cases distributed as 60 cases of cervical carcinoma, 30 cases of squamous intraepithelial lesion (SIL) and 10 cases with normal cervical tissue. Cancer specimens included 53 squamous cell carcinomas and 7 adenocarcinomas while SIL specimens included 15 low-grade squamous intraepithelial lesion (LSIL) and 15 high-grade squamous intraepithelial lesion (HSIL). These specimens were retrieved from the archives of Histopathology Lab of Department of Pathology, Faculty of Medicine, Minia University, Egypt. Cancer specimens were collected consecutively during the period from January 2008 to December 2016 and obtained from patients undergoing surgical resection of the tumor for diagnostic and therapeutic purposes. Clinical records were obtained to review patient data including patient’s age, tumor cell type, histologic grade, tumor size, FIGO stage, lymphovascular invasion and lymph node metastasis. All specimens included in this study are obtained prior to chemotherapy or radiotherapy. The histopathologic diagnosis and grading of cancer cases were revised by the author. Investigated carcinomas were categorized into well-differentiated, moderately differentiated and poorly differentiated based on WHO classification of histologic differentiation. All carcinomas were staged according to the International Federation of Gynecology and Obstetrics (FIGO) criteria.\textsuperscript{[11]} Age of patients ranged from 28-66 years with mean age 45.25 ± 9.04 years. The patient and tumor characteristics of investigated cases were shown in Table 1.

Immunohistochemical Staining: Immunohistochemical staining was performed on 4-μm thick sections. These sections were immunostained with primary antibodies against SATB1 (dilution 1:100, rabbit monoclonal [clone EPR3951], Abcam, Cambridge, UK) and DJ-1 (dilution 1:100, mouse monoclonal [clone A-9], Santa Cruz Biotechnology, Santa Cruz, CA, USA) along with DAKO universal LSAB2/HRP detection kit (DAKO, Glostrup, Denmark). Negative control was performed by omission of primary antibodies and replacement by PBS. Human tonsils served as positive control for SATB1 while human prostate was employed as positive control for DJ-1.

Interpretation of IHC Results: Positive immunostaining for SATB1 was nuclear and DJ-1 was cytoplasmic and nuclear. Positive cases were classified according to the rate of positive cell staining on one hand and their staining intensity on the other. Immunostaining in <10% of tumor cells is categorized as 0, immunostaining in 10-25% of tumor cells as 1, staining in 26-50% of tumor cells as 2, staining and staining >50% as 3. The staining intensity in each specimen was categorized as 0, 1, 2, 3 (negative, weak, moderate, or strong, respectively). The total immunostaining score was calculated by sum of the two above scores. Scores ≤ 2 were regarded as negative expression and scores of 3-6 were regarded as positive expression.

Statistical Analysis: The statistical analyses were performed using SPSS for Windows, version 16.0 (SPSS Inc., Chicago, IL). Chi-square and Fisher’s exact tests were used when appropriate to assess the relationships between biomarkers and clinicopathologic variables of included tumors. Two-sided \(p\)-values of <0.05 were considered significant.

Result

SATB1 Immunohistochemical Expression: SATB1 positive immunostaining was detected in 25 out of 60 cervical carcinomas (41.7%) versus 3 out of 15 HSIL (20%) and one case out of 15 LSIL (6.7%) (\(X^2 = 7.962, p = 0.019\)). In carcinomas, positive immunoreactivity for SATB1 was distributed as 22 out of 53 SCC (41.5%) and 3 out of 7 AC (42.9%). No immunostaining for SATB1 was noted in normal cervical tissue. Our study demonstrated a significant association between SATB1 expression and lymph node metastasis. The rate of positive SATB1 immunostaining in tumors with lymph nodal metastasis (12 out of 17 cases, 70.6%) was higher than in those without nodal metastasis (13 out of 43 cases, 30.2%) (\(X^2 = 8.163, p = 0.004\)). Also, a significant positive relationship was noted between positive SATB1 expression and higher TNM stages since SATB1 expression was detected in 14 out of 22 stage III tumors (63.6%) while it was detected in 3 out of 13 (23.1%) and in 8 out of 25 cases (32%) stage I and II tumors, respectively (\(X^2 = 7.178, p = 0.028\)).

