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RESEARCH ARTICLE

Interleukin-17 levels correlate with poor prognosis and vascular endothelial growth factor concentration in the serum of patients with non-small cell lung cancer

Bo Pan¹, Dehai Che¹, Jingyan Cao¹, Jing Shen¹, Shi Jin¹, Yongxu Zhou²#, Fang Liu¹, Kuo Gu¹#, Yingchun Man³#, Lihua Shang¹, and Yan Yu¹

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Abstract

Objective: The aim of this study was to explore the clinical role of serum interleukin-17 in patients with non-small-cell lung cancer (NSCLC).

Materials and method: IL-17 expression and microvessel density (MVD) were measured via immunohistochemistry in 58 NSCLC tissues. Serum IL-17 and VEGF levels in NSCLC patients (n = 43) and healthy controls (n = 37) were analyzed via enzyme-linked immunosorbent assay.

Results: Serum IL-17 was elevated and the levels positively correlated with VEGF concentration in NSCLC patients. Multivariate analyses revealed that serum IL-17 levels were an independent prognostic factor in NSCLC.

Conclusion: IL-17 may play a role in NSCLC progression by promoting angiogenesis.

Introduction

Non-small cell lung cancer (NSCLC) is the leading cancer-related cause of death globally (Govindan et al., 2008; Li et al., 2012). The outcome of patients with NSCLC remains poor, and the overall five-year survival rate after surgery, chemotherapy, radiotherapy and targeted therapy is less than 15%, largely due to lung cancer cell metastasis (Mantovani et al., 2008; Solan & Werner-Wasik, 2003). Tumor progression has been recognized as the product of evolving crosstalk between different cell types within the tumor (Mueller & Fusenig, 2004). The relationship between cancer and inflammation has long been appreciated, and inflammatory processes are reportedly associated with tumor metastasis via angiogenesis and tumor immunity (Carmi et al., 2011; Tsai & Hsu, 2010). However, the cytokines and immunocytes involved in this process remain to be validated.

Interleukin-17 (IL-17), also known as IL-17A, is the prototypical member of the IL-17 family, which is composed of six cytokines, IL-17A–F (Gaffen, 2008; Korn et al., 2009). IL-17 is a recently identified cytokine that is predominantly expressed by Th17 cells but that is also expressed by macrophages, eosinophils, neutrophils, monocytes and CD8⁺ T cells to a lesser extent (Murugaiyan & Saha, 2009). IL-17 primarily acts as a pro-inflammatory cytokine and plays an active role in inflammation and cancer. IL-17 has several biologic activities, including the induction of IL-6, IL-8, IL-18, G-CSF and tumor necrosis factor-α (TNF-α) and the stimulation of vascular endothelial cell migration and neangiogenesis (Numasaki et al., 2003; Tartour et al., 1999). Accumulating evidence indicates a potential role of IL-17 in cancer initiation, growth, and metastasis, but these results are controversial.

There is growing evidence that angiogenesis is involved in the development and progression of NSCLC. IL-17 has been reported to mediate angiogenesis in humans via the stimulation of vascular endothelial cell migration and cord formation and via the regulation of the production of proangiogenic factors, such as basic fibroblast growth factor (bFGF), hepatocyte growth factor (HGF), and vascular endothelial growth factor (VEGF) (Ferrara, 2002; Takahashi et al., 2005; Toi et al., 1995). IL-17 promotes angiogenesis in tumor models (Ma et al., 2014), and IL-17 expression strongly correlates with the microvessel density (MVD) in human ovarian cancer (Yang et al., 2014), hepatocellular carcinoma (HCC) (Sun et al., 2014), and colorectal cancer (CRC) (Liu et al., 2011). Other reports have indicated that IL-17 significantly enhances the net angiogenic activity and in vivo growth of NSCLC by promoting CXCR-2-dependent angiogenesis (Hayata et al., 2013).
To date, few reports have examined the relevance of IL-17 to clinical parameters or its function in NSCLC angiogenesis. In the present study, we first found that the expression of IL-17 in NSCLC tissues was associated with increased MVD. In addition, we compared the serum concentrations of IL-17 in patients with NSCLC to those in healthy control subjects. The relationships between the serum levels of IL-17 and the clinico-pathological characteristics, the angiogenic factor levels, the response to chemotherapy and the survival of NSCLC patients were also investigated.

