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IL-17 and VEGF are increased and correlated to systemic inflammation, immune suppression, and malnutrition in patients with breast cancer

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Abstract

Relationships between inflammation and innate immunity in cancer are widely accepted today; however, the precise cell mechanisms mediating these relationships have not yet been elucidated. Interleukin (IL)-17 is a proinflammatory cytokine that has been reported to induce inflammation in patients with autoimmune diseases. Myeloid-derived suppressor cells (MDSC) may contribute to the negative regulation of immune responses during cancer and inflammation. Vascular endothelial growth factor (VEGF) is reported to have multiple biological actions including increasing vascular permeability, neovascularization, and possible inhibition of immune function in malignant diseases. This study investigated the status of systemic inflammation and immune suppression associated with IL-17 and VEGF in patients with breast cancer. IL-17 production and the serum levels of VEGF were also increased in advanced stages of the disease. The production of IL-12, which induces Th1 cells, and the stimulation index (SI), which is a marker of cell-mediated immune function, were both shown to decrease along with disease advancement. Also, the production of IL-17 and the VEGF levels were both positively correlated with the levels of MDSC, the neutrophil-to-lymphocyte ratio (NLR), and C-reactive protein (CRP), and were inversely correlated with IL-12 production and the SI. Nutritional markers, including prealbumin (PA), transferrin (TF), and retinol-binding protein (RBP), were also shown to be significantly lower in patients with high production of IL-17 or high levels of VEGF. These data clearly showed that IL-17 and VEGF, whose levels correlated with each other and with those of MDSC, were significantly associated with disease advancement, systemic inflammation, suppression of cell-mediated immunity including Th1 induction, and malnutrition.

Keywords

breast cancer, cachexia, IL-17, immunosuppression, MDSC, VEGF

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Introduction

Breast cancer is the most commonly diagnosed tumor in women worldwide, its incidence is continuously increasing, and breast cancer-related death is the second leading cause of disease-related death.[1] It is therefore important to elucidate the pathogenic factors involved in breast cancer. We have studied several immunological factors, including myeloid-derived suppressor cells

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(MDSC), interleukin (IL)-17, and vascular endothelial growth factor (VEGF), in various types of cancer.[2–4]

Although a causal relationship between inflammation and innate immunity in cancer is more widely accepted today, the precise cell mechanisms mediating this relationship have not been elucidated. IL-17 is a proinflammatory cytokine that is primarily secreted by T helper (Th)17 cells and innate lymphoid cells including γδ T cells and natural killer cells.[5,6] The IL-17-producing γδ T cells/neutrophil axis has been a recent focus in breast cancer research.[7,8] The IL-17 family comprises six cytokines, including IL-17A to IL-17F. Among them, IL-17A and IL-17F share the highest sequence homology and have similar biological functions. Both bind to IL-17RA and IL-17RC chains.[5] Down-stream of the IL-17 receptor, NFκB activator 1 (Act1), and TNF (transforming growth factor) receptor associated factor (TRAF) 4 are important adapter proteins that transmit the intercellular signal cascade to activate NFκB. Suppressive myeloid cells were previously described in patients with cancer[9,10] although their functional significance in the immune system has only recently been evaluated. Accumulating evidence[11–14] suggests that a population of cells with suppressive activity, referred to as MDSC, may contribute to the negative regulation of immune responses during cancer and other conditions. We previously characterized circulating numbers of MDSC in patients with various types of malignant diseases and reported that increased production of IL-17 correlated with immune suppression involving MDSC and with malnutrition in patients with gastrointestinal cancers.[2,3,15]

VEGF, previously known as vascular permeability factor, a 45 kDa protein, belongs to a family of platelet-derived growth factors. To date, several forms of VEGF have been distinguished, including isoforms A, B, C, D, and E.[16–18] The biological significance of the different forms of VEGF has yet to be definitively determined. Elevated VEGF levels are reportedly associated with advanced melanoma, together with negative immune reactions, including type 2-helper T cell (Th2) dominance and impaired dendritic cell function.[19,20] We have also reported that elevated serum levels of VEGF are an effective marker of inflammation, immune suppression, and malnutrition in patients with ovarian cancer.[21]

Cachexia due to cancer is a complex metabolic disorder that includes loss of adipose tissue due to lipolysis, loss of skeletal muscle, elevation of resting energy consumption, anorexia, and reduction of food intake.[22–24] Immunological disorder and acute phase response proteins including VEGF have been reported to be associated with the development of cachexia in patients with cancer.

