Assessment of Maturation Status of Tumor-Infiltrating Dendritic Cells in Invasive Ductal Carcinoma of the Breast: Relation with Vascular Endothelial Growth Factor Expression

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Objective: Poor immunogenicity has been described in breast carcinoma although dendritic cells, the major antigen presenters, are known to infiltrate the tumor. Vascular endothelial growth factor has been proposed to reduce local immune response in tumors. We investigated the maturation status of dendritic cells in invasive ductal carcinoma of the breast in relation to vascular endothelial growth factor expression and clinicopathological parameters.

Material and Method: Fifty invasive ductal carcinomas of the breast were immunostained with CD1a (marker of immature dendritic cells); CD83 (marker of mature dendritic cells), vascular endothelial growth factor, estrogen receptor and progesterone receptor.

Results: Mature dendritic cells were detected in 36 cases (72%), and correlated with smaller tumor size, negative lymph nodes, positive steroid receptor status, and lower grade (P<0.001). Immature dendritic cells were found in 100% of cases and correlated only with negative steroid receptor expression (estrogen receptor and progesterone receptor) (P=0.006 and 0.020 respectively). Vascular endothelial growth factor expression was detected in 44 cases (88%), and correlated directly with positive nodal metastases (P=0.014), correlated inversely with mature dendritic cell count (P=0.005); and did not correlate with immature dendritic cell count (P=0.104).

Conclusion: Mature dendritic cell count correlates with good prognostic features in invasive ductal carcinoma of the breast, suggesting their role in initiating primary anti-tumor immune response. Vascular endothelial growth factor expression may play a role in inhibition of dendritic cell maturation sequence in the tumor microenvironment.

Key Words: Breast neoplasms, Dendritic cells, CD1a antigen, CD83 antigen, Vascular endothelial growth factor

Öz


Gereç ve Yöntem: Ellı invaziv meme duktal karsinomunda CD1a (olgunlaşmamış dendritik hücrelerin belirteci); CD83 (olgun dendritik hücrelerin belirteci), vasküler endotelyal büyüme faktörü, estrogen reseptörü ve progesteron reseptörüyle immün boyama yapıldı.

Bulgular: Olgun dendritik hücreler 36 vakada (%72) saşıtı ve daha küçük tümör, negatif lenf nodları, pozitif steroid reseptörü durumu ve daha düşük dereceli korelasyon gösterdi (P<0.001). Olgunlaşmamış dendritik hücreler vakaların %100’ünde bulundu ve sadece negatif steroid reseptörü (estrogen reseptörü ve progesteron reseptörü) ifadesiyle koreledi (sirasıyla P=0.006 ve 0.020). Vasküler endotelyal büyüme faktörü ifadesi 44 vakada bulundu (%88) ve pozitif nod metastazları (P=0.014) ile doğrudan korelasyon gösterirdi olgun dendritik hücre sayıımı ters korelesiyon gösterdiler (P=0.005) ve olgun olmayan dendritik hücre sayıımı korelasyon göstermedi (P=0.104).

Sonuç: Olgun dendritik hücre sayımının menenin invaziv duktal karsinomunun iyi prognostik özellikleriyle korelasyon göstermektedir ve bu durum primer anti tümör_immün cevabı başlatmakta bir rol düşünülmektedir. Vasküler endotelyal büyüme faktörü ifadesi tümör mikro ortamında dendritik hücre olgunlaşma düzeyinin inhibisyonunda bir rol oynayabilir.

Anahtar Sözcükler: Meme neoplazmları, Dendritik hücreler, CD1a antijeni, CD83 antijeni, Vasküler endotelyal büyüme faktörü

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INTRODUCTION

Dendritic cells (DCs) are the most efficient antigen-presenting cells of the immune system (1). They are present in peripheral tissues and in immunological organs such as the thymus, bone marrow, spleen, lymph nodes, and Peyer’s patches (2). Their lack could result in an inefficient primary immune response (1).