Methods

Patients and specimens

The study population included 101 patients with pathologically confirmed NSCLC and 37 healthy controls at the Harbin Medical University Cancer Hospital from January 2006 to January 2013. None of the patients received anticancer therapy before sampling. The tumor stage was determined according to the 2010 American Joint Committee on Cancer and International Union against Cancer tumor-node-metastasis (TNM) classification system. Tumor differentiation was graded according to the Edmondson and Steiner grading system. Tissue samples were obtained from 58 cases of NSCLC. Blood samples from all patients were collected before chemotherapy. In addition, blood was collected from all of these patients six weeks (two cycles) after the initiation of chemotherapy before sampling. The tumor stage was determined according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria based on their response to chemotherapy, which was recorded during regular clinical examinations.

Evaluation of the response to chemotherapy

All patients received platinum-based chemotherapy, including gemcitabine, vinorelbine, paclitaxel and docetaxel, every three weeks per cycle for a minimum of two cycles unless disease progression or unacceptable toxicity occurred. The 43 examined patients were categorized into two groups according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria based on their response to chemotherapy, which was recorded during regular clinical examinations.

Immunohistochemistry

To examine the relationship between the intratumoral density of IL-17+ cells and the MVD, 58 cases were selected for immunohistochemistry of serial sections of the entire tumor. The paraffin-embedded NSCLC samples were sliced into 5-μm sections. Each section was deparaffinized and rehydrated using an ethanol gradient. For antigen retrieval, the slides were incubated in 0.01 mmol/L citrate buffer (pH 6.0) for 15 min in a microwave oven. Endogenous peroxidase activity was blocked using a 3% hydrogen peroxide solution for 10 min at room temperature. After rinsing with PBS, the slides were incubated for 20 h at 4°C in the primary antibodies. The primary antibodies and dilutions were as follows: rabbit polyclonal antibody for IL-17 (1:100, Santa Cruz Biotechnology, Santa Cruz, CA) and rabbit monoclonal antibody for CD34 (1:200, Zhongshan Company, Beijing, China). The sections were washed in PBS three times and then incubated in a secondary antibody for 20 min at room temperature. Finally, the signal was developed using 3,3′-diaminobenzidine tetrahydrochloride (DAB), and all of the slides were counterstained with hematoxylin. The negative control sections were treated with PBS instead of the primary antibodies.

Microvessel immunostaining and counting

The MVD was assessed via immunohistochemistry using a CD34 marker. The stained sections were screened at 100× magnification for hot spots. The vessels were counted in five different fields at 200× magnification, and the average number of microvessels was recorded. Any red-staining cells that were morphologically compatible with endothelial cells which were in a cluster containing or lacking a lumen (rudimentary or well-formed) were considered as a microvessel and were counted. Two observers were responsible for the microvessel counting, and the mean value was used for analysis.

Enzyme linked immunosorbent assay

The serum levels of IL-17 and VEGF were detectable in all individuals examined via Enzyme linked immunosorbent assay (ELISA) according to the manufacturer’s instructions (USCN Life Science, Inc., Wuhan, China).

Statistical analysis

Statistical analysis was performed using SPSS 17.0 software (SPSS, Inc., Chicago, IL). The descriptive data are presented as the means ± SEM. Statistical comparisons between the NSCLC group and control group were performed using the Mann–Whitney U test. Correlations between the IL-17 tissue levels and the MVD and between the serum levels of IL-17 and VEGF were analyzed using the Spearman’s rank correlation coefficient. The Wilcoxon test was employed for comparisons between pre- and post-chemotherapy. The survival rates were calculated according to the Kaplan–Meier method and were compared using the log-rank test. Multivariate analysis of the prognostic factors of OS or PFS was performed using a Cox proportional hazards model. The criterion of statistical significance was \( p < 0.05 \).