In patients with breast cancer, tumor aggressiveness was reported to be enhanced by IL-17 via induction of angiogenic factors such as chemokines and VEGF.[25] IL-17 has also been reported to induce the secretion of CXCL1 and CXCL5 from mammary cancer cells and to increase the suppressive function of MDSC.[26] Immune responses have been classified into type I responses, which provide cell-mediated immune responses, and type II responses, which support B helper cells' function and humoral immune responses. These responses are regulated by the Th1 and Th2 subsets, respectively. The typical immunological status of patients with advanced stages of cancer has been demonstrated to be suppressed cell-mediated immunity, and the condition of Th2 dominance may be one of the major causes of this suppression. Production of IL-12, essential for the maintenance of Th1, has been reported to decrease with the advancement of cancer,[27] and to be a major cause of Th2 dominance. IL-12 production was also measured in this study and analyzed regarding its correlation with IL-17 and VEGF. This study investigated the status of systemic inflammation and immune suppression associated with IL-17, MDSC, and VEGF, and examined the relationships between these factors in patients with breast cancer. Their association with nutritional impairment was also assessed.

Patients and methods

Study subjects

Blood samples were collected from 108 patients with breast cancer including 18 patients with stage I disease, 37 with stage II, 17 with stage III, and 36 with stage IV, as well as from 18 healthy volunteers. The patients' characteristics are listed in Table 1. All of the enrolled patients received treatments including surgery and chemotherapy in the Department of Organ Regulatory Surgery at Fukushima Medical University Hospital (Fukushima, Japan) between May 2011 and August 2012. The patients' ages ranged from 38 to 85 years (median: 56.7 years) at

Table 1. Patients' characteristics.

Characteristic	n (%)
Age at diagnosis	
Median age	56.7 (range: 38–85)
>50	53 (49.1%)
≤50	55 (50.9%)
Tumor size	
>2 cm	62 (57.4%)
≤2 cm	46 (42.6%)
Nodal status	
N0	19 (17.6%)
N1	39 (36.1%)
N2	15 (13.9%)
N3	35 (32.4%)
TNM stage at diagnosis	
I	18 (16.7%)
II	37 (34.3%)
III	17 (15.7%)
IV	36 (33.3%)

histological confirmation of diagnosis, and blood samples were collected prior to initiation of any of the treatments. This study was approved by the ethics committee at Fukushima Medical University (2010–2017), and written informed consent was obtained from all of the enrolled patients and healthy volunteers.

Blood samples

Peripheral blood mononuclear cells (PBMCs) were separated on Ficoll-Hypaque (Pharmacia-Biotech, Uppsala, Sweden) columns. The isolated PBMCs were washed twice with RPMI-1640 (Wako Pure Chemical Industries Ltd, Osaka, Japan) and maintained at −80°C in freezing medium (BLC-1; Wako Pure Chemical Industries Ltd) until used.

Flow cytometric analysis of MDSC

In this study, $CD14^{-}$, CD11b+, and CD33+ cells were considered to be MDSC. PBMCs were labeled with fluorescent isothiocyanate (FITC), phycoerythrin (PE), and phycoerythrin cyanin 5.1 (PC5)-labeled antibodies. The antibodies used included FITC-conjugated anti-CD14 (Abcam, Cambridge, UK), PE-conjugated anti-CD11b (Beckman Coulter Inc., Marseille, France), and PC5-conjugated anti-CD33 (Beckman Coulter), diluted in phosphate-buffered saline (PBS) to a concentration of 10 and 50 μg/mL. Cells were incubated with the antibodies for 20 min at 4°C and were then washed with PBS. Data acquisition and analysis were performed with the FACSAriaII flow cytometer (BD Biosciences, Mountain View, CA) using Flow Jo software (TreeStar Inc., Ashland, OR).

Cytokine production by PBMCs

PBMCs (10^6 cells) were incubated in 1 mL of RPMI-1640 medium supplemented with 10% heat-inactivated fetal calf serum (Gibco BRL, Rockville, MD) and 20 μg/mL of phytohemagglutinin (PHA, Sigma, St. Louis, MO) in 5% CO2 at 37°C for 24 h. The supernatants of these cultures were aliquoted and frozen at −80°C until use. Aliquots of the supernatants of these samples were subsequently thawed and used for measurement of IL-17(A) and IL-12 concentrations using enzyme-linked immunosorbent assay (ELISA) test kits (R and D Systems, Minneapolis, MN, USA). Each sample was used only once after thawing. *Staphylococcus aureus* Cowan 1 was used for stimulation for the assay of IL-12 production.

