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Original Article

Synaptic vesicle protein isoforms (SV2A, SV2B, SV2C): expression in breast cancer and their association with risk factors and metastasis in Mexican women

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Abstract: Breast Cancer (BCa) is a global public health problem in that is one of the main causes of deaths due to cancer in women. Synaptic Vesicle Protein (SV2) is a neuronal protein with three isoforms. Recent research on tumor cells has identified Synaptic Vesicle SV2 receptor isoform A (SV2A) in different types of cancer, such as colon, prostate, and the BCa cell line. The aim of this research was to identify the protein expression of isoforms A (SVA), B (SV2B), and C (SV2C) of the SV2 receptor in the tissues of patients with a diagnosis of BCa, and its relation with clinicopathological factors. Tissues were obtained from patients treated with radical mastectomy, while control tissue was obtained by cosmetic mastoplasty. The technique used to determine the protein expression of SV2 isoforms in these tissues was immunohistochemistry. We found significant SV2A, SV2B, and SV2C overexpression in BCa tissues in comparison with normal breast tissue. A significant association among protein expression with smoking, biomass exposure, and comorbidities was found. Additionally, we observed differences in the expression of these proteins with regard to metastasis. SV2A, SV2B, and SV2C proteins are overexpressed in BCa tissues, and their expression is related with different clinicopathological features in patients with BCa.

Keywords: SV2A, SV2B, SV2C, patients with breast cancer

Introduction

Breast Cancer (BCa) is one of the most common types of cancer in women worldwide [1]. BCa prevalence and mortality have increased in Mexican population in recent years. BCa has become the leading cause of cancer-related mortality in Mexican women since 2006 [2-4]. Synaptic Vesicle Protein 2 (SV2) is an integral membrane glycoprotein [5] and plays an important role in exocytosis and in the secretory process of synaptic [6, 7] and endocrine cells [8, 9]. The following three SV2 isoforms have been described: A; B, and C. SV2A and SV2B protein expression are widely distributed in the nervous system, whereas SV2C protein expression is only observed in a small number of neurons in a few areas of the brain [10-13]. Recent studies have associated SV2 proteins with different tumor types, such as gastrointestinal stromal tumors and pancreatic tumors [14, 15], in prostate cancer-cell lines (inhibiting the growth of LNCaP *in vitro* and *in vivo*) [16, 17] and in BCa cell lines [18, 19]. Despite that SV2 proteins have been identified in cancer, their role is not yet clear; however, different studies have shown that this protein, stimulated by botulinum neurotoxin type A, has been related with apoptosis and less proliferation in different cell types [16, 20, 21]. For this reason, we performed this study in patients with BCa, and we related protein expression in tumor tissues with different

Table 1. Primary antibodies

Antibody	Origin	Catalog	Type
SV2A (R-300)	RABBIT	sc-28955	Polyclonal
SV2B (R-175)	RABBIT	sc-28956	Polyclonal
SV2C (R-300)	RABBIT	sc-28957	Polyclonal

clinicopathological features in Mexican patients with BCa.

Materials and methods

Biological samples

All samples of human mammary carcinomas were obtained from 41 patients with BCa diagnosed at the Pathology Service, Military Specialty Hospital for Women and Neonatology (SEDENA) in Mexico City. Ten normal mammary-gland tissues were obtained for mammary-gland reduction at the SEDENA Service of Plastic Surgery Service, Central Military Hospital. Tissue samples were collected during surgery and frozen at -80°C. Histological classification of carcinomas, as well as the evaluation of non-tumor breast lesions, was performed according to standard diagnostic procedures and confirmed by two Pathologists. Non-tumor samples were those without morphologically detected tumor-cell criteria. This project had the approval of the Hospital Research Ethical Commission (no. SI-378).

Antibodies

An immunohistochemical assay was carried out with primary (see **Table 1**) and secondary antibodies for recognizing SV2A, SV2B, and SV2C human antigens. All antibodies were positive for external controls.

