Strong prognostic value of SLAMF7 protein expression in patients with lymph node-positive breast cancer

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Abstract. Breast cancer (BC) in women is the second most commonly diagnosed type of cancer worldwide, and the leading cause of cancer-related mortality among women. To date, surgery is the main treatment option, often combined with other (neo)adjuvant therapeutic modalities to treat this malignancy and prevent relapse. Despite the invasive aspects of the majority of these therapeutic interventions and their associated side-effects, these treatments are still unable to effectively cure this disease and prevent relapse. Thus, there is an urgent need for the identification of more relevant biomarkers for more effective theranostics. Signaling lymphocytic activation molecule F7 (SLAMF7) is a glycosylated cell surface protein that plays a critical role in immune cell functions under both healthy conditions and in cancer. It is specifically targeted by elotuzumab for the treatment of multiple myeloma. The present retrospective study aimed to investigate the expression patterns of SLAMF7 and evaluate its associations with clinicopathological features, including the survival outcomes of patients with BC. The protein expression of SLAMF7 in BC was investigated in 278 lymph node-positive formalin-fixed and paraffin-embedded (FFPE) tissue blocks using tissue microarray and immunohistochemistry techniques. The results revealed a significant association between cytoplasmic SLAMF7 protein expression and several clinicopathological parameters, particularly age at diagnosis ($P<0.007$), tumor invasion ($P<0.008$) and vascular invasion ($P=0.05$). Kaplan-Meier analysis revealed that the overexpression of SLAMF7 was a strong positive prognosticator of both disease-free and disease-specific survival in the patients with BC (log-rank $P=0.001$ and $P=0.008$, respectively). This suggests that patients with SLAMF7 protein expression have a higher survival rate and a lower recurrence rate. On the whole, the present study demonstrated that a weak or no SLAMF7 expression was a powerful prognosticator of poor survival outcomes associated with both tumor and vascular invasion. Therefore, elotuzumab (as SLAMF7monoclonal antibody therapy) may be a promising option for targeted therapy worthy of clinical testing in patients with BC.

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Introduction

Female breast cancer (BC) is the second most diagnosed malignancy worldwide (1), accounting for over two million cases each year in the USA (2). It is also the cause of 1 in 6 deaths due to all cancer types (1). The incidence rate of BC is continually increasing by ~0.5% per year (3). According to the 2020 GLOBOCAN data, the age-standardized rates for both the incidence and mortality of BC in Saudi women were 28.8 and 8.4%, respectively (4). However, these rates continue to increase each year (3). Notably, the incidence numbers of BC in Saudi Arabia increased by 186% from 2004 to 2016 (5). It is considered that this steady increase in BC cases, particularly in Saudi Arabia, may be attributed to several factors related to lack of awareness, delayed diagnosis, aging populations and the unhealthy lifestyle choices related to low levels of physical activity, poor dietary habits and smoking (6,7).

To date, the main treatment modality implemented for patients with BC is surgery followed by chemotherapy, radiotherapy, hormonal therapy and/or immuno-/targeted therapy to prevent the recurrence of the disease (8). Despite the invasive aspects of the majority of these therapeutic interventions and their associated side effects, these treatments are still not sufficient to effectively cure this disease and prevent relapse. For instance, chemotherapy is a harmful procedure that has been shown to induce drug resistance in cancer cells. Moreover, hormonal therapy may lead to bone loss and thus, to frailty and fractures (9,10).

Several laudable studies have been performed to investigate BC and identify potential biomarkers. Only a few of these therapeutic targets have already been studied in clinical trials to evaluate the response to treatment and disease progression, such as estrogen receptor (ER) (11), progesterone receptor (PR) (12), human epidermal growth factor receptor 2 (HER2) (13), nuclear protein Ki67 (Ki67) (14), urokinase-type plasminogen activator (15), tumor protein p53 (p53) (16),

cyclin E (17) and neuropeptide substance P (18). Recent developments in cancer immunotherapy hold promise as possible treatment options for a variety of cancer types, including BC (19). For instance, programmed death-ligand 1 was the first immune checkpoint blockade drug approved by the US Food and Drug Administration (FDA) for the treatment of patients with triple-negative metastatic BC in 2019 (20). Other types of immunotherapies are currently available, including checkpoint blockade, adoptive cellular therapy and cancer vaccinology (21). Thus far, targeted anticancer therapies are not yet able to cure BC as single agents, which entails their combination with chemotherapy and/or radiotherapy to obtain improved survival outcomes. Furthermore, they were unable to provide reduced cytotoxicity on non-target tissues and to eradicate the cancer stem cells in the tumor mass (22,23). These hurdles to deliver effective and personalized BC therapeutics can be explained by the molecular pathophysiology of this aggressive tumor that remains poorly understood.