Human DCs comprise multiple subsets in terms of the expression of cell surface markers, but these might reflect differences in the maturation status rather than separate sub-lineages (3). Researchers have identified two entities of DCs that differ phenotypically and functionally, namely, the immature and mature DCs (4). Immature DCs possess high endocytic and phagocytic capacity permitting antigen capture, but are inefficient at presenting antigens to T cells (3). After receiving the correct cytokine signals, they undergo phenotypic and functional changes, resulting in a ‘mature’ stage. Mature DCs are characterized by loss of endocytic and phagocytic receptors, high expression of major histocompatibility complex II (MHC II) antigens and co-stimulatory molecules, and activation of the antigen-processing machinery, including a shift in lysosomal compartments and increase in DC lysosome-associated membrane protein (DC-LAMP) (3,5,6). They also become migratory and travel to the local lymph nodes, where they activate antigen-specific T cells (3). Mature DCs express CD83 and high CD40/80/86, whilst immature cells express CD1a and low CD40/80/86 (4). Thus theoretically, by identifying CD1a and CD83, both immature and mature DC populations can be studied (7).

It has been reported that DCs have a regulatory function in several processes, including cancer development and growth (8,9). They are conspicuous members of the microenvironment of several types of cancer such as breast carcinoma, papillary thyroid carcinoma, and ovarian carcinoma (10). Inhibition of the maturation of DCs by malignant cells would result in functional failure of the anti-tumor immunity (11). It has been suggested that microenvironmental signals, including cytokines, affect the maturation status of the tumor-infiltrating DCs (12), which remain immature and become dysfunctional in hosts bearing growing tumors (10). However, the mechanisms by which the maturation status of tumor-infiltrating DCs is regulated remain obscure (13).

Vascular endothelial growth factor (VEGF) is an important angiogenic factor that is expressed by a wide variety of tissues, and holds potential as both a predictive marker for anti-angiogenic therapy and a prognostic factor in various malignancies (14). It is a specific mitogen for endothelium, that induces proteolytic enzymes necessary for vascular remodeling (15). VEGF expression has been found to be associated with not only an enhancement of angiogenesis, but also a decline of local immune response in tumors (16).

It has been suggested that an interplay exists between DCs and VEGF resulting in modifications in DC biology and tumor vascularization and, in turn, affecting cancer progression. Recent basic research has shown that VEGF can inhibit DC maturation, however, very little is known about VEGF-dependent DC inhibition in a clinical setting (16).

Breast carcinoma has traditionally been thought of as a ‘non immunogenic’ tumor, despite the notable T-cell infiltrate in human and animal breast cancers (17), and the frequent infiltration of the tumor by DCs (13,18). In addition, unlike other malignancies, the incidence of breast cancer is not altered in immunocompromised patients, and some nonspecific immune-stimulating therapies might worsen the prognosis (18). However, specific anti-tumor responses by autologous T-lymphocytes infiltrating breast tumors were detected using short-term cultured breast carcinoma cells (19), and thus widespread interest in the possibility of generating immunotherapeutic responses against breast cancer has developed (17).

To date, only few studies have addressed the maturation status of DCs in breast carcinoma and its relation to the expression of VEGF, and the prognosis of breast cancer patients. The aim of this study was to investigate the maturation status of tumor-infiltrating DCs in invasive ductal carcinoma of the breast, and to assess its possible correlation with VEGF expression by the tumor and the different clinicopathological parameters.

MATERIAL and METHODS

Tissue Samples

This study was carried out on 50 cases of invasive ductal carcinoma (IDC) of the breast. Specimens were submitted to the Pathology Department, Faculty of Medicine, Alexandria University between February 2010 and August 2012. Specimens included: modified radical mastectomy (41 cases) and partial mastectomy with axillary lymph node dissection (9 cases). The patient medical records were reviewed for clinical information, and histological parameters were assessed on hematoxylin & eosin-stained slides. The evaluated parameters were: patient age at diagnosis, tumor size, histological tumor type, histological grade and lymph node status. Tumors were graded
according to the Nottingham modification of the Bloom-Richardson grading system (20). The tumor size was classified according to the American Joint Committee on Cancer (AJCC) (21). Patients who received chemotherapy or radiation therapy before surgery were excluded from the study. The research protocol was approved by the medical ethics committee in Alexandria Faculty of Medicine.

