Original Article
Characterization of desmoglein 2 expression in ovarian serous tumors and its prognostic significance in high-grade serous carcinoma

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Abstract: Desmogleins (Dsgs) are major members of the desmosomal cadherins that are critically involved in cell-cell adhesion and the maintenance of normal tissue architecture in epithelia. DSG2 is the most ubiquitous desmosomal cadherin; however, abnormal expression of DSG2 has been detected in several types of cancer with controversial results. So far, little is known about DSG2 expression in ovarian serous tumor (OST) and its associations with survival and clinicopathologic data. In this study, mRNA and protein expression of DSG2 was detected in 33 cases of nonfixed samples and 92 cases of paraffin-embedded OST specimens (including benign, borderline, low-grade, and high-grade) by using qRT-PCR and immunohistochemistry, respectively. DSG2 expression was then measured in 162 cases of high-grade serous carcinoma (HGSC) by immunohistochemistry, and the expression levels were correlated with clinicopathologic and prognostic data. As the results, DSG2 could be readily detected in benign tumor with relative weak expression at the mRNA level and showed weak but complete staining at the cell-cell borders. This was similar to the expression pattern in the normal fallopian epithelial tissue. However, the expression tendency of DSG2 at the mRNA and protein level was inconsistent in borderline and malignant OST. In addition, we found that a low DSG2 expression was associated with poor prognosis (P < 0.05) and high mitosis (P = 0.0042) of HGSC. Thus, DSG2 may be involved in the progression of ovarian cancer and plays a different role in different OST. Moreover, a low DSG2 expression was associated with poor prognosis of HGSC.

Keywords: DSG2, high-grade serous carcinomas (HGSC), ovarian serous tumor (OST), prognosis

Introduction

Ovarian cancer is the most lethal gynecologic malignancy in adult women and represents 30% of cancers of the female genital tract [1]. However, the overall survival of women with ovarian cancer has not changed in more than 50 years, and screening studies carried out over the past two decades have failed to provide a survival benefit [2]. Identifying the underlying biology and molecular pathogenesis of ovarian cancer is crucial for understanding and advancing the treatment of this disease.

The desmoglein (DSG) glycoproteins (DSG1-DSG4) are a group of essential cadherins in desmosomal intercellular junctions that establish a link between adjacent cells by both homophilic interactions with DSG molecules and heterophilic interactions with desmocollin molecules (DSC1-DSC3) on opposing cells in the extracellular space [3, 4]. Their intracellular ends then bind by several intermediate proteins to the filaments of the cytoskeleton; thus, they are essential for the maintenance of cell structure and integrity [3]. In addition to their pivotal function in cell-cell adhesion, desmosomes also play an important role in the regulation of cell proliferation, differentiation, and early embryonic development, and have been discovered to be involved in extracellular to cytoplasmic signal transduction processes [5, 6]. However, a dysregulation of desmosomal proteins plays a role in carcinogenesis. Particularly,
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Desmogleins have been reported to be involved in cancer progression by contributing to tumor cell growth and tissue invasion through the activation of oncogenic signaling pathways [5].

DSG2 is the most ubiquitous desmosomal cadherin that is expressed in all desmosome-forming tissues, including epithelia, myocardium, and melanoma cells [7]. Interestingly, expression by nondesmosome-forming human endothelial progenitor cells as well as their mature counterparts (endothelial cells) was noted recently [8]. Accordingly, abnormal expression of DSG2 has been detected in several types of cancers. However, there are some controversial results about DSG2 expression and the precise role of DSG2 in tumor development and progression. Thus far, it has been shown that DSG2 is upregulated in colon/colorectal cancer [9, 10], skin squamous cell cancer (SCC) [11], lung SCC [12], melanomas [13], and basal cell carcinoma [14], which correlates with enhanced tumor progression and/or shorter patient survival. In other epithelial cancers such as prostate cancer [15, 16], pancreatic cancer [17, 18], and diffuse-type gastric cancer [19], DSG2 was downregulated or even lost, which is associated with a poor clinical outcome. To date, no data are available in the literature concerning the expression of the clinical progression of ovarian carcinoma except for one study reported by Koyama-Nasu et al [20], who found that knockdown CD133 caused a reduction in the levels of DSG2, abrogation of cell-cell adhesion, and tumorigenicity in the cancer stem cell line established from clear cell carcinoma of the ovary.