BC is a heterogeneous disease with several clinical subtypes, cancer stem cells niches, molecular signatures and oncologic signaling pathways. This complexity is further amplified by additional contributing factors, including late-stage detection, an intricate network of crosstalks and signaling pathways, drug resistance and a higher recurrence of the disease. These challenges combined with the heavy burden of this malignancy on patients, their families and the healthcare system, are urging scientists to perform research focusing on the identification of effective diagnostic biomarkers that may pave the way towards better theranostics. In this context, signaling lymphocytic activation molecule F7 (SLAMF7; previously known as CS1, CD2 subset1, CRACC and CD319) is a glycosylated cell surface protein that has been found to play a critical role in immune cell functions (24). This transmembrane receptor is located on the long arm of chromosome 1 (1q23.3) and is a member of the signaling lymphocyte activation molecule SLAM family (25). Studies have indicated that SLAMF7 has a unique pattern that is ubiquitously expressed in several cancer types, while its expression in normal cells is restricted to selected immune cell types, mainly natural killer (NK) cells and mature dendritic cells, but not on normal hematopoietic stem cells or other lymphocytes/normal tissues (24,26,27). These properties have made SLAMF7 a promising therapeutic target given its ability to activate NK cells specifically in tumor cells and boost their immunogenic cell death (phagocytosis, apoptosis, immune cells activation, cell signaling and gene expression), particularly when triggered by an antibody or a natural ligand (28-30). This SLAMF7-driven interaction has been shown to result in an increase in NK cytotoxicity, macrophage super activation and an inflammatory cytokine storm in rheumatoid arthritis (31,32). Of note, the monoclonal antibody, elotuzumab, has been demonstrated to specifically target SLAMF7, which is abundantly expressed on multiple myeloma (MM) cells. It has been shown to attract NK cells and to exert anticancer effects via antibody-dependent cell-mediated cytotoxicity (ADCC) in MM cells (26,33,34).

In solid tumors, SLAMF7 has recently been shown to be expressed in colorectal cancer cells (35-37), ovarian and cervical cancers (38,39), as well as in liver cancer cell lines (40) and multiple murine cancer models (41). The promise of SLAMF7 as an immunotherapeutic target with possible clinical outcomes in patients with various types of tumors has rendered it the focus of several studies (as aforementioned).

To the best of our knowledge, the present study is the first to investigate the expression of SLAMF7 in BC. This study aimed to assess the protein expression levels of SLAMF7 and its correlation with clinicopathological features of BC patients to evaluate its potential value as a prognosticator of BC.

Patients and methods

Patient series. The present retrospective study included 278 lymph node-positive cases from 730 formalin-fixed and paraffin-embedded (FFPE) blocks of primary BC samples retrieved from the Pathology Department, King Abdulaziz University, Jeddah, Saudi Arabia covering the period from January 1995 to December 2014. The inclusion criteria included all available primary BC FFPE tissues collected from consenting patients who had full annotated clinicopathological data, regardless of their associated systemic diseases status. Only primary BC cases with unavailable FFPE sample and/or annotation data were excluded. FFPE blocks were processed routinely with hematoxylin and eosin for the evaluation of histopathological features, histological grading and the TNM-based staging of the tumor. The patient clinicopathological parameters were obtained from their medical records and are summarized in Table I.

Treatment and follow-up. All (100%) consenting patients with BC were subjected to surgery, i.e., lumpectomy, radical or modified radical mastectomy with axillary clearance. Post-operative early adjuvant systemic therapy in the form of chemotherapy, radiotherapy and hormonal therapy was administered to 77, 60 and 25% of the patients, respectively. Following treatment, the patients were observed at 6-12-month intervals until mortality or the end of the follow-up period in June, 2016 (date of data collection). The mean follow-up time for the whole series was 37 months (range, 1-252 months). During the follow-up, patients were subjected to repeated clinical examinations and bone isotope scan, chest and abdominal-pelvic CAT scans were performed whenever needed. In most instances, the causes of death were obvious on clinical grounds alone. The autopsy was not performed in any case.

Tissue microarray (TMA) and immunohistochemistry (IHC). A total of 730 BC FFPE blocks were used to construct a TMA as previously described (42). TMA slides were utilized for the evaluation of SLAMF7 expression pattern using IHC with anti-SLAMF7/CS1 primary antibody (1:100 dilution; cat. no. ab202840, Abcam). Anti-SLAMF7 primary antibody was applied manually. Staining and processing were performed as previously described (43). Briefly, a fully automated protocol was designed to include deparaffinization with EZ Prep (Ventana Medical Systems, Inc.; Roche Diagnostics) at 75˚C and incubation with the anti-SLAMF7/CS1 primary antibody for 1 h at 37˚C. Staining and processing were thereafter performed with the ready-to-use iView DAB Detection kit (Ventana Medical Systems, Inc.; Roche Diagnostics) which contains a pre-diluted secondary antibody solution that is processed by the automated staining system (Ventana Medical

Table I. Association between SLAMF7 protein expression patterns and the clinicopathological features of patients with breast cancer.