**Immunohistochemistry**

**Primary antibodies:**

The following primary antibodies were used for immunohistochemical staining: CD1a, Ab-5 (Clone O10; Thermo Fisher Scientific, Fremont, CA, USA; dilution 1:50) for detection of immature DCs; CD83, Ab 49324 (Clone 1H4b; Abcam plc, Cambridge, UK; dilution 1:20) for detection of mature DCs; VEGF, Ab-7 (Clone VG1; Thermo Fisher Scientific, Fremont, CA, USA; dilution 1:100); Estrogen Receptor (ER) (Clone SP1; Thermo Fisher Scientific, Fremont, CA, USA; dilution 1:100) and Progesterone Receptor (PR) (Clone SP2; Thermo Fisher Scientific, Fremont, CA, USA; dilution 1:100). CD1a, CD83 and VEGF were mouse monoclonal antibodies; ER and PR were rabbit monoclonal antibodies.

**Immunohistochemical staining technique:**

Immunohistochemical staining was performed applying the streptavidin-biotin-peroxidase method. The UltraVision LP detection system (Thermo Fisher Scientific, Fremont, CA, USA) was used. For each case, a set of 5 micrometer-thick paraffin sections were cut from one representative block of the tumor. The slides were deparaffinized in xylene and rehydrated in descending grades of alcohol. All reactions were carried out at room temperature with phosphate buffered saline washes in triplicate.

Endogenous peroxidase activity was blocked by incubating the slides in 0.3% hydrogen peroxide in methanol for 10 minutes. Then, antigen retrieval was performed by heating tissue sections in a 700 W microwave oven (in 1 mM EDTA, pH 8.0 for CD1a and VEGF; and in 10mM citrate buffer, pH 6.0 for CD83, ER and PR) for 10 minutes, followed by cooling to room temperature. The sections were incubated overnight in a humidified chamber with the primary antibody. The slides were then incubated in biotinylated secondary antibody, and then in streptavidin-HRP for 20 minutes each. The reaction was visualized by incubating tissue sections with 3,3’-diaminobenzidine (DAB), followed by counterstaining with hematoxylin. Sections without primary antibodies served as negative controls.

**Interpretation of immunohistochemical staining:**

* Dendritic cell count was scored in CD1a- and CD83-stained sections. The five most densely infiltrated areas (hot spots) were first identified by scanning the entire section at low power (x100 magnification), then all positively-stained cells in five high power fields (HPFs, x 400 magnification), one in each hot spot, were counted, obtaining five counts for each tumor, the mean of which was considered as the dendritic cell count, expressed as the number of cells/ HPF (12). Cells displaying membranous staining, cytoplasmic staining, nuclear counterstaining and typical DC morphology were counted. DC counts were classified into: ‘low’ and ‘high’ infiltration groups at 10 cells/ HPF for immature (CD1a+) DCs, and 3 cells / HPF for mature (CD83+) DCs respectively according to the previous report by Iwamoto et al (13).

* VEGF expression was assessed as follows (22,23): (score 0): 0-<5% positive cells; (score 1): 5-<25% positive cells; (score 2): 25-<50% positive cells; (score 3): ≥50% positive cells.

* ER and PR staining was considered positive if nuclear staining of moderate to strong intensity was present in at least 10% of tumor cells (24).

**Statistical analysis**

Statistical analysis was carried out using Statistical Package for Social Sciences (SPSS) software, version 18.0 (SPSS, Chicago, IL, USA). Continuous variables were expressed as mean ± standard deviation (SD), whereas categorical variables were expressed as numbers and percentages. The significance of relationship between DC infiltration, VEGF expression and clinicopathological parameters was assessed using the Chi-square (χ2) test or the Fisher’s exact test. For statistical purposes, on assessment of VEGF expression, cases were classified into two groups: a “low expression” group (scores 0 and 1; n=13) and a “high expression” group (scores 2 and 3; n= 37). Comparison between the groups in VEGF expression and DC infiltration was carried out using the Mann-Whitney U test. P<0.05 was considered significant.

**RESULTS**

**Clinicopathological data**

This study included 50 cases of IDC. All patients (100%) were women. Their ages ranged from 33 to 75 years (mean 50.04±8.84 years, median 48 years). The clinicopathological data of the patients are presented in Table I.