Ovarian cancer is a heterogeneous tumor with multiple histophenotypes, growth patterns, and differential response to treatment. Rather than existing as a single entity, epithelial ovarian cancer (EOC) appears to be a group of distinct diseases that can be further classified into the following 5 histologic subtypes: serous, endometrioid, mucinous, clear cell, and undifferentiated carcinoma [21, 22]. Because serous carcinoma usually represents the archetypical EOC and is responsible for the highest fatality rate, in the current study, we aimed to clarify the correlation of DSG2 expression with clinical parameters and prognosis in ovarian serous tumors, especially high-grade serous carcinoma (HGSC).

Material and methods

Patients and samples

Tissue samples were obtained from patients who underwent surgery between 2010 to 2015 at the Tianjin Central Hospital of Gynecology Obstetrics (TCHGO), China. All patients gave consent for the use of their tissue samples and clinical data. The ethics review board at the TCHGO approved the study. Fresh nonfixed serous ovarian tumors (n = 33; 2 cases of serous cystadenoma (SCA), 4 cases of serous borderline tumor (SBT), 6 cases of low-grade serous carcinoma (LGSC), 21 cases of HGSC) were obtained at the time of surgery at TCHGO. Formalin-fixed paraffin-embedded surgical specimens were retrieved from the archives of the Department of Pathology (n = 92; 14 cases of SCA, 30 cases of SBT, 18 cases of LGSC, 30 cases of HGSC). In addition, 162 cases of formalin-fixed paraffin-embedded surgical HGSC specimens with follow-up data were collected.

The ages of the patients at diagnosis ranged from 18 to 72 years, with a median of 54.9±8.1 years. Of all cases, 162 HGSC patients were followed up until September 2016, with a follow-up time from 5 to 91 months in 142 patients; 20 patients were lost to follow-up. The primary tumors were histologically analyzed according to the World Health Organization classification of serous tumor in epithelial ovarian tumors [21]. Patients with borderline tumor or carcinoma were clinically staged by the criteria of the International Federation of Gynecology and Obstetrics (FIGO) stage [23].

RNA extraction and real-time quantitative polymerase chain reaction analysis

Total RNA from tumor tissues was isolated using the RNaseasy Kit (Qiagen, Germany). One microgram of total RNA was then reverse transcribed using SuperScript II Reverse Transcriptase kit (Invitrogen, USA). Real-time quantitative polymerase chain reaction (RT-qPCR) was performed with LightCycler 480 SYBR Green I Master (Roche, Germany) according to the manufacturer’s instructions. Signals were detected with Light Cycler 480 II (Roche, Germany). The amounts of target gene mRNA were normalized to a reference gene GAPDH. The primer sequence was as follows: For DSG2, the forward primer was 5’-CTA ACA GGT TAC
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GCT TTG GAT GC-3' and the reverse primer was 5'-GTG AAC ACT GGT TCG TTG TCA T-3'. For GAPDH, the forward primer was 5'-CCC TTC ATT GAC CTC AAC TAC-3' and the reverse primer was 5'-CCA CCT TCT TGA TGT CAT CAT-3'.

Immunohistochemistry

For immunohistochemistry (IHC), formalin-fixed, paraffin-embedded 4-μm-thick sections of tumor tissues were stained using the streptavidin-peroxidase method. Briefly, tumor sections were deparaffinized, and antigen retrieval was performed by steaming the sections in citrate buffer (pH 6.0) for 25 min. Endogenous peroxidase activity was blocked using 3% hydrogen peroxide for 15 min. The slides were incubated with primary antibodies anti-DSG2 (ab150372, Abcam; dilution 1:250) for 1 h at 37°C and visualized using 3, 3'-diaminobenzidene. Then, the sections were counterstained with hematoxylin solution.