No significant relationship was observed between SATB1 expression and age (\(p = 0.861\), histologic subtype (\(p =
0.946), tumor grade \( (p = 0.190) \), tumor size \( (p = 0.315) \), and LVI \( (p = 0.241) \). (Table 2) (Figure 1, 2).

**DJ-1 Immunohistochemical Expression:** DJ-1 positive immunoreactivity was detected in 41 out of 60 investigated cancer cases (68.3%) versus 5 out of 15 HSIL (33.3%) and 2 out of 15 LSIL (13.3%) \( (X^2 = 17.478, p = 0.001) \). In carcinomas, positive immunostaining for DJ-1 was distributed as 37 out of 53 SCC (69.8%) and 4 out of 7 AC (57.1%). Dj-1 immunostaining in SIL cases was mainly cytoplasmic. Normal cervical tissue did not show any immunoreactivity to DJ-1. The present study demonstrated a significant positive association between DJ-1 expression and lymph node metastasis. The rate of positive DJ-1 expression was higher in tumors positive for nodal metastasis (15 out of 17 cases, 88.2%) than in those negative for nodal metastasis (26 out of 43 cases, 60.5%) \( (X^2 = 4.342, p = 0.037) \). Meanwhile, no significant relationship was observed between DJ-1 expression and age \( (p = 0.630) \), histologic subtype \( (p = 0.498) \), tumor grade \( (p = 0.247) \), tumor size \( (p = 0.919) \), FIGO stage \( (p = 0.354) \) and LVI \( (p = 0.072) \). (Table 3) (Figure 3, 4)

The Relationship Between SATB1 and DJ-1 Immunoreactivity: The present study demonstrated a significant positive relationship between SATB1 and DJ-1 immunoreactivity in investigated cervical carcinomas \( (X^2 = 4.861, p = 0.027) \).

### Table 1: Tumor and Patients Characteristics.

| Characteristics                                | N   | (%)  |
|------------------------------------------------|-----|------|
| Age at diagnosis (range 28-66 years; mean 45.25 ± 9.04 years) |     |      |
| ≤ 45 years                                     | 28  | (46.7)|
| > 45 years                                     | 32  | (53.3)|
| Histologic types:                              |     |      |
| - Squamous cell carcinoma (SCC)                | 53  | (88.3)|
| - Adenocarcinoma (AC)                         | 7   | (11.7)|
| Tumor Differentiation                          |     |      |
| Well differentiated                            | 9   | (15) |
| Moderately differentiated                      | 25  | (41.7)|
| Poorly differentiated                          | 26  | (43.3)|
| Tumor Size                                     |     |      |
| ≤ 4cm                                          | 31  | (51.7)|
| >4cm                                           | 29  | (48.3)|
| pN status                                      |     |      |
| N0                                             | 43  | (71.7)|
| N1                                             | 17  | (28.3)|
| FIGO stage                                     |     |      |
| I                                              | 13  | (21.7)|
| II                                             | 25  | (41.7)|
| III                                            | 22  | (36.7)|
| LVI                                            |     |      |
| Negative                                       | 41  | (68.3)|
| Positive                                       | 19  | (31.7)|

\(N= number; \(\%\)= percentage; pN, lymph node status; LVI, lymphovascular invasion\)