Immunohistochemistry

Immunohistochemical analyses were performed on slides prepared with histological tissues previously fixed with 10% formalin and embedded in paraffin. The slices included on the slides were deparaffinized and heated to unmask antigenic sites, while endogenous peroxidase activity was blocked with 0.03% H_2O_2 in absolute methanol. Tissue sections were incubated overnight at 4°C at a 1:200 dilution of polyclonal antibody against SV2A, SV2B, and SV2C (Santa Cruz Biotechnology, Santa Cruz, CA, USA), respectively, in TRIS solution. Primary antibody was removed and washed twice and repeatedly with TRIS solution; the sections were incubated in a 1:500 dilution of rabbit or goat polyclonal antibody as secondary antibody (Santa Cruz Biotechnology) and were washed twice and repeatedly with TRIS solution. We used the ABC-kit (Vectastain) and counterstained with hematoxylin. All specimens were examined by the Axiovert 200 M Inverted Confocal Microscope (Carl Zeiss, Jena, Germany). Percentage and density of positive cells (brown in color) were determined with a KS-3003.0 Computerized Image Analyzer (Carl Zeiss). Five random fields were examined at a magnification of 40× (total area, 1,584,000 m^2). The positive control of this procedure (brain tissues) is depicted in **Figure 1**.

Statistical analysis

The X^2 test or Fisher exact test was utilized to estimate the association between SV2 proteins and the most relevant risk factors for *BCa*. The Mann-Whitney *U* test was employed to compare means between groups, and the Spearman correlation was applied. Statistical analysis was performed utilizing SPSS ver. 19 for Windows XP statistical software (SPSS UK, Ltd., Woking, UK). $P<0.05$ was regarded as significant.

Results

Tissue samples were collected from Mexican females who ranged in age from 31-87 years and average age at diagnosis of patients with BCa was 58.29±10.9 years. With respect to frequency of exposure to traditional risk factors for BCa, we found that 20.8% of patients consumed tobacco and 16.7% occasionally consumed alcohol. Exposure to biomass was positive in 14.6% of these women, 98.5% of patients had a sedentary lifestyle, and 37.5% had a history of relatives with BCa. The frequency of overweight and obesity was 83.3%, and 14.6% of patients used oral contraceptives. Finally, 97.9% of patients were multiparous when diagnosed with BCa. Estrogen Receptor (ER) was positive in 43.8% of cases, and Progesterone Receptor (PR), in 31.3%. P53 protein was identified in 50% of tumors. The angiogenesis and proliferation Ki67 marker was identified in 43.8%, while HER2 receptor was found in 43.8% of cases. In **Figure 1**, we pres-