Lymphocyte proliferation assay

Lymphocyte proliferation assays were performed using PBMC suspended in RPMI-1640 (Wako Pure Chemical Industries) containing 10% fetal calf serum (Gibco BRL). Following the addition of 10 μg/mL PHA into the PBMC culture wells, the cells were kept at 37°C in a 5% CO_2 atmosphere. PHA blastogenesis was observed for a period of 80h. ^{3}H-thymidine (Japan Radioisotope Association, Tokyo, Japan) was added to the wells for the last 8 h of incubation. The cells were then harvested and ^{3}H-thymidine incorporation was determined using a liquid scintillation counter (PerkinElmer Inc., Waltham, MA) and expressed as counts per minute (cpm). The stimulation index (SI) was obtained by calculating the total cpm/control cpm and was utilized as a marker of cell-mediated immunity. The controls used were PBMCs that were treated as above except for PHA addition.

Serum levels of VEGF and of nutritional and inflammatory markers

Peripheral venous blood sera from all subjects were stored at −80°C until use. Serum concentrations of VEGF were measured using an ELISA (R and D systems) according to the manufacturer's

protocol. To evaluate the nutritional status of the subjects, serum concentrations of prealbumin (PA; determined by turbidimetric immunoassay), retinol-binding protein (RBP; determined by latex agglutination immunoassay), and transferrin (TF; determined by turbidimetric immunoassay) were measured using standard protocols. C-reactive protein (CRP; determined by nephelometry) and the neutrophil-to-lymphocyte ratio (NLR) in peripheral blood samples were used as indicators of inflammation. Moreover, these patients were divided into two groups: the IL-17 production group was further subdivided into patients with higher or lower than 1200 pg/mL, and the VEGF group was further subdivided into patients with levels higher or lower than 339 pg/mL. The cut-off values chosen for each group were the median levels in the patients enrolled in this study. The IL-17 production and the VEGF groups, as well as the subdivisions of each of these two groups, were compared in terms of their correlations with parameters such as VEGF; MDSC; inflammatory markers including the NLR, CRP, and white blood cell count (WBC); markers for cell-mediated immune function including the SI and IL-12 production; and rapid turnover proteins used as nutritional markers including PA, TF, and RBP.

Statistical analysis

Differences between the groups were determined using Student's t-test. Relationships between two variables were quantified by Spearman's rank correlation coefficient. Significance was assumed at $P < 0.05$. Inadequate amounts of blood were obtained from some patients, and in these cases, certain measurements were not possible.

Results

PBMCs and sera were collected from 108 patients with breast cancer and 18 healthy volunteers, and these samples were investigated as follows.

Production of IL-17

The production of IL-17 by PBMCs in stages I, II, III, and IV was 806.3 ± 46.5, 826.7 ± 32.8, 1062.3 ± 168.1, and 1668.9 ± 265.4 pg/mL, respectively. IL-17 levels were significantly higher in stage IV than in healthy volunteers (549.3 ± 109.2 pg/mL, $P < 0.05$), or in stage I ($P < 0.05$), stage II ($P < 0.05$), or stage III ($P < 0.05$, Figure 1).

Serum VEGF levels

The serum concentrations of VEGF in healthy volunteers, and in patients with stages I, II, III, and IV were 243.1 ± 58.2, 238.9 ± 31.9, 259.4 ± 38.2, 384.0 ± 61.9, and 421.3 ± 51.0 pg/mL, respectively, and were significantly higher in stage IV than in healthy volunteers ($P < 0.05$), or in stage I ($P < 0.05$) or stage II ($P < 0.05$, Figure 2).

Production of IL-12

The production of IL-12 in healthy volunteers and in stages I, II, III, and IV was 204.2 ± 8.2, 178.5 ± 22.3, 174.9 ± 59.2, 116.8 ± 6.2, and 97.2 ± 9.0 pg/mL, respectively. IL-12 levels were significantly lower in stage IV than in healthy volunteers ($P < 0.05$), or in stage I ($P < 0.05$) or stage II ($P < 0.05$). IL-12 levels were also significantly lower in stage III than in healthy volunteers ($P < 0.05$), or in stage I ($P < 0.05$) or stage II ($P < 0.05$, Figure 3).

Stimulation index

The SI of patients with stages I, II, III, and IV was 600.7 ± 56.3, 491.7 ± 138.9, 441.9 ± 32.0, and 359.7 ± 58.2, respectively. The index was significantly lower in stage IV than in stage I ($P < 0.05$), II ($P < 0.05$), or III ($P < 0.05$, Figure 4).

Correlations of IL-17 production and VEGF levels with inflammation, MDSC, and cell-mediated immune function

Figure 5 shows the correlations of IL-17 production with the levels of VEGF, numbers of MDSC, the NLR, and the SI. IL-17 production was significantly positively correlated with the levels of VEGF ($P < 0.05$), MDSC ($P < 0.05$), and the NLR ($P < 0.05$), and was inversely correlated with the SI ($P < 0.05$) and with IL-12 production ($P < 0.05$). Figure 6 shows the correlation of VEGF levels with parameters other than IL-17. The levels of VEGF were significantly positively correlated with numbers of MDSC ($P < 0.05$) and the NLR ($P < 0.05$) and were inversely correlated with IL-12 production ($P < 0.05$) and the SI ($P < 0.05$).