Features	No. of cases	SLAMF7 protein expression (Low) (%)	SLAMF7 protein expression (High) (%)	P-value
Age, years				0.007[a]
<50	143 (51.4%)	105 (73)	38 (27)	
>50	134 (48.2%)	116 (87)	18 (13)	
Missed data	1 (0.4%)			
Tumor invasion				0.008[a]
Negative	3 (1.1%)	0 (0)	3 (100)	
Positive	258 (92.8%)	209 (81)	49 (19)	
Missed data	17 (6.1%)			
ER and PR hormonal status				0.912
ER^-, PR^-	72 (25.9%)	59 (82)	13 (18)	
ER^+, PR^+	126 (45.3%)	104 (83)	22 (17)	
Missed data	80 (28.8)			
HER2 protein status				0.255
Negative	150 (54%)	118 (84)	23 (16)	
Positive	79 (28.4%)	70 (78)	20 (22)	
Borderline	13 (4.7)			
Missed data	36 (12.9%)			
ER, PR and HER2 status				0.579
Triple-negative	30 (10.8%)	26 (87)	4 (13)	
Triple-positive	42 (15.1%)	33 (79)	9 (21)	
Missed data	206 (74.1%)			
Vascular invasion				0.050
Negative	84 (30.2%)	64 (76)	20 (24)	
Positive	126 (45.3%)	109 (86)	17 (14)	
Missed data	68 (24.5%)			
Tumor margin				0.713
Negative	222 (79.9%)	182 (82)	40 (18)	
Positive	29 (10.4%)	23 (79)	6 (21)	
Missed data	27 (9.7%)			
Tumor size, cm				0.298
0-3	76 (27.3%)	56 (74)	20 (26)	
3-6	136 (48.9%)	112 (82)	24 (18)	
>7	40 (14.4%)	33 (83)	7 (17)	
Missed data	26 (9.4%)			
Tumor grade				0.844
Grade 1	34 (12.2%)	27 (79)	7 (21)	
Grade 2	135 (48.6%)	110 (82)	25 (18)	
Grade 3	81 (29.1%)	64 (79)	17 (21)	
Missed data	28 (10.1%)			
Histopathological type				0.466
Invasive ductal	258 (92.8%)	207 (80)	51 (20)	
Other	18 (6.5%)	13 (72)	5 (28)	
Missed data	2 (0.7%)			
Disease recurrence				0.542
Yes	40 (14.4%)	34 (85)	6 (15)	
No	112 (40.3%)	90 (80)	22 (20)	
Missed data	126 (45.3%)			

Table I. Continued.

Features	No. of cases	SLAMF7 protein expression (Low) (%)	SLAMF7 protein expression (High) (%)	P-value
Status at end point				0.338
Succumbed to the disease	25 (9%)	18 (72)	7 (28)	
Alive	66 (23.7%)	53 (80)	13 (20)	
Missed data	187 (67.3%)			

Data were analyzed using Fisher's exact text. [a]P<0.05. SLAMF7, signaling lymphocytic activation molecule F7.

Systems, Inc.; Roche Diagnostics) Ventana BenchMark XT for 1 h at 37˚C. Counterstaining was performed using hematoxylin II (Ventana Medical Systems, Inc.; Roche Diagnostics) at room temperature for 4 min and Bluing Reagent (Ventana Medical Systems, Inc.; Roche Diagnostics) for 4 min. The stained TMA slides were washed with water and mild detergent followed by 3 min of several successive immersions into alcohol buffer at increasing concentrations (70, 95 and 100%). Tissue-Tek glass mounting medium was applied to each slide and covered with a glass coverslip.

Evaluation of SLAMF7 staining intensity. The expression of SLAMF7 in the tumor tissue was assessed in a manner blinded to the clinical data using a Nikon light microscope (Model no. 6132, Nikon Corporation) at a magnification of x40. The tumor cells which exhibited cytoplasmic staining were graded into four categories as follows: 0, Negative, no detectable staining; 1+, weak, yet detectable staining; 2+, moderate, clearly positive yet still weak; 3+, heavy staining, intense. As previously described (44,45), the cytoplasmic index score was calculated where both the intensity of the staining and the fraction of positively stained cells were taken into account using the following formula: I=0 x f0 + 1 x f1 + 2 x f2 + 3 x f3, where (I) is the staining index and (f0-f3) are the fractions of the cells showing a defined level of staining intensity (from 0 to +3). Theoretically, the index scores could vary between 0 and 300. The expression patterns were imaged and digitized using a Coolsnap Pro Color camera and ImagePro® Plus software (Media Cybernetics, Inc.).

Statistical analysis. Fischer's exact test was used to assess the significance of the association between different categorical variables. Univariate survival analysis for the outcome measure [disease-specific survival (DSS) and disease-free survival (DFS)] was based on the Kaplan-Meier method, with the log-rank (Mantel-Cox) comparison test. Additionally, Cox regression multivariate analysis was performed to assess the possible independent prognostic impact of SLAMF7 protein expression in relation to the age, lymph node status, tumor grade and histological type of the patients. In all tests, a value of P<0.05 was considered to indicate a statistically significant difference. SPSS® (IBM Corp.) software packages (PASW Statistics for Windows, version 19) were used to perform all statistical analyses.

In silico analysis of SLAMF7 mRNA expression. To further validate the findings of the present retrospective study that assessed the SLAMF protein expression in BC, transcription data from The Cancer Genome Atlas (TCGA) were analyzed using the freely available web application, The University of ALabama at Birmingham CANcer data analysis Portal (UALCAN; available at: http://ualcan.path.uab.edu/analysis.html) (46) and the online multi-omic exploration tool of the University of California, Santa Cruz (UCSC Xena; available at: https://xena.ucsc.edu/#overview) (47). Using the TCGA data repository, which is a comprehensive, user-friendly and interactive web resource allowing graphical and statistical analyses of cancer OMICS data, *SLAMF7* mRNA expression in BC was then analyzed and compared with normal breast tissues as a control (available from the same platform) using Student's t-test (P<0.05 was considered to indicate a statistically significant difference).