DSG2 protein expression was scored according to the percentage of cells of interest (value of 0 for absent, 1 for positive cells < 25%, 2 for positive cells 25% to 50%, 3 for positive cells 50-75%, and 4 for positive cells > 75%) and intensity (value of 0 for negative, 1 for weak, 2 for moderate, and 3 for strong) of staining [24]. The intensity of the SCA tissue sample was indicated as “1”. Finally, the staining results were analyzed as dichotomous variables, defining total scores (the percentage of cells + the intensity) and were analyzed further using statistical software. The morphology and immunostaining were independently evaluated by two experienced pathologists (LC and YXL), who were blinded to the patient’s clinical outcome and clinicopathological parameters. In case of differences between the two scorings, the core was reevaluated to reach a consensus.

Statistical analyses

GraphPad Prism 5 and SPSS software (version 19.0) was used for statistical analyses. Multiple variance analysis was assessed by one-way analysis of variance. Associations between cat-

Figure 1. A. The relative mRNA expression levels of DSG2 in ovarian serous tumors. (no statistical significance indicated with n.s.) B. IHC staining of DSG2 in ovarian serous tumors. (SCA (a), SBT (c), LGSC (e), and HGSC (g), HE×200, IHC×200). C. Protein expression levels of DSG2 in ovarian serous tumors. (P < 0.05, indicated with *, **; P < 0.001, indicated with **).
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Categorical variables were assessed by chi-square tests (Pearson). Survival analyses of progression-free survival (PFS) and overall survival (OS) were executed using the Kaplan-Meier method and log-rank test. For all the analyses, a \( P < 0.05 \) was considered significant.

**Computational expression data analysis**

Publicly available RNA-Seq expression data and corresponding clinical data from 1,582 ovarian carcinoma samples and 1,207 serous ovarian carcinoma samples were retrieved from the database (http://kmplot.com). The expression of DSG2 was then correlated with patient survival times in terms of OS and PFS.

**Results**

The mRNA and protein expression of DSG2 in ovarian serous tumors

The mRNA expression of DSG2 was detected using RT-qPCR in ovarian serous tumors, including 2 cases of SCA, 4 cases of SBT, 6 cases of LGSC, and 21 cases of HGSC. RT-qPCR analysis

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**Figure 2.** A. Survival analysis of DSG2 in ovarian cancer showed that higher DSG2 expression had significantly worse OS \( (P = 0.021, \text{left}) \), but better PFS \( (P = 0.065, \text{right}) \). B. Survival analysis of DSG2 in ovarian serous cancer showed that higher DSG2 expression had significantly worse OS \( (P = 0.031, \text{left}) \) and worse PFS \( (P = 0.07, \text{right}) \).
showed that DSG2 could be readily detected in SCA and showed relative weak expression at the mRNA level. The relative mRNA expression levels of DSG2 showed no significant difference between the four types of serous tumors ($P > 0.05$) analyzed using Graph-Pad Prism 5 (Figure 1A). However, the expression level increased gradually from benign tumor, borderline tumor, and low-grade malignant tumor to high-grade malignant tumor.

To detect the protein expression of DSG2, immunohistochemical staining was carried out in 14 cases of SCA, 30 cases of SBT, 18 cases of LGSC, and 30 cases of HGSC. DSG2 was clearly present in all the SCA tissue samples and showed weak but clear and complete staining at the cell-cell borders (Figure 1Ba, 1Bb). In SBT and LGSC tissue samples, DSG2 staining intensity was stronger than that in benign tissues (Figure 1Bc-f). However, the membrane staining for DSG2 was distinctly weaker in most of the HGSC samples, and the distribution of DSG2 staining was heterogeneous in every case (Figure 1Bg, 1Bh).