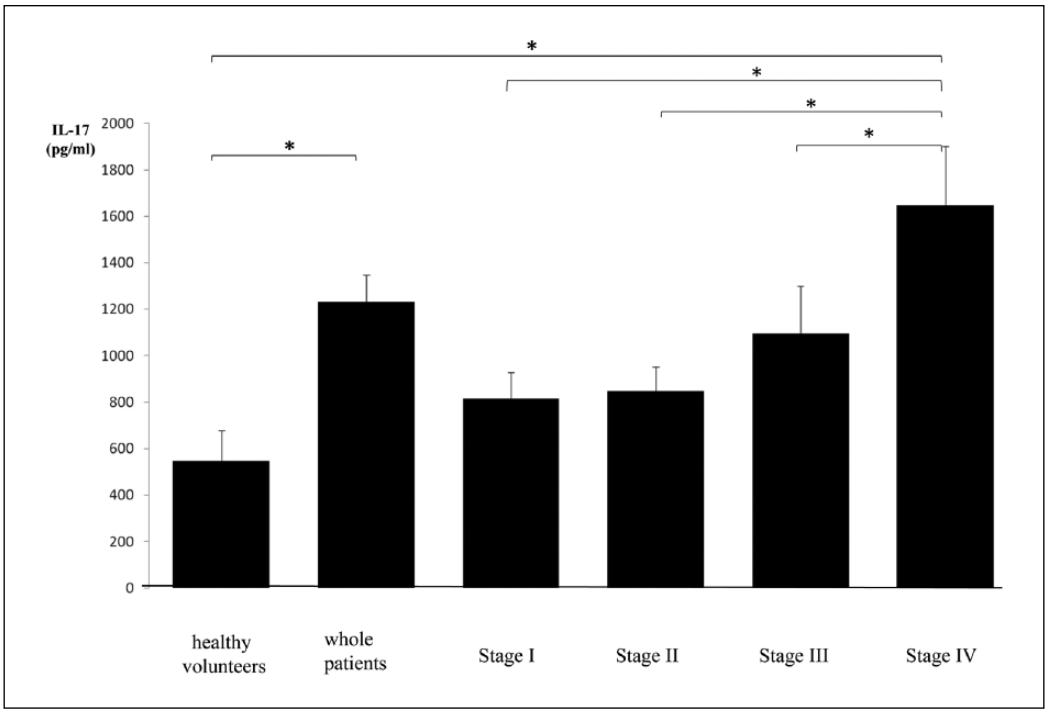


Figure 1. Production of interleukin (IL)-17 in patients with breast cancer.
The production of IL-17 significantly increased in patients with stage IV compared with healthy volunteers and patients with stages I, II, and III breast cancer. *$P < 0.05$.