Results

Expression profile of SLAMF7 in primary BC samples. The results revealed that the cellular localization of SLMAF7 protein expression was mainly cytoplasmic in the primary BC samples, as well as in the lymph node-positive cases. It was found that ~20% of the primary samples exhibited moderate/strong (high) expression patterns, while the majority of the samples (80%) had either negative or weak (low) expression profiles (Fig. 1A-E). On the other hand, ~70% of the cancerous tissues in the lymph node-positive samples exhibited a high cytoplasmic expression (2+, 3+) while 30% of the samples exhibited low cytoplasmic expression patterns (0, 1+) (data not shown). The cytoplasmic expression patterns of 278 lymph node-positive primary BC cases are illustrated in Fig. 1. Of note, a perinuclear-like staining was observed. However, it was uncommon and difficult to confirm.

Association of SLAMF7 protein expression patterns with clinicopathological features. The association of cytoplasmic SLAMF7 protein expression in lymph node-positive BC with the patient clinicopathological characteristics using different cut-off values revealed that the cut-off value for low (0, 1+) SLAMF7 protein expression compared to high (2+, 3+) SLAMF7 protein expression (low expression vs. high expression) was the strongest discriminator. Based on the aforementioned discriminator, the results revealed that there were significant associations between

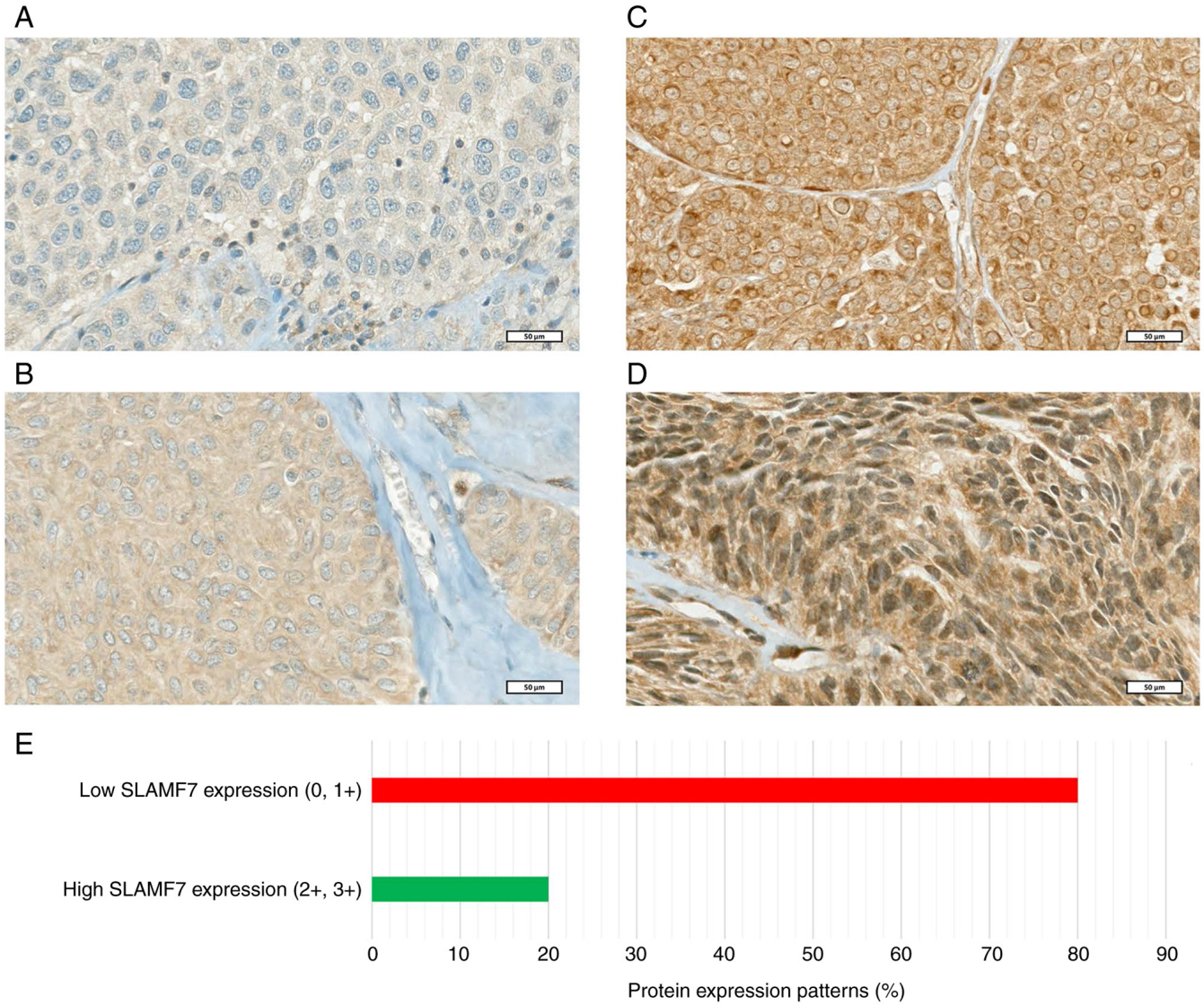

Figure 1. Cytoplasmic expression patterns of signaling lymphocytic activation molecule F7 in primary BC tissues, as shown using immunohistochemical staining. (A) Negative (0) cytoplasmic expression, (B) weak (1+) cytoplasmic expression, (C) moderate (2+) cytoplasmic expression, (D) strong (3+) cytoplasmic expression, (E) distribution of low (0, 1+) vs. high (2+, 3+) protein expression of SLAMF7 among primary BC tissues of the studied cohort. BC, breast cancer.

the cytoplasmic SLAMF7 protein expression profile and the age of the patients at diagnosis, in that the proportion of primary BC tissues with higher SLAMF7 protein expression was greater in younger patients (<50 years; 27%) compared with that in older patients (>50 years; 13%) (P<0.007; Table I). In addition, a significant association was found between the SLAMF7 expression profile and tumor invasion. BC tissues with a high invasive characteristic had a lower SLAMF7 protein expression than less invasive tumors (P<0.008; Table I).