To further quantify the expression of DSG2 in the different tissue samples, the stained slides
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were processed to calculate the staining intensity and percent for each sample as described in Methods. The total scores for the four groups of serous ovarian tumors are shown in Table S1 and were analyzed using Graph-Pad Prism 5 (Figure 1C). Although the intensity of DSG2 staining was slightly increased between SCA and SBT as well as LGSC, the percentage of cells with demonstrable DSG2 staining decreased with the severity of disease. Thus, DSG2 protein expression was not statistically significant between these three groups (P > 0.05). However, the examination of DSG2 immunoreactivity revealed a marked decrease in intensity and percentage in HGSC samples when compared with other types (P < 0.0005).

Survival analysis of computational expression data

Table 1. DSG2 expression score in HGSC and survival cases

<table>
<thead>
<tr>
<th>DSG2 Score</th>
<th>N</th>
<th>Mean Estimate</th>
<th>P value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>24</td>
<td>49.14</td>
<td>0.051</td>
<td>41.08-55.21</td>
</tr>
<tr>
<td>3</td>
<td>27</td>
<td>44.92</td>
<td>0.012</td>
<td>34.42-55.42</td>
</tr>
<tr>
<td>4</td>
<td>29</td>
<td>53.72</td>
<td>0.002</td>
<td>45.29-62.15</td>
</tr>
<tr>
<td>5</td>
<td>45</td>
<td>65.89</td>
<td>0.002</td>
<td>62.08-69.71</td>
</tr>
<tr>
<td>6</td>
<td>16</td>
<td>76.13</td>
<td>0.002</td>
<td>60.87-91.38</td>
</tr>
</tbody>
</table>

Table 2. DSG2 expression and survival (months)

<table>
<thead>
<tr>
<th>DSG2 expression</th>
<th>Cases</th>
<th>Mean Estimate</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DSG2 (2-4)</td>
<td>80</td>
<td>51.48</td>
<td>46.388-56.576</td>
<td>0.012</td>
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<tr>
<td>DSG2 (5-6)</td>
<td>62</td>
<td>80.53</td>
<td>73.747-87.314</td>
<td>0.006</td>
</tr>
<tr>
<td>PFS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DSG2 (2-4)</td>
<td>80</td>
<td>49.28</td>
<td>44.284-54.276</td>
<td>0.006</td>
</tr>
<tr>
<td>DSG2 (5-6)</td>
<td>62</td>
<td>76.18</td>
<td>67.924-84.439</td>
<td>0.006</td>
</tr>
</tbody>
</table>

was further performed on patients with ovarian serous cancer, and the results showed higher DSG2 expression had significantly worse OS (P = 0.031, log-rank test) and PFS (P = 0.07, log-rank test) (Figure 2B).

Because of the inconsistencies we found between DSG2 mRNA and protein expression, the correlation of DSG2 protein expression with patient survival was also analyzed. To avoid the effect of different histologic types on prognosis, 162 HGSC patients had follow-up data produced by IHC, using the normal fallopian tube epithelium as control. The normal fallopian tube epithelium was characterized by weak staining in all the cell borders (Figure 3Aa, 3Ab). In 6 cases of serous tubal intraepithelial carcinoma (STIC), the expression of DSG2 was higher than that in normal fallopian tube epithelium (Figure 3Ba, 3Bb). However, HGSC tumor samples showed a varied expression pattern (Figure 3Ca-j). Interestingly, a diffuse granular staining in the cytoplasm was also detected in some populations of cells in 36 HGSC tumor samples, in which the DSG2 expression was much lower in the cell membrane (Figure 3Cb). In addition, 11 cases of HGSC tumor showed the transformation from borderline, low-grade, to high-grade, and the expression of DSG2 showed strong staining in SBT and LGSC components, but showed markedly decreased staining in HGSC component (Figure S1).