Results

Correlation between intratumoral IL-17-positive cells and the MVD in NSCLC tissues

Chen and colleagues detected IL-17 expression in NSCLC tissues (Chen et al., 2010). Other studies have reported a
significant association between high levels of IL-17 expression and tumor vascularity in CRC, indicating that IL-17 may promote tumor growth by enhancing angiogenesis (Liu et al., 2011). To verify the precise distribution of IL-17 expression and to investigate the role of IL-17 in angiogenesis in NSCLC patients, we stained a series of NSCLC sections for IL-17 and CD34 using a modified immunohistochemistry technique. The majority of the IL-17-positive staining was localized to the cytoplasm of the mononuclear cells in the cancer tissues (Figure 1), similar to the previous reports on NSCLC (Numasaki et al., 2005) and CRC (Wang et al., 2014). The MVD of the 58 tumor specimens ranged from 10 to 75 microvessels per field, with a mean MVD of 29.57 ± 1.91. Our results indicated that the patients displaying higher IL-17 expression exhibited a higher MVD, and increased MVD correlated with increased IL-17 expression (Figure 2, Spearman’s rho = 0.593; p<0.01).

### Relationships between the serum IL-17 levels and clinico-pathological characteristics

The concentrations of serum IL-17 were determined in patients with NSCLC (n=43) and in healthy controls (n=37). The data were analyzed using the Mann–Whitney U test. The mean cytokine levels were significantly higher in the patients than in the control subjects (38.66 pg/ml versus 29.85 pg/ml; p<0.01; Figure 3). To determine the clinical relevance of the IL-17 levels, we examined the relationship between clinico-pathological characteristics and the IL-17 levels. No significant association was detected between the serum IL-17 levels and smoking status, histological type, differentiation status, age, or sex (Table 1). The mean serum concentrations of IL-17 in stage IV NSCLC patients were significantly higher than those of stage I and II patients (p<0.05).

In addition, high IL-17 expression significantly correlated with the TNM stage (p = 0.043) in the tissue from the NSCLC patients.
Correlation between serum IL-17 and VEGF levels

Recently, IL-17 was reported to stimulate the production of angiogenic mediators, such as VEGF, in the synovial fluid and in chondrocytes (Hu et al., 2014; Ryu et al., 2006). To investigate the relationship between IL-17 and VEGF levels in serum from NSCLC patients, we measured the VEGF concentration in serum from the patients and the healthy controls. As shown in Table 2, the mean serum VEGF level was 70.8 pg/ml and 51.51 pg/ml in the NSCLC patients and the healthy controls, respectively; this difference was significant ($p = 0.003$). Moreover, the serum IL-17 levels positively correlated with the serum VEGF levels in the NSCLC patients (Spearman’s rho = 0.474; $p < 0.01$; Figure 4).

### Comparison of the serum levels of IL-17 between pre- and post-chemotherapy

Changes in the tumor microenvironment, including increased cytokine levels, are important for the treatment response of cancer cells. Based on this rationale, we examined the changes in the IL-17 and VEGF levels between pre-chemotherapy and post-chemotherapy (two cycles). No significant differences in the cytokine levels were detected between pre- and post-chemotherapy in the overall group. For the patients in the responder group, the serum VEGF expression levels were significantly decreased following chemotherapy ($p = 0.01$, Table 3). However, for the patients in the non-responder group, the VEGF expression levels were not significantly different following chemotherapy. No significant change in the IL-17 levels was detected in either the responder or non-responder group (Table 3).

Serum IL-17 levels and patient prognosis

To further evaluate whether serum IL-17 levels predicted prognosis, we performed survival analysis on the NSCLC patients. By the time of data analysis, 35 of the 43 patients had died due to disease progression within the follow-up period of 36 months, and the median progression-free survival (PFS) and the cumulative overall survival (OS) were 10 and 17 months, respectively. The three-year PFS and OS rates were 9.3% and 18.6%, respectively. Using the median serum IL-17 level (35.14 pg/ml) in the NSCLC patients as the threshold value, the patients were separated into the high (>35.14 pg/ml) and low serum IL-17 (≤35.14 pg/ml) groups. The median PFS was 7 and 13 months in the patients displaying high and low serum IL-17 levels, respectively ($p = 0.009$; Figure 5A). The OS of the patients displaying a serum IL-17 level ≤35.14 pg/ml was also significantly longer than that of the patients displaying a serum IL-17 level >35.14 pg/ml (3-year OS: 28.6% and 9.1%, respectively $p = 0.020$; Figure 5B).