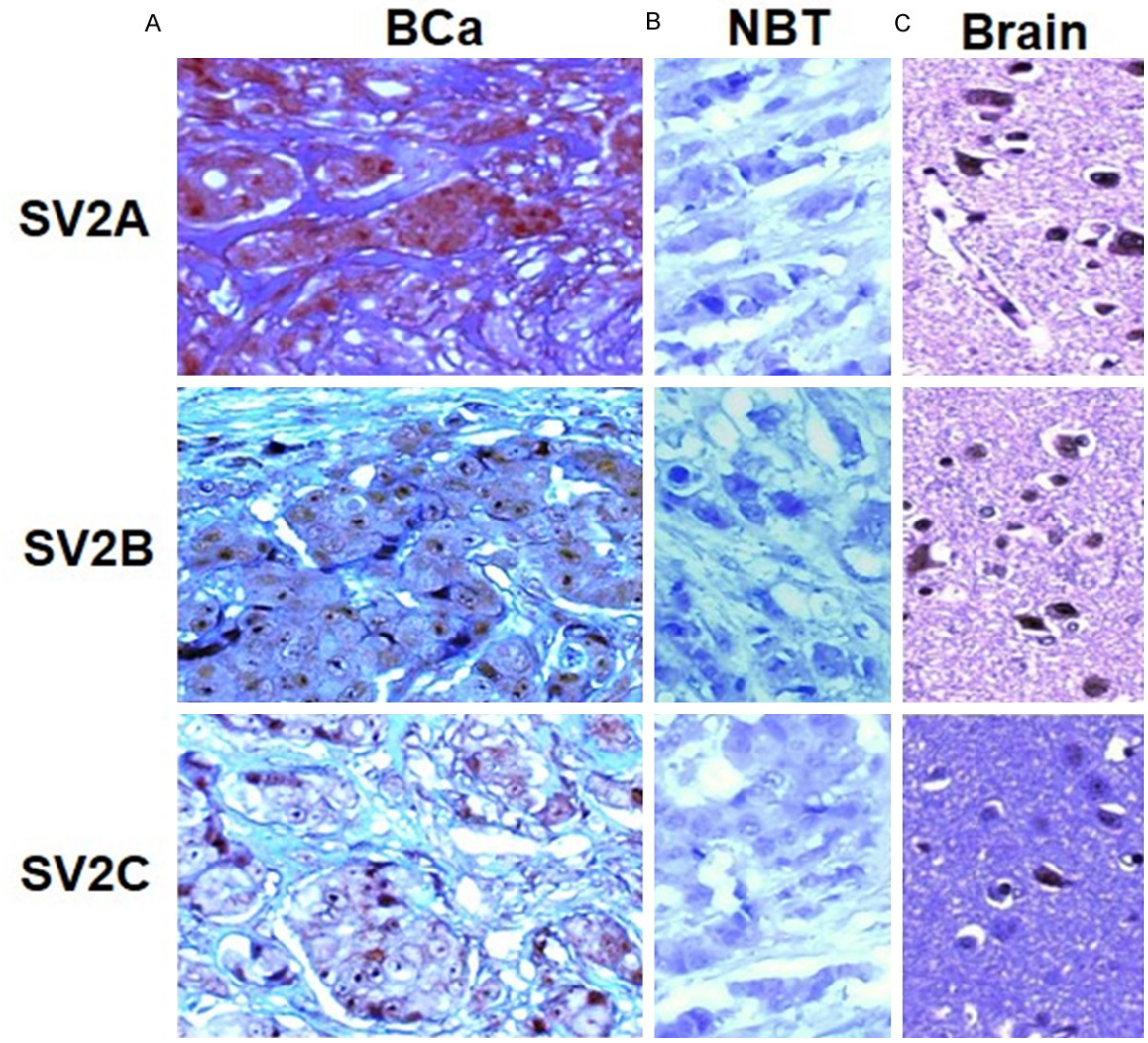

Figure 1. SV2 isoforms (A-C) protein expression in Breast Cancer (BCa), Normal Breast Tissue (NBT), and the human brain. In BCa and NBT groups, immunoreactivity was determined per field (40×).

ent the results of the immunohistochemistry of SV2A, SV2B, and SV2C isoforms performed in BCa and in Normal Breast Tissues (NBT). We can observe that the immunoreactivity was localized in the cytoplasm of tumor cells near the nuclear area. The percentage of isoform A, B, and C immunoreaction are illustrated in **Figure 2**. The three isoforms revealed high protein expression in BCa tissues compared with NBT; however, the only significant difference ($P<0.05$) was found in the SV2A isoform. In **Table 2**, we can observe the result of the relationship between risk factors for BCA and the result of the expression of SV2 isoform receptor. All three isoforms were associated with biomass exposure and comorbidity. The SV2A isoform was also related with tobacco consumption, while the SV2C isoform was associated with a familial history of BCa ($P<0.05$), respectively). **Table 3** sets forth the average percentage of the immunoreactivity of isoforms relative to the three patients' positive findings in relation to the positive Estrogen Receptor (ER+), the positive Progesterone Receptor (PR+), and HER2+. **Table 4** demonstrates that the average percentage of immunoreactivity of SV2A and SV2B isoforms is higher in patients with metastases ($P<0.05$). It is noteworthy that the C isoform correlated with cholesterol levels (Rho = 0.83; $P = 0.005$).

Discussion

SV2-A, -B, and -C protein expression was found higher in BCa tissues vs. NBT, but only the SV2