The same tendency was observed between the SLAMF7 protein expression patterns and vascular invasion. Indeed, tumors with highly vascular invasive cells exhibited a lower SLAMF7 expression pattern than those with low vascular invasion (P=0.05). However, the other clinicopathological features did not exhibit any significant associations with the SLAMF7 protein expression profiles, including the hormonal and HER2 protein status (P=0.9 and P=0.2, respectively), as well as tumor grade (P=0.8), tumor margin (P=0.7) and tumor size (P=0.2) (Table I).

Association of SLAMF7 protein expression patterns with survival outcomes. In Kaplan-Meier analysis, the tier two cut-off [no expression (0) vs. expression (1+, 2+ and 3+)] was the strongest discriminator. Using this cut-off, survival analysis revealed that patients with BC with positive SLAMF7 protein expression patterns in their lymph node positive tissues (1+, 2+ and 3+) had a lower relapse rate (DFS) than those without SLAMF7 expression profiles. For example, after 5 years of follow-up, all patients with lymph node-positive BC without SLAMF7 expression (100%) exhibited disease recurrence, compared with a recurrence rate of only 40% in the lymph nodes of with BC with a positive SLAMF7 protein expression (P<0.001, log-rank; Fig. 2).

The assessment of DSS using the same cut-off points [negative (0) vs. positive (1+, 2+ and 3+)] also revealed a significant association. In fact, patients with lymph node-positive BC positive for SLAMF7 protein expression survived for a longer period of time. After 5 years of follow-up, ~30% of patients with BC with lymph node-positive tumors with a positive

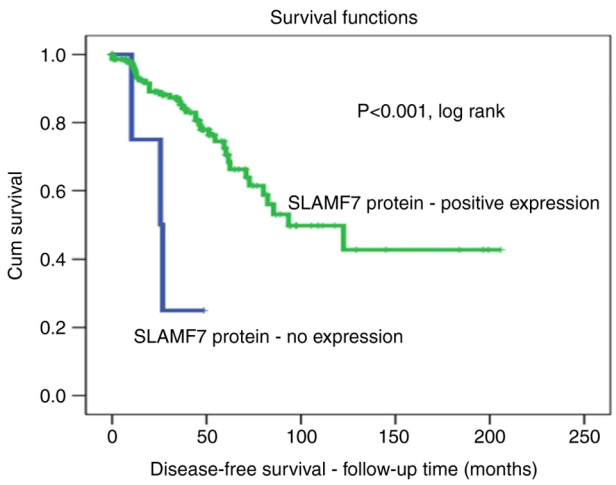

Figure 2. Cytoplasmic SLAMF7 expression patterns in the primary lymph node-positive breast cancer cohort using the cut-off [negative (0) vs. positive (1+, 2+ and 3+)] as a determinant of disease-free survival in univariate (Kaplan-Meier) analysis (P<0.001, log-rank test). SLAMF7, signaling lymphocytic activation molecule F7.

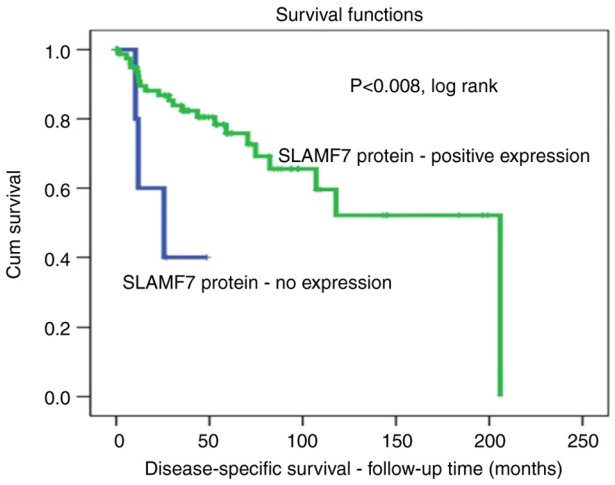

Figure 3. Cytoplasmic SLAMF7 expression patterns in the primary lymph node-positive breast cancer cohort using the cut-off [negative (0) vs. positive (1+, 2+ and 3+)] as a determinant of disease-specific survival in univariate (Kaplan-Meier) analysis (P<0.008, log-rank test). SLAMF7, signaling lymphocytic activation molecule F7.

SLAMF7 expression died compared to a 100% death rate in those without a SLAMF7 expression pattern (P<0.008, log-rank; Fig. 3).

Multivariate Cox regression analysis revealed that the SLAMF7 expression profile (low, 0 and 1+; vs. high, 2+ and 3+) was not an independent factor for a poor DFS and DSS in relation to patient age, lymph node status, tumor grade and vascular invasion (Table II).