Univariate analysis revealed that serum IL-17 level was an independent indicator of NSCLC prognosis. However, no association was detected the patients’ prognosis and age, sex, smoking status, differentiation status or histological subtype (Table 4). Furthermore, multivariate Cox regression analysis confirmed that the serum IL-17 levels and the TNM stage were independent prognostic factor of OS and PFS in the NSCLC patients (Table 4). These results suggest that elevated serum IL-17 levels were associated with NSCLC progression and might serve as an independent predictor of shorter survival.

### Discussion

Chronic inflammation has been implicated in the pathogenesis of many different forms of cancer, including NSCLC (Gutschner & Diederichs, 2012). IL-17 is a pro-inflammatory...
cytokine that is mainly produced by activated CD4\(^+\)T helper cells, termed Th17 cells. In present study, we observed increased serum IL-17 levels in NSCLC patients. In addition, we demonstrated that elevated serum IL-17 levels correlated with poor survival and increased angiogenesis in NSCLC.

There is evidence that pro-inflammatory cytokines perform an important anti-tumorigenic function, but other results suggest that these cytokines contribute to the growth and spread of malignancy (Eiro´ & Vizoso, 2012). Recently, forced ectopic overexpression of IL-17 in tumor cells has been shown to either suppress tumor progression via enhanced antitumor immunity (Hinrichs et al., 2009; Prabhala et al., 2010) or promote tumor progression via an increase in angiogenesis (Chang et al., 2014). In the current study, we found that the levels of serum IL-17 were higher in NSCLC patients than in healthy subjects. Analysis of the relationship between the serum IL-17 levels and the clinical characteristics of the NSCLC patients revealed that increased serum IL-17 levels significantly correlated with advanced tumor stage (TNM stage IV), further suggesting that IL-17 may play a role in the development of NSCLC. These data suggest that the serum IL-17 level might serve as a useful predictor of advanced tumor stage in the clinical setting. Previous studies have reported that IL-17 is primarily produced by Th17 cells in a variety of cancers. In our study, we examined IL-17 expression in tumor tissue via immunohistochemistry and found that the majority of the IL-17-positive staining was localized to the cytoplasm of mononuclear cells in cancer tissues, similar to the results of previous reports on NSCLC (Numasaki et al., 2005). Liu et al. (2011) found a close association between the expression of IL-17 and the TNM stage. One possible explanation for this result is that the elevated serum IL-17 concentration in tumor patients reflects increased production of this cytokine in the tumor and its entry into the systemic circulation. These findings suggest a role of IL-17 in NSCLC.

Clinico-pathological characteristics related to the prognosis of NSCLC have been widely reported. Of these conventional pathological characteristics of NSCLC, the pTNM stage is a significant prognostic factor. Previous results have demonstrated a pro-tumor effect of IL-17 on HCC and CRC.

![Figure 4. Correlation between serum IL-17 and VEGF levels in NSCLC patients. This correlation was significant at \( p < 0.01 \).](image)

<table>
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<th>Non-responders</th>
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<td><strong>After treatment</strong></td>
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<td>VEGF (pg/ml)</td>
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![Figure 5. Kaplan–Meier progression-free survival curves (A) and OS curves (B) of patients displaying serum IL-17 levels less than or equal to 35.14 pg/ml and those displaying serum IL-17 levels greater than 35.14 pg/ml.](image)
tissues and that IL-17 expression in these tissues was an independent prognostic factor of OS and PFS (Zhang et al., 2009; Zhu et al., 2008). However, very few studies have demonstrated a positive correlation between elevated serum IL-17 levels and advanced tumor stage or poor survival in various human cancers. Our results indicate that the OS and PFS of patients with high-serum IL-17 levels were significantly shorter than those of patients with low-serum IL-17 levels. Univariate and multivariate Cox analyses demonstrated that IL-17 expression was an independent factor of prognosis, which verified our hypothesis that IL-17 plays an important role in NSCLC development.