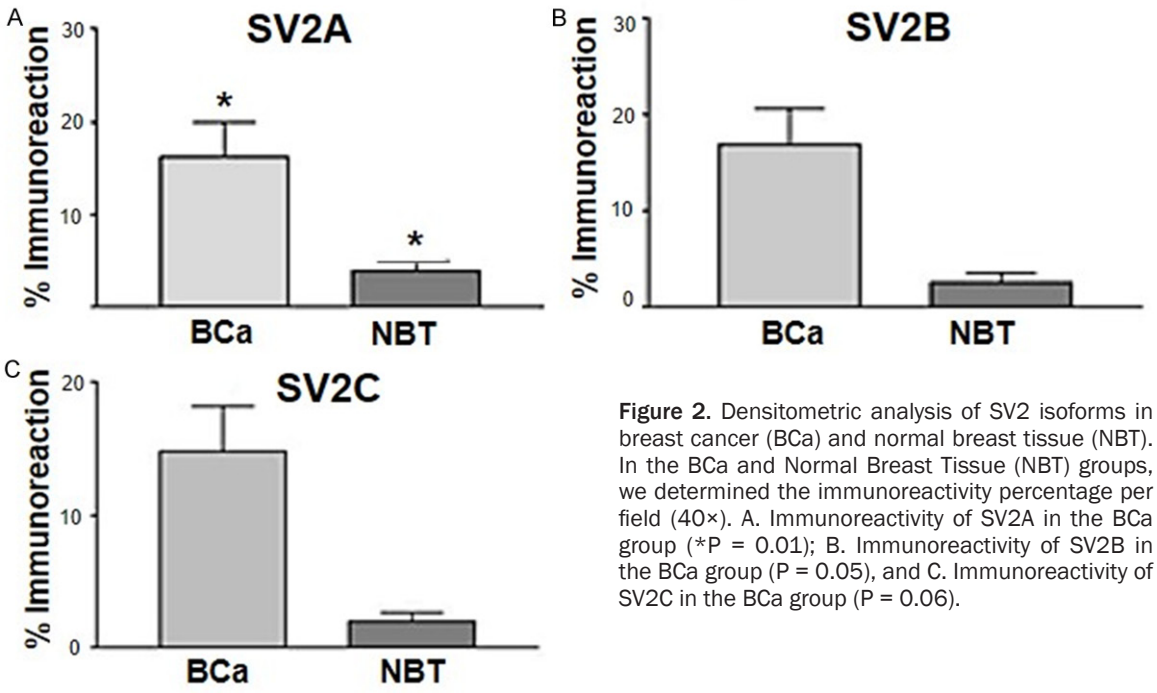

Figure 2. Densitometric analysis of SV2 isoforms in breast cancer (BCa) and normal breast tissue (NBT). In the BCa and Normal Breast Tissue (NBT) groups, we determined the immunoreactivity percentage per field (40×). A. Immunoreactivity of SV2A in the BCa group (*P = 0.01); B. Immunoreactivity of SV2B in the BCa group (P = 0.05), and C. Immunoreactivity of SV2C in the BCa group (P = 0.06).

Table 2. Breast cancer (BCa) risk factors in relation to SV2 isoforms

	SV2 Isoforms		
Risk factor	SV2A	SV2B	SV2C
Obesity	P = 0.09	P = 0.04	NS
Tobacco consumption	P = 0.04	NS	NS
Alcohol consumption	NS	NS	P = 0.07
Biomass exposure	P = 0.01	P = 0.01	P = 0.009
Familial history of BCa	NS	P = 0.09	P = 0.04
Comorbidity	P = 0.01	P = 0.01	P = 0.04
Triple negative	P = 0.04	NS*	P = 0.01
Triple positive	P = 0.03	NS	NS
CD34+	P = 0.01	P = 0.01	P = 0.07

*NS = Not Significant.

Table 3. SV2 isoform immunoreaction (%) related with triple positive (ER+/PR+/HER2+) in patients with BCa

(ER+/PR+/HER2) in patients with Breast Cancer (BCa)			
	Triple Positive		
	Yes (n = 10)	No (n = 20)	P
SV2A	401.92±2.23	110.85±1.35	0.004
SV2B	361.4±1.95	129.64±1.52	0.01
SV2C	411.52±1.95	89.13±9.71	0.001

isoform A exhibited a statistical difference with respect to healthy tissue. This finding is similar to our protein expression report on T47D, MDA-MB-231, and SKBR BCa cell lines and on MC-10A (a non-BCa cell line) with variability associated with different types of BCa cell lines and the SV2 isoform [18, 19]. Immunoreactivity was found in the cytoplasmatic region very near the nuclear area in the tumor cells; this is very similar to other studies on BCa cell lines and on Prostate Cancer (PC) cell lines and tissues of brain tumors [7, 17-19]; different authors have considered SV2A as a neuroendocrine-type marker in healthy and tumor tissues [5], because this protein was found in different types of neuroendocrine (non-tumor and tumoral) tissues with a different intensity of expression related with the organ and the specific area; however, it has not been found in exocrine tissue [5]. The frequency of SV2-immunoreactive cells in neuroendocrine tumors was related with other neuronal proteins, such as chromogranin A and synaptophysin, except in hindgut carcinoids, where SV2 had higher expression compared with chromogranin A and synaptophysin in the tumor cells displayed, and SV2 exhibited the same pattern in midgut carcinoids, pituitary neuroendocrine tumors, and medullary thyroid carcinoma. Poorly differentiated endocrine carcinomas lack large, dense core vesicle markers (chromogranin A), while they widely express synaptophysin (small, syn-