### Table 2: SATB1 expression and clinicopathologic variables in cervical carcinomas.

| Variables                              | N   | Negative n (%) | Positive n (%) | P    |
|----------------------------------------|-----|----------------|----------------|------|
| Age                                    |     |                |                |      |
| ≤ 45 years                             | 28  | 16 (57.1%)     | 12 (42.9%)     | 0.861|
| > 45 years                             | 32  | 19 (59.4%)     | 13 (40.6%)     |      |
| Histologic subtype                     |     |                |                |      |
| - Squamous cell carcinoma              | 53  | 31 (58.5%)     | 22 (41.5%)     | 0.946|
| - Adenocarcinoma                       | 7   | 4 (57.1%)      | 3 (42.9%)      |      |
| Variables                      | N   | Negative n (%) | Positive n (%) | P    |
|-------------------------------|-----|----------------|----------------|------|
| **Tumor Differentiation**     |     |                |                |      |
| Well differentiated           | 9   | 7 (77.8%)      | 2 (22.2%)      | 0.190|
| Moderately differentiated     | 25  | 16 (64%)       | 9 (36%)        |      |
| Poorly differentiated         | 26  | 12 (46.2%)     | 14 (53.8%)     |      |
| **Tumor Size**                |     |                |                |      |
| ≤ 4cm                         | 31  | 20 (64.5%)     | 11 (35.5%)     | 0.315|
| >4cm                          | 29  | 15 (51.7%)     | 14 (48.3%)     |      |
| **pN status**                 |     |                |                |      |
| Negative (N0)                 | 43  | 30 (69.8%)     | 13 (30.2%)     | 0.004|
| Positive (N1)                 | 17  | 5 (29.4%)      | 12 (70.6%)     |      |
| **FIGO stage**                |     |                |                |      |
| I                             | 13  | 10 (76.9%)     | 3 (23.1%)      | 0.028|
| II                            | 25  | 17 (68%)       | 8 (32%)        |      |
| III                           | 22  | 8 (36.4%)      | 14 (63.6%)     |      |
| **LVI**                       |     |                |                |      |
| Negative                      | 41  | 26 (63.4%)     | 15 (36.6%)     | 0.241|
| Positive                      | 19  | 9 (47.4%)      | 10 (52.6%)     |      |

Table 3: DJ-1 expression and clinicopathologic variables in cervical carcinomas.
Discussion
SATB1 represents a novel class of transcription regulators as it functions as master genome organizer. SATB1 participates in the maintenance and compaction of chromatin architecture by organizing it into distinct loops via periodic anchoring of matrix attachment regions (MARs) to the nuclear matrix.\(^\text{[4]}\) Also, SATB1 can regulate distant genes by selectively tethering MARs to the nuclear matrix resulting in the formation of a characteristic ‘cage-like’ network that circumscribes heterochromatin.\(^\text{[4-6,12,13]}\) Moreover, SATB1 seems to serve two different but related purposes, structurally as a component of chromatin architecture and functionally as a transcription factor via binding to the upstream regulatory elements and recruiting chromatin remodeling enzymes.\(^\text{[4,5,14]}\) Recently, SATB1 was shown to provide a nuclear architectural platform regulating the expression of >1000 genes involved in many biologic processes, including proliferation, apoptosis, cell cycle, cell adhesion, signaling, extracellular matrix formation and epithelial-mesenchymal transition, indicating a potential role of SATB1 in malignant transformation and progression.\(^\text{[14]}\) This role was demonstrated in breast and prostate cancer cell lines as when SATB1 gene was transfected into non-aggressive cell lines of these cancers; these cells acquired aggressive phenotype with invasion and metastasis characteristics. On the contrary, silencing of the SATB1 gene in the aggressive cancer cell lines inhibited the tumor growth, invasion and metastasis.\(^\text{[13,14]}\) SATB1
appears to orchestrate specific epigenetic modifications at target gene loci by directly upregulating metastasis-associated genes while downregulating tumour-suppressor genes. In correspondence with these biologic effects, SATB1 overexpression and its association with advanced clinicopathologic variables and poor prognosis have been reported in a variety of malignant tumors including breast, prostate, gastric, colorectal, liver, ovarian and laryngeal carcinomas in addition to malignant melanoma.\[^{[6,12-20]}\]

In agreement with these reports, the present study has demonstrated a significant positive association between SATB1 overexpression and advanced clinicopathologic parameters of cervical carcinoma including lymph node metastasis and higher FIGO stage. Our results are consistent with those of a single recent study which was conducted by Wang and his colleagues in China on 167 cervical SCC and demonstrated a significant correlation of SATB1 expression with lymph node metastasis and FIGO stage in addition to histologic grade, lymphovascular invasion and recurrence.\[^{[25]}\] Up to our knowledge, no more studies concerning SATB1 expression and clinicopathologic variables in cervical cancer are available in literature so far.