SLAMF7 mRNA expression. The *in silico* analysis of *SLAMF7* mRNA expression available in the freely available UCSC Xena or UALCAN transcriptomic databases confirmed that the *SLAMF7* transcript was expressed in the breast invasive carcinoma cohort. Using the Student's t-test, the expression of this mRNA was shown to be higher than that in normal breast tissues according to the UALCAN database (P<0.001; Fig. 4).

An overview of the main molecular, cellular and signaling functions of SLAMF7 as regards its role in the immune system, as well as in other tissues is presented in Fig. 5.

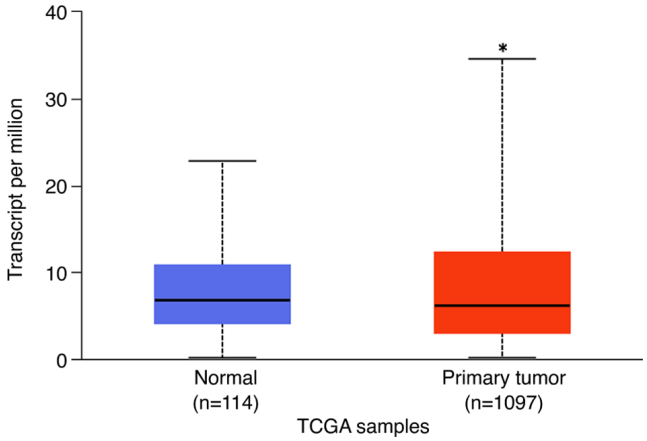

Figure 4. Student's t-test comparison between the number of signaling lymphocytic activation molecule F7 transcripts in breast invasive cancer compared to normal breast tissue according to the UALCAN database. *P<0.001 vs. normal. TCGA, The Cancer Genome Atlas.

Discussion

BC remains a major health concern and a very common cause of cancer-related mortality among women worldwide, with an inherent complexity and molecular heterogeneity (48,49). Moreover, the current treatment modalities for BC are based on histopathological features, such as age, stage, grade, tumor size and receptor status (50). However, patients with BC with similar conditions and diagnoses may have different prognoses, responses to treatment and disease courses when treated with the same therapeutic regimen. This inherent complexity is due to different morphological, pathophysiological, clinical and environmental characteristics (51). In the post-genomic era, great efforts have been made to overcome this heterogeneity of BC and to further elucidate this complexity. In addition to ER, PR and HER2 receptors, other promising biomarkers have been proposed to further elucidate the molecular heterogeneity of BC (52). Since the majority of tumors are no longer considered as a single disease with predefined molecular features, the identification of more relevant clinical and molecular features of BC is urgently required in order to identify therapeutic targets and define pathways of disease progression leading to an earlier diagnosis, better prognosis and more precise therapeutics (53).

Multiomics approaches have led to substantial progress being made in the accurate molecular stratification of BC into different subtypes to identify more appropriate/precise therapeutic options (54-56). However, much still remains to be done before precision theranostics for BC can be achieved, and thus more molecular biomarkers are required for this aggressive disease.

In this context, SLAMF7 is expressed in selected immune cells and functions as an inhibitor in monocytes to modulate pro-inflammatory immune responses (57). Chen *et al* (30) recently discovered that SLAMF7 is required for the phagocytosis of hematopoietic malignancy cells, which is crucial

Table II. Cox regression analysis of the prognostic values of cytoplasmic SLAMF7 protein expression, age at diagnosis, lymph node status, grade and tumor vascular invasion in association with the survival of patients with breast cancer.

Parameter	P-value	SE value	Relative risk	95% CI
SLAMF7	0.58	0.431	1.270	0.338-1.830
Age at diagnosis	0.12	0.425	0.512	0.848-4.490
Lymph node status	0.10	0.453	0.478	0.861-5.077
Tumor grade	0.42	0.307	1.282	0.428-1.423
Tumor vascular invasion	0.060	0.489	2.50	0.154-1.043

SLAMF7, signaling lymphocytic activation molecule F7.