The stained slides were processed to calculate the staining intensity and percent for each sample, and the total staining intensity scores and the corresponding expression levels are shown in Table 1 and Figure 3Ca-j. In summary, the survival time was significantly correlated with the expression level of DSG2, and the lower DSG2 expression was associated with a shorter overall survival (P = 0.02) (Figure 3D). Then, after comparison among the five groups, a cutoff value of score of 4 for DSG2 expression was used because patients whose DSG2 expression in tumor was score 5-6 had longer OS (P =
The association of DSG2 expression with clinicopathologic parameters

To obtain a better understanding of DSG2 expression in HGSC, the relationship between DSG2 expression and the clinicopathologic characteristics of patients with HGSC were analyzed. The expression of DSG2 was defined as low (2-4 score) and high (5-6 score). The expression levels of DSG2 did not significantly correlate with any clinicopathologic parameters such as FIGO stage; recurrence; family history; ascites; and the expression of P53, P16, and WT-1 (P > 0.05, Table 3), except for mitosis (P = 0.0042). Table 4 shows that low DSG2 expression was associated with high mitosis.

Discussion

Cell adhesion plays an important role with respect to invasion and metastasis of tumors. Consequently, cadherin-type molecules, the components that form the adhesive core of desmosomes, were observed to be dysregulated in many types of cancers [5]. DSG2, as the most ubiquitous desmosomal cadherin, is no longer regarded as merely a simple desmosomal adhesion molecule for maintaining tissue integrity. The more complex possible functions of DSG2 have been disputed in recent years, including its contribution to proliferation, differentiation, apoptosis, cell migration, and signal transduction [5, 6]. Although some studies proposed that a lack of DSG2 might be related to tumorigenesis and poor prognosis [15-19], other reports postulated a correlation between the overexpression of DSG2 and tumor progression [9-14]. In particular, the role of DSG2 in ovarian carcinoma has not yet been established. Here, we showed for the first time the expression pattern of DSG2 in ovarian carcinoma and the prognostic implication in HGSC patients.

The results revealed that DSG2 could be readily detected in benign tumors (SCA) with relatively weak expression at the mRNA level and was consistently detected weakly but clearly and with complete staining at the cell-cell borders at the protein level. The protein expression pattern of DSG2 in benign tumors was almost the same as that in the normal fallopian tube epithelium. This finding provided us evidence of the most basic function of DSG2 in cell-cell adhesion which is to sustain normal tissue integrity.
Interestingly, the results also showed that the expression of DSG2 at the mRNA level and protein level was inconsistent in borderline and malignant ovarian serous tumors. That is, the mRNA expression level was increased gradually from SBT, LGSC, to HGSC, although no statistically significant difference was found. However, DSG2 immunoreactivity revealed a marked decrease in HGSC samples not only in intensity but also in percentage when compared with other types. In fact, the inconsistency we found between DSG2 mRNA and protein level was not an isolated event. Pietkiewicz et al suggested that Dsg2 and Dsg3 expression level correlated in basal cell carcinoma at the mRNA level but not at the protein level; this may depend on desmosome internalization or may reflect separate specific posttranslational mechanisms for the regulation of the protein abundance of specific Dsg isoforms [14]. In addition, Saaber et al found downregulation of DSG2 was significantly associated with promoter methylation in lung cancer cell lines [12]. Moreover, a recent study identified two cysteine residues in the juxtamembrane domain of Dsg2 that inhibit its palmitoylation when mutated. The transport of mutant Dsg2 to the plasma membrane was delayed, resulting in accumulation in the cytoplasmic pool, and the mutant was more soluble than the wild-type protein because of being co-localized with lysosomal markers [25]. Taken together, the inconsistent Dsg2 mRNA and protein expression may be due to the disorder of posttranscriptional translation or transport.

This aberrant localization of Dsg2 in the cytoplasm was also found in the present study and other studies [12, 15, 26-28]. Gupta et al found that loss of Dsg2 disrupted cell-cell adhesion, and this effect was further amplified with loss of CSTA. In turn, knockdown of CSTA in keratinocytes resulted in cytoplasmic relocalization of Dsg2, breakage of cytokeratin intercellular connections, and loss of the desmosomal protein desmoplakin [27]. In addition, Brennan et al demonstrated that Dsg2 is proteolytically processed, resulting in a 95-kDa ectodomain-shed product and a 65-kDa membrane-spanning fragment. Both the full-length 160-kDa and the truncated 65-kDa intracellular fragment associated with Caveolin-1 and mobilized into membrane lipid rafts, where they most likely undergo internalization and degradation. Disruption of lipid rafts may lead to relocalization of this truncated 65-kDa product, and its accumulation may disturb desmosome assembly and disrupt cell-cell adhesion, which play a role in tumor progression [28]. It will be worthy to further study whether there any significant findings regarding cytoplasmic localization of Dsg2 and the possible mechanism in HGSC.