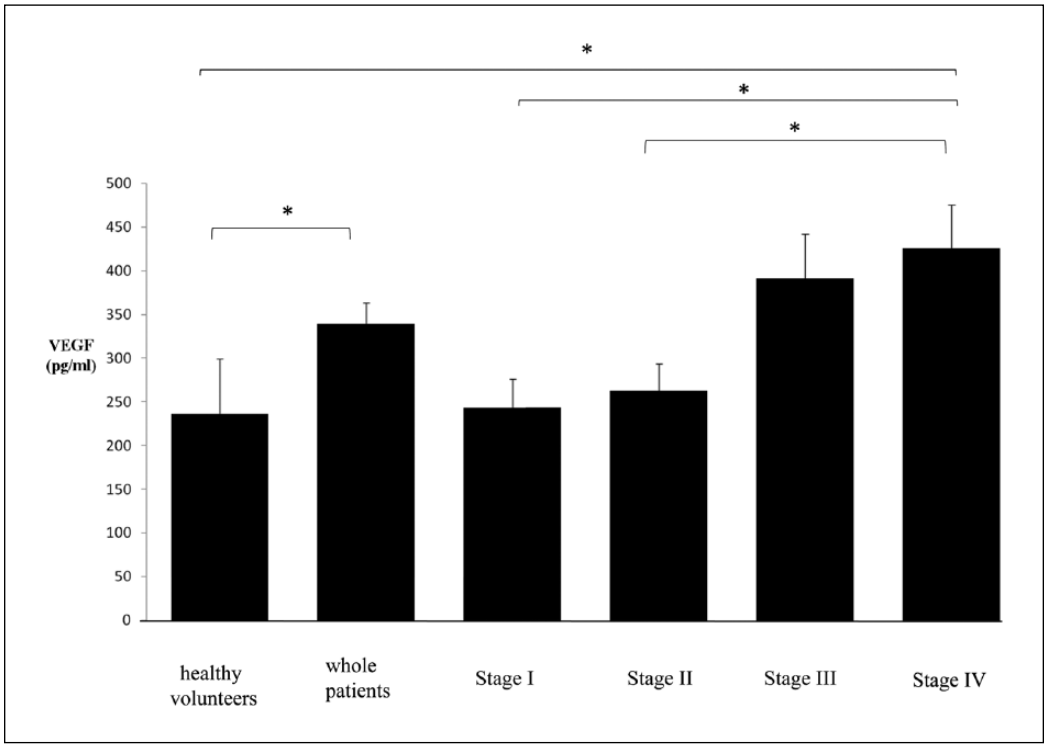


Figure 2. Serum concentrations of vascular endothelial growth factor (VEGF) in patients with breast cancer.
Serum levels of VEGF significantly increased in patients with stage IV compared with healthy volunteers and patients with stages I, II, and III breast cancer. *$P < 0.05$.

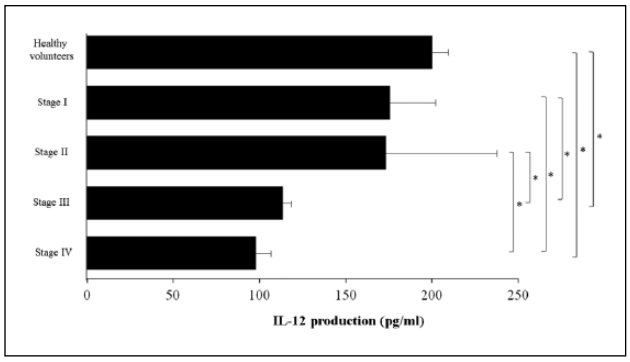


Figure 3. Production of interleukin (IL)-12 in patients with breast cancer.
The production of IL-12 significantly decreased in patients with stages III and IV compared with patients with stages I and II and healthy volunteers. The methodology of IL-12 production is described in the text. *$P < 0.05$.

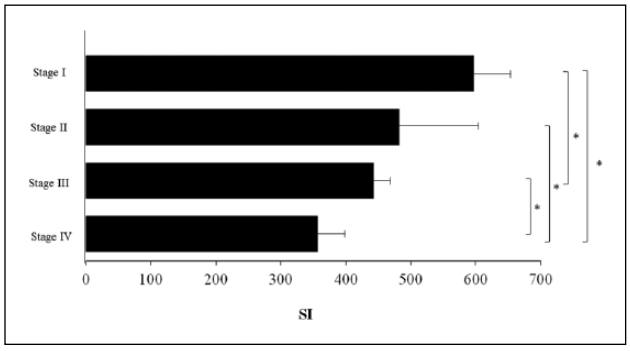


Figure 4. Stimulation Index (SI) in patients with breast cancer.
The SI decreased with advancement of breast cancer and lowest in stage IV. The methodology for obtaining the SI is described in the text. *$P < 0.05$.

Comparisons of patients with high and low levels of IL-17 and VEGF

The patients were divided into two groups; these groups were subdivided based on values higher or lower than the median level of IL-17 production or of the serum level of VEGF. Table 2 shows the correlation between high and low levels of IL-17 production with the levels of VEGF and numbers of MDSC, inflammatory markers, nutritional markers, and markers of cell-mediated immune function. The levels of VEGF, numbers of MDSC, the NLR, CRP, and WBC were significantly lower ($P < 0.01$, $P < 0.05$, $P < 0.05$, $P < 0.01$, $P < 0.05$, respectively), and those of PA, TF, RBP, the SI, and IL-12 production were significantly higher (all $P < 0.05$) in patients with lower levels of IL-17 production than in patients with higher IL-17 production. Table 3 shows the correlation between high and low VEGF levels and these parameters except for IL-17. The numbers of MDSC, the NLR, CRP, and WBC were significantly higher ($P < 0.05$, $P < 0.05$, $P < 0.01$, $P < 0.05$, respectively) and the levels of PA, TF, RBP, the SI, and IL-12 production were significantly lower (all $P < 0.05$) in patients with higher VEGF levels than in patients with lower VEGF levels.