**Infiltration of IDC tissues by DCs**

IDC cases were examined for cells expressing CD1a and
CD83. As regards immature DCs labeled with CD1a, areas of densest infiltration (hot spots) were generally found within the tumor beds, distributed at random, with no specific predilection to a certain location within the tumor. CD1a-positive cells were seen around ductal formations in low-grade tumors, and intermixed with tumor cells in higher grade tumors. In both cases, immature DCs appeared to make contact with tumor cells (Figure 1A, B). CD1a-expressing cells with typical DC morphology were detected in all cases (100%), with a mean of 11.3 cells/HPF and median of 7.5 cells/HPF (range, 1-48 cells/HPF). Concerning mature DCs, identified by expression of CD83, hot spots were located invariably in the areas surrounding the tumors, frequently within lymphoplasmacytic reaction in case of tumors showing such a reaction in the peritumoral areas (Figure 1C, D). CD83-positive cells were identified in 36 cases (72%), with a mean of 5.8 cells/HPF and median of 2.5 cells/HPF (range, 0-26 cells/HPF).

### Relationship between DC counts and clinicopathological parameters

The relationship between DC counts, and clinicopathological factors are demonstrated in Table I. The count of immature DCs, labeled with CD1a, was significantly higher in cases with negative steroid receptor status (ER and PR) ($P=0.006$ and $0.020$ respectively). Meanwhile, there was no significant relationship between CD1a $^+$ DC count and patient age, tumor size, lymph node status and tumor grade ($P=0.263$, $0.077$, $0.430$ and $0.122$ respectively). The number of mature DCs, expressing CD83, correlated directly with positive steroid receptor status (ER and PR) ($P<0.001$), whereas it correlated inversely with tumor size, positive lymph node metastases, and tumor grade ($P<0.001$). There was no significant relationship between CD83 $^+$ DC count and patient age ($P=0.380$).

### Table I: Relationship between dendritic cell (DC) infiltration, vascular endothelial growth factor (VEGF) expression and clinicopathological parameters in invasive ductal carcinoma (IDC) of the breast

<table>
<thead>
<tr>
<th></th>
<th>No. of pts.</th>
<th>Immature (CD1a$^+$) DC infiltration</th>
<th>Mature (CD83$^+$) DC infiltration</th>
<th>VEGF expression</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Low No. (%)</td>
<td>High No. (%)</td>
<td>$P$</td>
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<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
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<tr>
<td>&lt; 50</td>
<td>26</td>
<td>14 (46.7)</td>
<td>12 (60.0)</td>
<td>0.263</td>
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<tr>
<td>≥ 50</td>
<td>24</td>
<td>16 (53.3)</td>
<td>8 (40.0)</td>
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<tr>
<td><strong>Tumor size:</strong></td>
<td></td>
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<tr>
<td>T1&amp;T2</td>
<td>30</td>
<td>21 (70.0)</td>
<td>9 (45.0)</td>
<td>0.077</td>
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<tr>
<td>T3&amp;T4</td>
<td>20</td>
<td>9 (30.0)</td>
<td>11 (55.0)</td>
<td></td>
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<tr>
<td><strong>LN status:</strong></td>
<td></td>
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<tr>
<td>Negative</td>
<td>17</td>
<td>11 (36.7)</td>
<td>6 (30.0)</td>
<td>0.430</td>
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<tr>
<td>Positive</td>
<td>33</td>
<td>19 (63.3)</td>
<td>14 (70.0)</td>
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<td><strong>Steroid receptors:</strong></td>
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<td>ER Negative</td>
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<td>5 (16.7)</td>
<td>11 (55.0)</td>
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<tr>
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<td>25 (83.3)</td>
<td>9 (45.0)</td>
<td></td>
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<tr>
<td>PR Negative</td>
<td>20</td>
<td>8 (26.7)</td>
<td>12 (60.0)</td>
<td>0.020*</td>
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<tr>
<td>Positive</td>
<td>30</td>
<td>22 (73.3)</td>
<td>8 (40.0)</td>
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<tr>
<td><strong>Grade:</strong></td>
<td></td>
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<tr>
<td>1&amp;2</td>
<td>36</td>
<td>24 (80.0)</td>
<td>12 (60.0)</td>
<td>0.122</td>
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<tr>
<td>3</td>
<td>14</td>
<td>6 (20.0)</td>
<td>8 (40.0)</td>
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</tr>
</tbody>
</table>

LN: lymph node, ER: estrogen receptor, PR: progesterone receptor.