The role of Dsg2 in different cancers is equally controversial, and the expression level is dependent on the tumor type. We have shown that decreased expression of Dsg2 is associated with poor prognosis in HGSC. Barber’s group and other researchers showed that the low Dsg2 expression phenotype is a useful prognostic biomarker of prostate cancer and pancreatic cancer, thus suggesting a complex role for Dsg2 in oncogenesis, serving as a tumor enhancer or suppressor [15-18, 24]. However, Dsg2 is found upregulated in colon/colorectal cancer [9, 10], skin SCC [11], lung SCC [12], melanomas [13], and basal cell carcinoma [14], which correlates with enhanced tumor progression and/or shorter patient survival. The reasons for these differences, to our knowledge, are not yet known. Of note, several recent publications have highlighted the significance of heterogeneity within tumor samples subjected to gene expression profiling. In particular, it is becoming increasingly recognized that the varying stromal content of tumors can dramatically influence the outcome of these analyses, including data within TCGA [29, 30]. In addition, different primary antibodies of Dsg2 used in different studies and inconsistent interpretation of the staining results may also lead to different results. However, based on our findings, we predict that Dsg2 may play a different role in SCC and glandular cancer as well as in differentiated cancer cells and cancer stem cells.

To obtain a better understanding of DSG2 expression in HGSC, the relationship between DSG2 expression and the clinicopathologic characteristics of patients with HGSC was analyzed. The low expression of DSG2 did not significantly correlate with any clinicopathologic parameter except for higher mitosis. As described previously, Brennan et al predicted that the truncated DSG2 (65 kDa) can be cleared from the plasma membrane and in the process possibly activate mitogenic cell signaling through their interaction with Caveolin-1,
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thereby promoting cancer development and progression [28]. Ebert et al also conceived that DSG2 may play an important, as-yet unidentified role in symmetric cell division and progenitor renewal [8]. In summary, our data showed that the expression tendency of DSG2 was inconsistent with that of SCA, SBT, and LGSC to HGSC at the mRNA and protein levels. This may be due to different pathogenesis between different types of ovarian serous tumors, especially LGSC and HGSC. We also found that a low DSG2 expression was associated with poor prognosis of HGSC. To our knowledge, this is the first study to investigate the expression of DSG2 and its associations with survival in ovarian serous tumors. Further studies are needed to explore the expression of the other desmoglein family members in ovarian serous cancer and to clarify the biologic function of DSG2 as well as its signaling pathway involved in ovarian tumor development and prognosis.

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Disclosure of conflict of interest

None.

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Table S1. DSG2 expression in ovarian serous tumors

<table>
<thead>
<tr>
<th>Histopathology type</th>
<th>Cases</th>
<th>DSG2 expression (Score)</th>
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<tbody>
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<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>SCA</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>SBT</td>
<td>34</td>
<td>0</td>
</tr>
<tr>
<td>LGSC</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>HGSC</td>
<td>30</td>
<td>1</td>
</tr>
</tbody>
</table>

Note: serous cystadenoma (SCA), serous borderline tumor (SBT), low-grade serous carcinoma (LGSC), high-grade serous carcinomas (HGSC).

Figure S1. DSG2 expression in HGSC tumors shows the transformation from borderline, low-grade to high-grade. The expression of DSG2 showed strong staining in SBT (B) as well as LGSC (D) components but showed a marked decrease in staining intensity in HGSC component (F). Hematoxylin and eosin (HE) staining sections for SBT (A), LGSC (C), and HGSC (E) components. (HE×200, IHC×200).