Discussion

The aim of this study was to characterize IL-17, VEGF, and MDSC in patients with breast cancer. The production of IL-17 and the serum levels of VEGF increased in advanced stages of the disease. The production of IL-12, which induces Th1 cells, and the SI, a marker of cell-mediated immune function, were both shown to decrease along with disease advancement. Additionally, the production of IL-17 and the VEGF levels were both positively correlated with the numbers of MDSC and the NLR, and were inversely correlated with IL-12 production and the SI. Moreover, CRP and WBC were significantly higher, and IL-12 production, the SI and nutritional markers including PA, TF, and RBP were significantly lower in patients with high production of IL-17 or high levels of VEGF. These data clearly showed that IL-17 and VEGF levels correlated with each other, and were significantly associated with disease advancement, systemic inflammation, suppression of cell-mediated immunity including Th1 induction, and malnutrition.

Suppression of cell-mediated immune reactions in patients with malignant diseases has been long studied,[27,28] and it is well known that systemic inflammation plays a major role in such suppression. In this study, the SI and the production of IL-12 decreased along with disease advancement and were lowest in stage IV; thus, a decrease in Th1 differentiation seems to be one of the mechanisms of immune suppression, as we have also reported previously.[27] IL-10, one of the major products of MDSC, is supposedly increased in patients with cancer. This might decrease the number of type I macrophages or dendritic cells that produce IL-12, and result in Th2 dominance.[10] Since the levels of MDSC, IL-17 production, and VEGF were all correlated with each other, and these three parameters were tightly associated with markers of systemic inflammation and suppression of cell-mediated immune reactions in this study, this inflammation-related axis is another

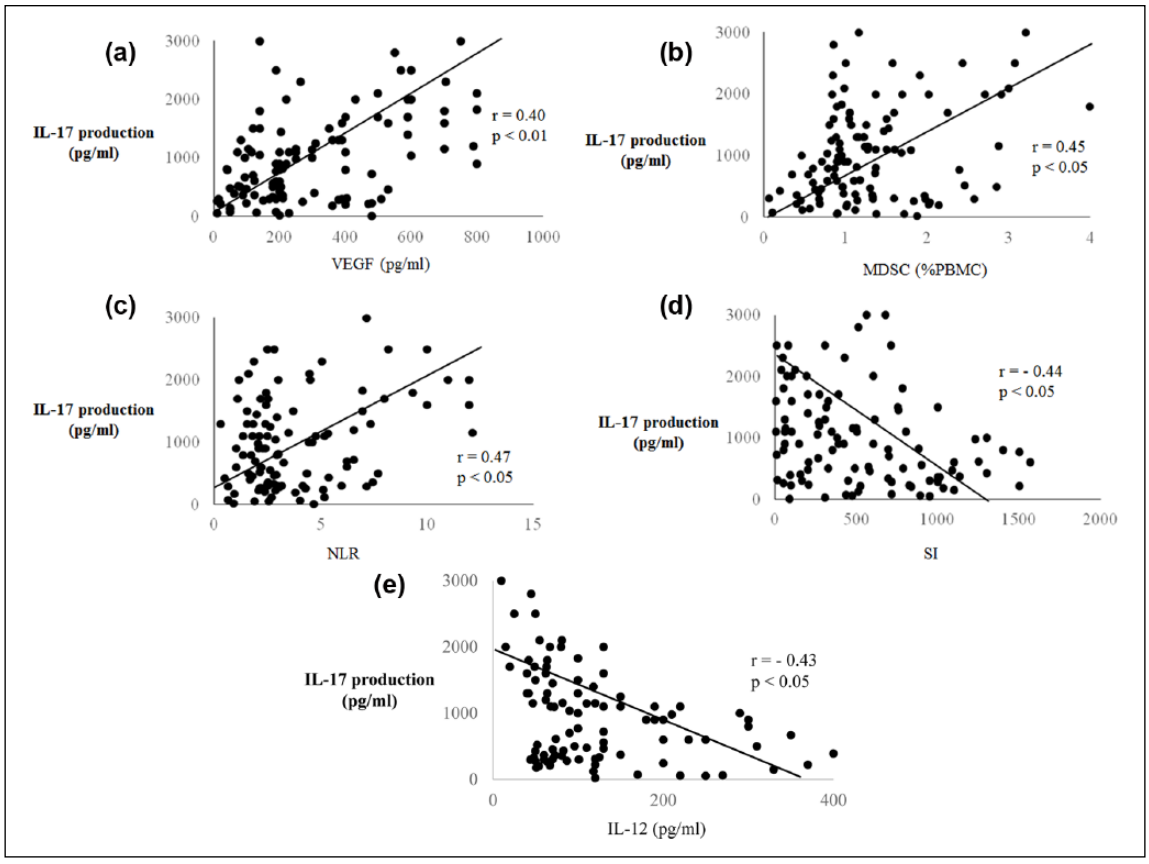


Figure 5. Correlations of interleukin (IL)-17 production with various immunological parameters.
Production of IL-17 was positively correlated with (a) serum levels of VEGF, (b) circulating numbers of MDSC, and (c) the NLR, and inversely with the (d) SI and (e) IL-12 production. The methodology for obtaining IL-17 production is described in the text.
VEGF: vascular endothelial growth factor; MDSC: myeloid-derived suppressor cells; NLR: neutrophil-to-lymphocyte ratio; SI: stimulation index.

important mechanism of immune suppression in breast cancer.