*Significant at $P<0.05$. 
Figure 1: Immunohistochemical staining of primary invasive ductal carcinoma (IDC) of the breast: (A) Immature (CD1a+) dendritic cells infiltrating among tumor cells. Inset: CD1a+ dendritic cells establishing an intimate contact with tumor cells that form a duct (CD1a x100, inset x400); (B) Immature (CD1a+) dendritic cells intermixed with tumor cells in a high grade tumor (CD1a x400); (C) Mature (CD83+) dendritic cells seen in the peritumoral area (CD83 x400); (D) Mature (CD83+) dendritic cells scattered among lymphocytes at the margin of the tumor (CD83 x400); (E) Low VEGF expression: positive brown cytoplasmic staining in less than 25% of tumor cells (VEGF x 200); (F) High VEGF expression: brown cytoplasmic staining in almost all tumor cells (VEGF x 200).
Relationship between VEGF expression and clinicopathological parameters

Forty-four of the 50 cases studied (88%) showed positive VEGF expression. VEGF was mainly localized in the cytoplasm of the tumor cells (Figures 1E, F). Table I shows the relationship between VEGF expression and clinicopathological factors. VEGF expression by IDC correlated directly with positive lymph node metastases ($P=0.014$), and negative steroid receptor status (ER and PR) ($P=0.039$ and 0.049 respectively). No significant relationship was found between VEGF expression and age of the patient ($P=0.623$), tumor size ($P=0.147$) and tumor grade ($P=0.645$).

Relationship between DC counts and VEGF expression

No significant relationship was found between the CD1a+ DC count and the VEGF score ($P=0.104$) (Figure 2A). On the other hand, a significant inverse relationship was detected between the CD83+ DC count and VEGF expression ($P=0.005$) (Figure 2B).

DISCUSSION

The present study investigated the maturation-specific tumor infiltration by DCs in IDC of the breast. Immature and mature DCs were defined by their expression of CD1a and CD83 respectively. CD1a+ DCs were detected in all cases, with a mean of 11.3 cells/HPF, whereas CD83+ DCs were identified in 72% of cases, with a mean of 5.8 cells/HPF. The lower number of cases showing CD83+ cells, and the lower mean number of mature DCs compared with immature ones indicate that some breast cancers fail to drive DCs into the maturation phase, possibly due to tumor-related or local microenvironmental factors.

In the present work, CD1a+ DCs were observed within the tumor nests, in close association with tumor cells, whereas CD83+ DCs were seen in the peritumoral areas. This compartmentalization has been previously described in carcinomas of the breast (7), cervix (25), and oral cavity (22). In our study, CD83+ cells were commonly observed scattered among lymphocytes that infiltrated the area adjacent to the tumor. Bell et al (7) suggested that peritumoral clustering of T cells and mature DCs may resemble DC-T cell clustering of secondary lymphoid organs, which characterize immune reactions, possibly tumor-specific.

In the current study, the CD83+ DC count correlated with good prognostic features of breast carcinoma (namely, smaller tumor size, negative lymph node status, positive steroid receptor status, and lower tumor grade), suggesting that mature DCs may be of great importance in initiating the primary anti-neoplastic immune response. Meanwhile, there was no significant relationship between the CD1a+ DC count and the VEGF score ($P=0.104$) (Figure 2A). On the other hand, a significant inverse relationship was detected between the CD83+ DC count and VEGF expression ($P=0.005$) (Figure 2B).