Table 4. SV2 isoform immunoreaction (density) related with metastasis in patients with breast cancer (BCa)

	Metastasis		
	Yes (n = 9)	No (n = 16)	P
SV2A	114.11±8.43	106.94±15.96	0.03
SV2B	114.89±6.99	104.06±13.47	0.02
SV2C	116.11±3.94	104.38±16.23	0.07

aptic-like vesicles) and cytosol endocrine markers [5, 22]. In this tumor type, Schmitt-Gräff and coauthors mentioned that low levels of chromogranin A and synaptobrevin are common in high-grade malignant carcinomas, which may even lose these proteins. In contrast, the protein expression of synaptophysin and SyNaptosomal-Associated Protein 25 (SNAP25) is higher, even in small-cell carcinomas. These authors concluded that the immunohistochemical diagnosis of high-grade malignant neuroendocrine tumors should be based mainly on the identification of neuron-like Small Synaptic Vesicles (SSV) and SNAP (Soluble NSF Attachment Protein Receptor (SNARE) proteins, especially synaptophysin and SNAP25. The authors also noted that these proteins could be employed as marker molecules, valuable tools for the diagnosis and classification of neuroendocrine tumors [22]. On the other hand, Jakobsen et al. reported that SV2 was expressed in neuroendocrine tumors of the gastrointestinal tract and pancreas, but not in non-endocrine tumors [15]. There are few studies in which SV2 proteins are related with clinicopathological features. In brain tumors, SV2A expression has been identified in neocortical specimens of patients with focal malformations of cortical development [7, 23]. de Groot and coauthors stated in their report that reduction in SV2A expression might have been expected in the epileptogenic zone of the lesions (peritumoral cortex in the case of glial tumors and the tumor itself in the case of glioneuronal tumors); these authors noted that the functioning mechanisms of SV2A are far from being completely understood, and that reduction in SV2A expression appears to lead to abnormal neurotransmission and to the development of seizures [7, 24, 25]. The relationship between SV2A expression and the efficacy of LEV etiracetam (LEV) is not clear either, but recently, SV2A has been identified as the binding site for LEV and its analogs, Brivaracetam and Selectracetam, also suggesting that SV2A is involved in neuronal (hyper-excitability [7, 26-30]. We found that three SV2 isoforms (protein expression) were related with BCa risk factors, including high levels of cholesterol, hormone immunohistochemical markers, and metastasis. Our findings are interesting in that according to this viewpoint, the pathological process of tumors could be related with tumor Extracellular Vesicles (EV), also known as oncosomes, exosomes, or microvesicles. The latter are associated with cancer because they may act as regulators of cell growth, clonogenicity, angiogenesis, thrombosis, and reciprocal tumor-stromal interactions [31]. The molecular content of EV appears to be highly dependent on the source and conditions of the system at the time of vesicle biogenesis [32, 33]; EV were found to transfer surface-bound receptors and their ligands, proteins, genetic material, infectious particles, prions, and probably even organelles among cells and in addition, even growth factors [33]. The exact mechanism underlying the formation of EV has not been clearly elucidated to date. We could think that different types of synaptic vesicle protein are involved, such as SV2 protein, mainly SV2A, because neuroendocrine mechanisms of secretion comprise the most effective and specialized system. It may be that, for these aspects, transdifferentiation in neuronal-glial cells has been described in cancer [34, 35] with the aim of promoting a neuroendocrine-like secretion system related with EV. However, these hypotheses require further and specific studies.

Conclusions

In conclusion, we found, to our knowledge for the first time, that SV2 isoforms are related with BCa in Mexican women. This study showed an association between SV2 isoforms and different risk factors and histological and malignancy features. We suggest that SV2 isoforms could be important for different trafficking mechanisms in the formation of specialized oncosomes, but we need to perform further studies to clarify their function.

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Disclosure of conflict of interest

None.

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