One of the events linking inflammation and cancer is an increase in inflammatory cytokines such as IL-17 and stress growth factors such as VEGF. It has also been reported that IL-17 induces VEGF-A expression via signal transducer and activator of transcription (STAT)3 signaling mechanisms.[28–31] Tumor aggressiveness is enhanced by IL-17 via induction of angiogenic factors including chemokines and VEGF. The tumor-derived IL-1β induce IL-17 expression by γδ T cells, which results in expansion and polarization of neutrophils with MDSC characteristics.[32] Therefore, it is reported that the pathogenic mechanisms driven by IL-17 during breast cancer progression include direct effects of IL-17 on tumor cells promoting tumor cell survival and invasiveness, regulation of tumor angiogenesis, and interaction with MDSC to inhibit antitumor immune response.[25] MDSC have been reported to express receptors for VEGF-A and be activated by VEGF-A, and regulatory T cells (Treg) may also increase through MDSC-associated mechanisms.[19,20] Although our results were limited to peripheral circulating samples, an MDSC-IL-17-VEGF axis seems to exist in patients with breast cancer and, very importantly, this axis seems to be closely related to cancer-related systemic inflammation, immune suppression, and nutritional impairment. The present data also suggest that this axis may be activated further in terminal stages of cancer when nutritional status is impaired, as evidenced by low levels of rapid turnover proteins including PA, TF, and RBP. Previously reported results have indicated that this axis is closely related to nutritional status and appears to play a key role in the development of cancer cachexia.

Conclusion

This study demonstrated that increased numbers of MDSC and increased production of IL-17 and