Tumor growth is an angiogenesis-dependent process that requires sustained new vessel growth. Angiogenesis is essential for the progression of the neoplastic process and is a characteristic of cancer (Zhang et al., 2009); therefore, angiogenesis is an independent factor of NSCLC prognosis. A correlation between IL-17 expression and the MVD in human HCC has been reported, suggesting that IL-17 at the tumor site may promote angiogenesis and tumor growth. Similar conclusions have been drawn by Wang et al. (2010) with respect to skin cancer, as they demonstrated that the disruption of IL-17 expression dramatically reduced tumorigenesis via the IL-17-STAT3 pathway in an IL-17 knock-out mouse model. However, the effect of IL-17 on angiogenesis in human cancer remains to be determined. In our study, we found a positive association between the expression of IL-17 and the MVD in NSCLC tissue, suggesting a role of IL-17 during angiogenesis in NSCLC. IL-17 may exert an effect on angiogenesis either directly (by binding to IL-17R on endothelial cells) (Korn et al., 2009; Weaver et al., 2007) or indirectly (by inducing angiogenic factors, such as VEGF) (Alexandrakis et al., 2006). A large body of clinical and experimental evidence supports the role of VEGF in vascular permeability, endothelial cell migration, proliferation and vessel maturation (Ferrara & Davis-Smyth, 1997; Song et al., 2002; Tischer et al., 1991; Vincenti et al., 1996). The finding that IL-17 stimulates the production of VEGF in CRC cells may indicate a further mechanism underlying the correlation between the IL-17 levels and poor prognosis and angiogenesis. In NSCLC, the serum VEGF levels were significantly elevated in patients compared to the healthy controls. The serum levels of VEGF have been correlated with the extent of disease (Konno et al., 2003) and the response to chemotherapy (Kaminska et al., 2006). Our results revealed a significant increase in the serum levels of VEGF in patients with NSCLC. Based on these data, we analyzed the potential correlations between the circulating levels of IL-17 and the angiogenic factor VEGF in NSCLC patients. Interestingly, we clearly demonstrated that the serum levels of IL-17 significantly correlated with the levels of VEGF in NSCLC patients. This finding is consistent with previous in vitro data that IL-17 induces the secretion of VEGF (Honorati et al., 2007). Based on these findings, we hypothesized that IL-17 in the tumor microenvironment participates in the progression of NSCLC and that this process may be associated with angiogenesis. Our hypothesis requires further investigation.

The change in the tumor microenvironment, including the alteration in the expression of many cytokines, is important for the cancer cell response to treatment. In this study, we

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Table 4. Univariate and multivariate of variables with overall survival and recurrence.
measured the serum levels of IL-17 and VEGF pre- and post-chemotherapy. Consistent with the results of other studies, we found that patients who responded to treatment displayed a significantly decreased serum VEGF levels. However, in this study, we did not detect a significant correlation between the pre- and post-chemotherapy serum levels of IL-17 or in the cytokine levels between pre- and post-chemotherapy in the non-responder group. Thus, the clinical utility of the serum IL-17 levels as a predictor of the tumor response to chemotherapy could not be demonstrated.

**Conclusion**

In conclusion, our findings indicate that increased level of IL-17 was seen in patient serum with NSCLC, and elevated serum levels of IL-17 in association with higher disease stage. Serum IL-17 may be a useful independent predictor of prognosis in NSCLC. These results suggest that IL-17 is central to the tumor progression of NSCLC. Then, we clearly showed that the serum levels of IL-17 significantly correlated with the levels of VEGF in NSCLC patients. Therefore, targeting IL-17 can be a potential approach to control angiogenesis and progression in NSCLC.

**Declaration of interest**

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**References**


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