DJ-1 plays a crucial role in tumorigenesis, tumor cell survival, proliferation, invasion and metastasis. There are multiple molecular mechanisms underlying DJ-1 biological effects. DJ-1 upregulates PI3K/AKT/mTOR signaling pathway and its downstream effectors through negative regulation of PTEN tumor suppressor gene expression leading to removal of the inhibitory effect of PTEN on PI3K/AKT/mTOR pathway, thereby promoting cell viability, growth and proliferation.\[^{[9,10]}\]

Recent studies have also shown that DJ-1 promotes tumor cells invasion and migration by activating urokinase plasminogen activator (uPA) system and matrix metalloproteinase-2 (MMP2) through the SRC/ERK pathway.\[^{[21]}\] Moreover, DJ-1 enhances epithelial-mesenchymal transition (EMT) and cell invasion capacity by downregulating E-cadherin, KLF17 and increasing Snail expression.\[^{[7]}\]

Also, DJ-1 has been shown to promote survival of tumor cells by providing them a protection against hypoxia-induced cell death and increasing their adaptation to severe hypoxic stress through several mechanisms including upregulation of AMP-activated protein kinase (AMPK) pathway, negative regulation of p53-dependent pro-apoptotic gene expression programs that are activated under hypoxia and finally through stabilization of hypoxia-inducible factor-1 α (HIF-1α) partly via upregulation of PI3K/AKT/mTOR pathway and partly via inhibition of Von Hippel Lindau (VHL) –induced degradation of HIF-1 α.\[^{[25]}\] Additionally, DJ-1 has been reported to inhibit apoptosis through upregulation of survivin anti-apoptotic gene and suppression of both tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-induced apoptosis and p53-Bax-caspase pathway.\[^{[21,24]}\]

Consistent with these biologic activities, DJ-1 overexpression along with its association with tumor progression and poor outcome has been reported in several malignancies including non-small cell lung carcinoma, laryngeal squamous cell carcinoma as well as gastric, pancreatic, urothelial, breast and endometrial carcinomas.\[^{[7,10,23-26]}\]

In concordance with these reports, the present study demonstrated DJ-1 overexpression in cervical cancer where it was associated with lymph node metastasis. Up to our knowledge, limited data is available in the literature regarding DJ-1 expression in cervical cancer. However, our findings are consistent with a recent Chinese study (its abstract is available online in English) which demonstrated a significant correlation between DJ-1 overexpression and lymph node metastasis as well as higher tumor grade in cervical squamous cell carcinoma.\[^{[27]}\] Otherwise, two more studies have demonstrated significant higher level of DJ-1 expression in cervical carcinoma tissue versus normal cervical tissue which was noted in our study but none of them has studied the relationship between biomarker expression and clinicopathologic variables.\[^{[28,29]}\]

Our findings regarding DJ-1 overexpression in cervical cancer could be supported by the finding that transfection of non-metastatic cancer cell lines by DJ-1 has increased their invasion capacity.\[^{[7]}\] On the contrary, knocking down of DJ-1 by small interfering RNA (siRNA) in breast, endometrial, cervical, pancreatic, and laryngeal carcinoma cell lines has led to impaired cancer cell viability, proliferation, invasion and migration in addition to enhanced sensitivity of tumor cells to chemotherapeutic drugs.\[^{[7,9,21,24,29]}\]

**Conclusion**

The present study has pointed out the possible role of SATB1 and DJ-1 in cervical carcinogenesis as shown by complete absence of their expression in normal cervical tissue along with significant increase in the expression of both biomarkers upon progression from SIL to carcinoma. Also, SATB1 and DJ-1 are shown to be promising potential prognostic biomarkers in cervical carcinoma since their overexpression is correlated with advanced clinicopathologic variables including lymph node metastasis. A significant positive association between SATB1 and DJ-1 immunoreactivity was detected in
investigated cervical carcinomas. Our findings suggest SATB1 and DJ-1 to be promising therapeutic targets for cervical cancer.

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*Corresponding author:
Ashraf Ishak Fawzy Tawadros (Lecturer of pathology) Pathology Department, Faculty of Medicine, Minia University, El Minia, Egypt
Phone: +91 02-01207746686
Email: ash_han2012@yahoo.com

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