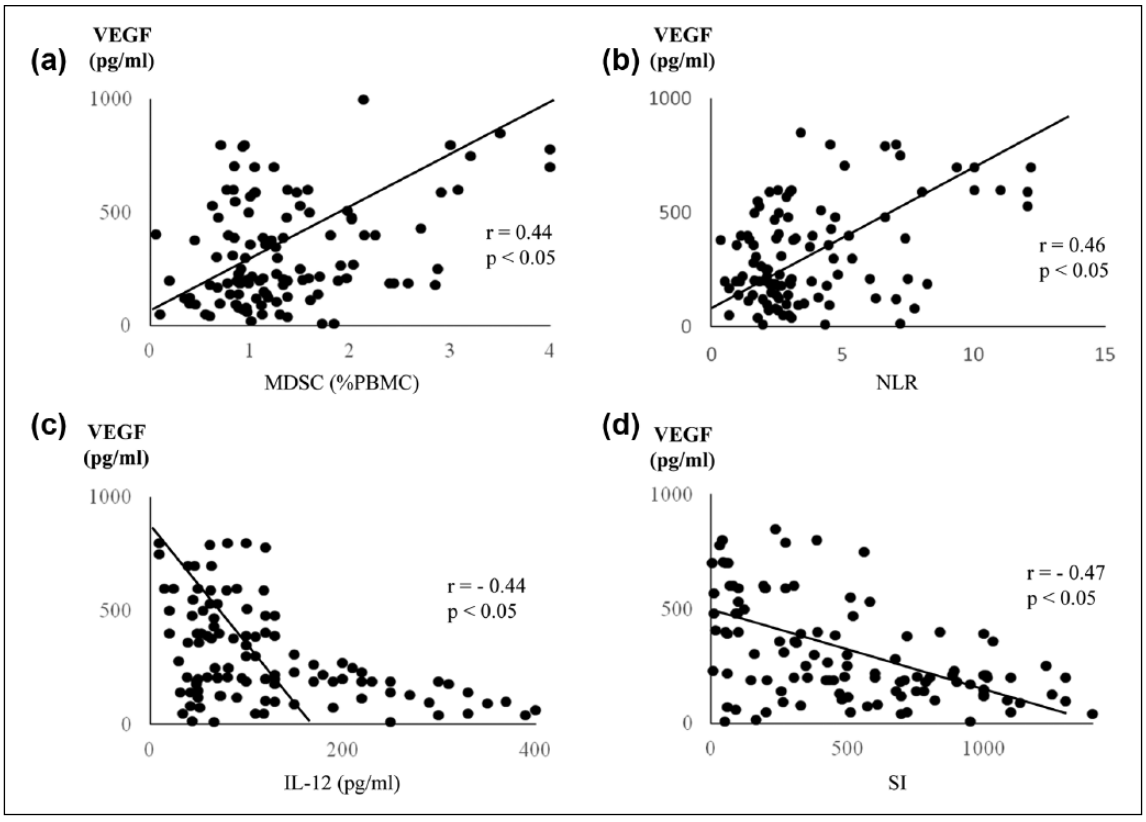


Figure 6. Correlations of serum concentration of vascular endothelial growth factor (VEGF) with various immunological parameters.
Serum concentrations of VEGF were significantly correlated with (a) circulating numbers of MDSC and (b) the NLR and inversely with production of (c) IL-12 and (d) the SI.
MDSC: myeloid-derived suppressor cells; NLR: neutrophil-to-lymphocyte ratio; IL: interleukin; SI: stimulation index.

Table 2. Comparisons of patients with high and low levels of IL-17.

IL-17 (pg/mL)	≥1200	<1200	*P* value
VEGF (pg/mL)	480.6 ± 326	250.6 ± 117	<0.01
MDSC (%PBMC)	2.54 ± 2.48	1.16 ± 1.44	<0.05
NLR	5.66 ± 2.13	2.56 ± 1.52	<0.05
CRP	0.80 ± 1.93	0.26 ± 0.89	<0.01
WBC	6874.2 ± 824	5229.8 ± 261	<0.05
SI	367.5 ± 312	622.8 ± 483	<0.05
PA (mg/dL)	18.1 ± 1.08	24.5 ± 0.70	<0.05
TF (mg/dL)	202.6 ± 9.54	253.7 ± 5.46	<0.05
RBP (mg/dL)	2.26 ± 0.08	3.03 ± 0.16	<0.05
IL-12	80.6 ± 6.89	124 ± 16.2	<0.05

IL-17: interleukin-17; PBMC: peripheral blood mononuclear cell; VEGF: vascular endothelial growth factor; MDSC: myeloid-derived suppressor cells; NLR: neutrophil-to-lymphocyte ratio; CRP: C-reactive protein; WBC: white blood cell count; SI: stimulation index; PA: prealbumin; TF: transferrin; RBP: retinol-binding protein; IL-12: interleukin-12.
The levels of VEGF, MDSC, the NLR, CRP, and WBC were significantly lower ($P < 0.01$, $P < 0.05$, $P < 0.05$, $P < 0.01$, $P < 0.05$, respectively), and those of PA, TF, RBP, the SI, and IL-12 production were significantly higher (all $P < 0.05$) in patients with lower levels of IL-17 production compared to those in patients with higher IL-17 production.

Table 3. Comparisons of patients with high and low levels of VEGF.

VEGF (pg/mL)	>346	<346	*P* value
MDSC (%PBMC)	2.54 ± 2.48	1.16 ± 1.44	<0.05
NLR	5.66 ± 2.13	2.56 ± 1.52	<0.05
CRP	0.80 ± 1.93	0.26 ± 0.89	<0.01
WBC	6874 ± 824	5229 ± 261	<0.05
SI	367.6 ± 312	622.9 ± 483	<0.05
PA (mg/dL)	18.1 ± 1.08	24.5 ± 0.70	<0.05
TF (mg/dL)	202.6 ± 9.54	253.9 ± 5.46	<0.05
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IL-12	80.6 ± 6.89	124.0 ± 16.2	<0.05

VEGF: vascular endothelial growth factor; PBMC: peripheral blood mononuclear cell; MDSC: myeloid-derived suppressor cells; NLR: neutrophil-to-lymphocyte ratio; CRP: C-reactive protein; WBC: white blood cell count; SI: stimulation index; PA: prealbumin; TF: transferrin; RBP: retinol-binding protein; IL-12: interleukin-12.
The levels of MDSC, the NLR, CRP, and WBC were significantly higher ($P < 0.05$, $P < 0.05$, $P < 0.01$, $P < 0.05$, respectively) and the levels of PA, TF, RBP, the SI, and IL-12 production were significantly lower (all $P < 0.05$) in patients with higher VEGF levels compared to those in patients with lower VEGF levels.

VEGF correlate with systemic inflammation, nutritional impairment, and inhibition of cell-mediated immunity in breast cancer and thus may be involved in an immunological mechanism for the induction of cancer cachexia. Future studies are required to investigate the possibilities for clinical control of such immune suppression, chronic inflammation, and malnutrition (typically cancer cachexia) through modulation of the activation process of this inflammation-related immune disorder using selective inhibition by molecular targeting.

Declaration of conflicting interests

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