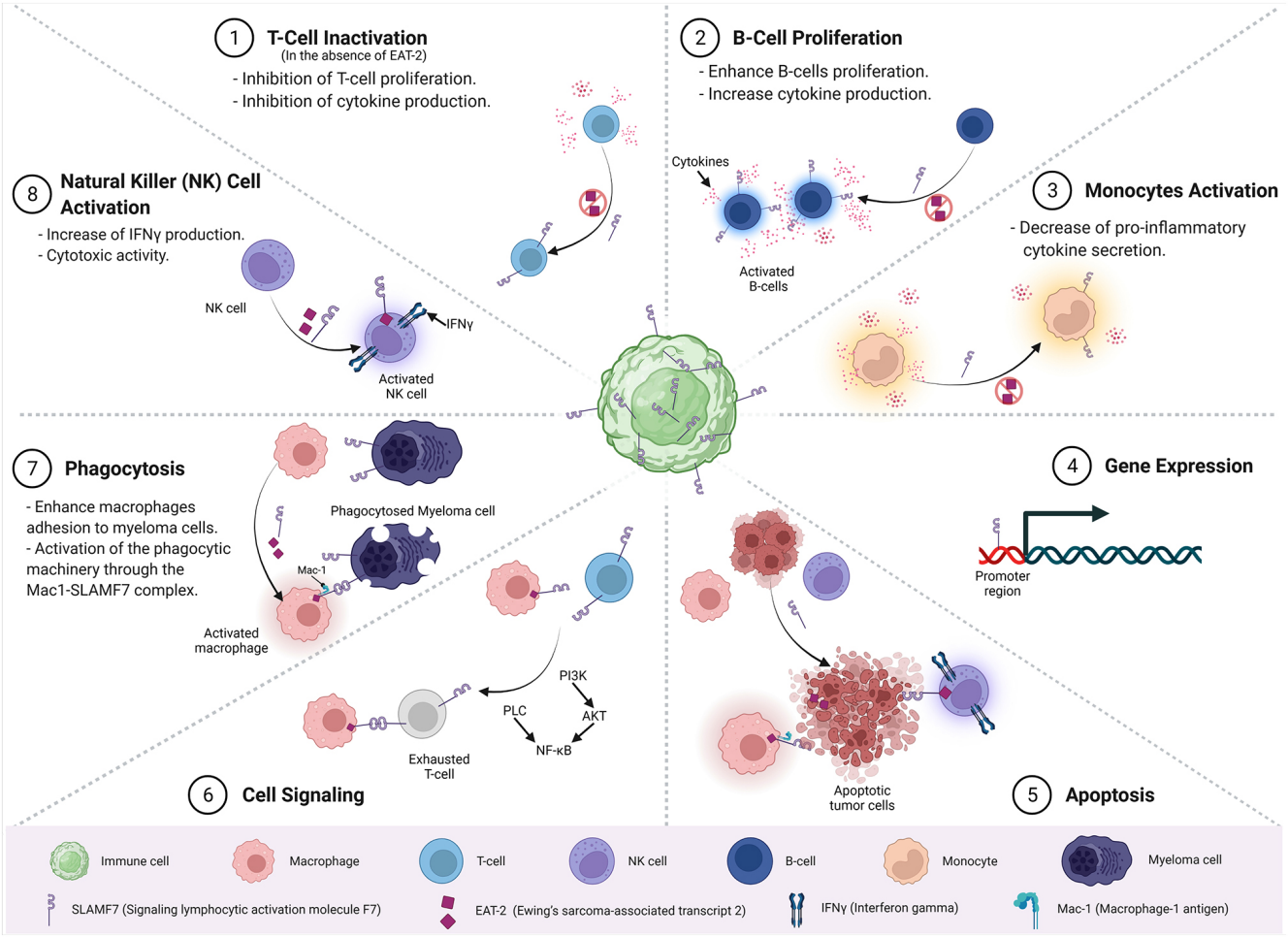

Figure 5. An overview of the main molecular, cellular and signaling functions of SLAMF7 as regards its involvement in the immune system, as well as in other tissues. SLAMF7, signaling lymphocytic activation molecule F7.

for cancer treatment. Notably, elotuzumab is the targeted drug that specifically targets SLAMF7 in patients with myeloma via ADCC (26,33,34).

Although SLAMF7 has been reported to be rarely expressed in normal tissues, it is expressed in certain types of cancer, such as colorectal cancer and multiple myeloma (26,58). In addition, analysis of data from TCGA has demonstrated that SLAMF7 is also expressed in certain solid tumors at either the RNA and/or protein level (59-61); however, no specific study has yet been conducted using BC tissue, at least to the best of our knowledge. In addition, it is considered that the availability of an approved anti-SLAMF7 monoclonal antibody (elotuzumab) would be an advantage that would not only increase the value of studies on patients with BC, but would also be beneficial for oncologists, pathologists and cancer researchers.

To the best of our knowledge, this is the first study to investigate the expression patterns of SLAMF7 in BC tissue and to demonstrate its potential prognostic value in BC. The results of the present study confirmed the presence of SLAMF7 protein in BC tissues. Indeed, SLAMF7 was strongly expressed in the

cytoplasm of BC tissue. Of note, it was more overexpressed in the samples from patients with BC with a positive lymph node status (advanced stages) than in those with only primary BC. Moreover, the cytoplasmic expression of SLAMF7 was significantly associated with several clinicopathological characteristics in the present cohort, including age (P<0.007), tumor invasion (P<0.008) and vascular invasion (P=0.05). The results of the present study clearly demonstrated that a low expression of SLAMF7 protein was associated with more aggressive and invasive BC cases. In fact, the low expression of SLAMF7 was found in 81 and 86% of patients with BC with positive tumor invasion and positive vascular invasion, respectively (Table I).

Several studies among Saudi women have reported that the majority were diagnosed with BC at <50 years of age (62-65). These findings were also confirmed in the present study cohort, in which >51% of the patients with BC were <50 years of age when they were diagnosed with BC. However, in the USA, the SEER cancer statistics review reported that the median age of American women at the time of diagnosis of BC was 62 years (66). These results indicate that the onset of BC is delayed by >10 years in the USA as compared to Saudi women. This significant early-onset of BC among Saudi women may be due to a number of factors, including population ageing, economic and social disparities, lifestyle choices and environmental factors (62,67). Of note, the results of the present study demonstrated that the expression of SLAMF7 was higher in younger patients with BC than in their older counterparts, which may be attributed to, at least in part, the lower activity of immune cells in the elderly (68).