Figure 2: The relationship between (A) immature (CD1a+), and (B) mature (CD83+) dendritic cell (DC) counts and VEGF expression score in invasive ductal carcinoma (IDC) of the breast.
DC count and any of the prognostic features except for negative steroid receptor expression. These findings are in agreement with those of Iwamoto et al. (13), who reported that the number of mature DCs in breast carcinoma correlated inversely with lymph node metastasis, whereas the number of immature DCs did not. They also reported that the number of mature DCs was significantly associated with both relapse-free and overall survival rates, suggesting that DC maturation is an important predictor of prognosis. Treilleux et al. (18), found that the presence of immature DCs showed no relationship with survival of early breast cancer patients, whereas the presence of mature DCs correlated with more aggressive tumors. The discrepancy between their results and ours regarding mature DCs may be attributed to their use of a different marker of mature DCs (CD208/DC-LAMP), and the different study population (early breast cancer). The lack of availability of follow-up data was a limitation of the present study, so the relationship between the DC count and prognosis could not be assessed.

In the present work, the inverse relationship between CD83+ DC count and tumor size, together with their striking peritumoral location suggest that their presence may aid in limiting tumor growth. In addition, the inverse relationship between CD83+ DC count and tumor grade, suggests that the degree of tumor differentiation may affect the maturation status of tumor-infiltrating DCs. Coventry et al (17) found no association between the density of CD1a+ cells and grade of breast cancer, whereas only the more differentiated tumors could attain full maturation of a subset of their DC population. Poindexter et al (12) reported that negative sentinel lymph nodes (SLNs) from patients with breast cancer contained more CD83+ cells than positive SLNs, whereas the numbers of CD1a+ cells within these two groups were similar, suggesting that a tumor-free SLN is immunologically competent. They also reported that more CD1a+ DCs were found in the tumor-containing SLNs when grade III tumors were analyzed, suggesting that the undifferentiated state of the tumor inhibits DC maturation.

The clinical significance of tumor-infiltrating dendritic cells has been reported in a variety of other human solid tumors as well. In gastric carcinoma, the number of CD1a+ and CD83+ DCs in the tumor border was inversely correlated with positive lymph node metastases, and patients with a low number of CD83+ DCs had shorter survival rates (26). In non-small cell lung cancer, the well-differentiated tumors tended to show a higher number of S100+ DCs, and a high DC infiltration was significantly related to a better prognosis (16). In colorectal carcinoma, higher DC infiltration was positively associated with survival (27,28), and the number of S100+ DCs was significantly lower in patients with larger tumor size, nodal metastasis, hepatic metastasis, and tumors more advanced than stage III (TNM) (28). In cervical neoplasia, a lower population of CD83+ DCs was observed within the squamous cell carcinoma group compared with cervical intraepithelial neoplasia 3 (CIN3), suggesting the existence of an active immune response in the CIN3 lesions that prevents their progression to invasive carcinoma (25).

The suitability of DCs as a basis for immunotherapy for cancer has been recently challenged, as it was found that cancer cells may escape immune surveillance by secretion of immunosuppressive cytokines that induce a defective immune cell function (22). Gabrilovich et al (29) demonstrated that VEGF production by cancer cells inhibits functional maturation of DCs from CD34+ precursors, allowing tumors to avoid induction of an immune response. Accordingly, in the current work, we assessed the expression of VEGF by IDC of the breast, and its relationship to DC infiltration. No significant relationship was found between CD1a+ DC count and the VEGF score. On the other hand, the number of CD83+ DCs was significantly greater in tumors showing lower VEGF expression. Similar observations have been previously reported in breast carcinoma (13). Furthermore, an inverse relationship was detected between the S100+ DC count and the expression of VEGF in gastric carcinoma (30) and non-small cell lung cancer (16), with a high VEGF expression / low DC infiltration being a poor prognostic factor. It has been reported that VEGF can inhibit DC maturation in vitro, block DC development, and reduce the number of DCs in vivo (29), whereas anti-VEGF antibodies increased the number and function of DCs in vivo (31). These results of basic research closely correlate with our observations in human breast carcinoma specimens. This inverse relationship between VEGF expression and mature DCs might be attributable to inhibition of DC maturation by tumor-derived VEGF, and can partly explain why tumor immunity may not be effectively induced in patients with breast carcinoma.

Full understanding of the human immune response against tumors may open up new horizons for treating these tumors. Findings of the present study strongly suggest that mature DCs expressing CD83 play an important role in the initiation of the primary anti-tumor immune response in breast carcinoma, and that VEGF seems to clinically act as an inhibitor to DC function.
REFERENCES