Using Kaplan-Meier analysis, significant associations were found between SLAMF7 expression in BC and both DFS and DSS (P<0.001 and P<0.008; log-rank test, respectively). The results revealed that patients with BC who overexpressed SLAMF7 had better survival outcomes with longer survival and lower recurrence rates. In fact, all (100%) the patients with BC without SLAMF7 expression had disease recurrence after 5 years of follow-up, whereas only 35% of patients with a positive expression of SLAMF7 relapsed during the same period (Fig. 2). Similarly, as regards DSS, 100% of the patients without SLAMF7 expression succumbed to the disease during the 5-year follow-up period compared with only 25% of those with expressed SLAMF7 protein (Fig. 3). The survival results of the patients with BC in the present study are consistent with those in patients with MM, in whom a higher *SLAMF7* mRNA expression was a significant prognosticator of a longer survival and has been proposed as a useful tool for classifying hematologic malignancies into molecular subgroups for therapeutic purposes (69). In addition, elotuzumab (a monoclonal antibody against SLAMF7 approved by the FDA in November, 2015), in combination with other targeted antimyeloma therapies that stimulate host immunity, has been shown to exert an effective immunotherapeutic effect (70), improving DFS and thus reducing relapse [as reviewed by Boudreault *et al* (71)]. Although immunotherapy is an established adjunct therapeutic strategy that improves the survival and treatment of cancer patients (72), SLAMF7 remains poorly studied in solid tumors. In addition to the present study, which documented the clear cytoplasmic protein expression in BC, SLAMF7 has also been shown to be expressed in colorectal cancer (37), and at the transcript level in both ovarian and cervical cancers (38,39); however, those studies did not evaluate its prognostic/predictive value. Consistent with the findings presented herein, data from TCGA have revealed that a low *SLAMF7* gene expression is strongly associated with poor survival outcomes in ovarian cancer (61). Furthermore, the findings obtained herein were compared with those from other freely available transcriptomic data of *SLAMF7* in cancer genomics databases, mainly the UCSC Xena or UALCAN databases. Using the UCSC Xena portal, the SLAMF7 transcript was expressed in the majority of the TCGA breast invasive carcinoma cohort (47), and this expression was significantly higher than that in normal breast tissues according to the UALCAN database (P<0.001) (73).

SLAMF7 is a transmembrane marker and a promising molecular marker that plays multiple immune-molecular and signaling roles in modulating the cellular immune response (Fig. 5). SLAMF7 is involved in the inhibition of T-cell proliferation, the overexpression of growth-promoting cytokines in B-cells and cytokine production following antigen stimulation (74). In NK cells, SLAMF7 mediates activating signals via Ewing's sarcoma-associated transcript 2 involving phospholipase Cγ1 and the ERK1/2 signaling pathways and calcium influx, leading to cell-mediated cytotoxicity (28,75). It also plays a critical role in mediating cellular adhesion in macrophages through SLAM family receptors (76).

Since SLAMF7 has an FDA-approved monoclonal antibody (elotuzumab), the results of the present study suggest that once validated, it may have immense potential for monoclonal antibody therapy, which could improve the prognosis and therapeutic outcomes of patients with BC. It can also serve as an additional molecular classifier and make a noticeable contribution as a prognosticator and therapeutic target, particularly for patients with TNBC where outcomes are still challenging. The present study revealed that only 10% of TNBC cases expressed SLAMF7, whereas, on the other hand, 78% of TPBC cases had no expression of SLAMF7. Further studies are warranted to further investigate the association between TNBC cases and SLAMF7 using larger BC cohorts. This research approach is essential in order to identify a promising therapeutic option for the aggressive TNBC molecular subtype, known by the limited treatment modalities compared with its TPBC counterpart.

It is important to highlight that the lack of *SLAMF7* mRNA expression in the studied tumor tissues is a limitation of the present study, since it would be a valuable validation of the protein expression findings. Moreover, and as aforementioned, the molecular effects of SLAMF7 are affected not only by its level of expression, but also by its soluble fraction (sSLAMF7) shown to be involved in lymphocyte proliferation. The authors aim to perform additional studies in the future to investigate the mRNA expression patterns, roles and molecular mechanisms underlying the action of SLAMF7/sSLAMF7 in solid tumors in general and BC, in particular, in order to validate the IHC findings and optimize its use towards precision BC therapies.

In conclusion, to the best of our knowledge, the present study was the first to report the cytoplasmic expression of SLAMF7 in BC. The lack of or a low expression of SLAMF7 protein was associated with both tumor and vascular invasion. It was also a strong prognosticator of poor survival outcomes,

including a higher number of BC recurrences and mortality. Therefore, elotuzumab may prove to be an additional targeted therapy for patients with BC.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Author's contributions

MA is the sole contributor to this work. MA conceived and designed the study, analyzed the data and wrote the whole manuscript. MA confirms the authenticity of all the raw data. The author has read and approved the final manuscript.

Ethics approval and consent to participate

Ethical approval for the present study was obtained from the Research Ethics Committee of The Center of Excellence in Genomic Medicine Research (IRB no. 08-CEGMR-02-ETH). The study was in line with the declaration of Helsinki. All participants provided signed informed consent before inclusion in this study.

Patient consent for publication

Not applicable.

Competing interests

The author declares that he has no competing interests.

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