Clinical Study

Association between IL17 Polymorphisms and Risk of Cervical Cancer in Chinese Women

Yi Quan, 1 Bin Zhou, 2 Yanyun Wang, 2 Ruiqi Duan, 1 Kana Wang, 1 Qianqian Gao, 1 Shaoqing Shi, 2 Yaping Song, 2 Lin Zhang, 2 and Mingrong Xi1

1 Department of Obstetrics and Gynecology, West China Second University Hospital, Sichuan University, Chengdu 610041, China
2 Laboratory of Molecular Translational Medicine, West China Institute of Women and Children’s Health, Key Laboratory of Obstetric & Gynecologic and Pediatric Diseases and Birth Defects of Ministry of Education, West China Second University Hospital, Sichuan University, Chengdu 610041, China

Correspondence should be addressed to Mingrong Xi, doctormingrongxi@163.com

Received 9 June 2012; Revised 31 July 2012; Accepted 31 July 2012

1. Introduction

Cervical cancer, the second most common cancer among women worldwide, is a leading cause of cancer death in Chinese women. Each year, nearly 500,000 women develop this disease worldwide and about 80% of the cases occur in the developing country [1]. Cervical cancer is generally thought a multifactor disease. Human papillomavirus (HPV) infection has been established as the main cause of cervical cancer. Previous studies have suggested that the susceptibility to HPV can be affected by the polymorphisms in genes involved in immune response; thus, the polymorphisms in genes may play a crucial role in the pathogenesis of cervical cancer [2]. Further, accumulating researches reported that polymorphisms of a series of genes, including interleukin (IL)-1, IL-6, and IL-12 [3–5], were associated with the susceptibility to cervical cancer. Collectively, these findings strongly suggest that genetic polymorphisms may influence susceptibility to cervical cancer.

IL-17 is a relatively novel cytokine family, which plays important role in innate and adaptive immune systems. IL-17 consisted of six members (IL-17A-F), and five receptors (IL-17RA-RD and SEF) have been identified [6, 7]. IL-17A and IL-17F are reported to be secreted by Th17 cells, a distinct lineage of CD4+ effector cells [8]. IL-17 acts as a proinflammatory cytokine that can induce the release of certain cytokines, chemokines, matrix metalloproteinases (MMPs), and antimicrobial peptides from mesenchymal and myeloid cells. Increasing evidence has indicated that inflammation affects the microenvironment around tumors, which involves in the proliferation, migration, and survival of cancer cells [9]. Several studies have found high expression of IL-17 in various tumor tissues, including multiple myeloma, ovarian cancers, gastric cancer, and breast cancer.
[10–13]. Meanwhile, Zhang et al. reported that patients with cervical cancer do not only have significantly higher Th17 cell population but also higher IL-17 than normal controls [14]. In vivo studies in murine models also suggest that IL-17 promotes tumorigenicity of human cervical tumors [15].

Although underlying mechanism is still not quite clear, studies showed that genetic polymorphisms of IL17 were associated with the susceptibility to a range of inflammation-related diseases, including rheumatoid arthritis, ulcercative colitis, gastric cancer, and breast cancer [16–19]. However, the role of IL17 polymorphisms participating in the oncogenesis of cervical carcinoma remains unknown. In this study, we aimed to determine the association between the polymorphisms of IL17 (IL17A and IL17F) and the risk of cervical cancer in Chinese women.

2. Materials and Methods

2.1. Subjects. This case-control study enrolled 311 unrelated Chinese female patients with cervical squamous cell carcinoma (mean ± SD, 41.78 ± 8.56). They were hospitalized in the West China Second University Hospital of Sichuan University, between July 2008 and May 2011. The clinical diagnosis was confirmed by histological examination of biopsy or resected tissues. Patients with cervical adenocarcinoma were excluded. The control group consisted of 463 healthy women (mean ± SD, 39.33 ± 10.24) from a regular gynecological examination. All subjects were Chinese Han population living in Sichuan province of Southwest China. All subjects have given written consent, and the study was approved by Ethics Committee of the West China Second University Hospital, Sichuan University.

2.2. TaqMan Probe Real-Time PCR. Genotyping of IL17 polymorphisms was analyzed using the TaqMan SNP genotyping assay (Applied Biosystems, ABI, Foster City, CA, USA) with the assay ID C_15879983_10 for rs2275913 and C_2234166_10 for rs763780, resp.). For IL17A rs2275913, TaqMan probe real-time PCR was conducted in a total volume of 4 μL reaction mixture containing 2 μL of 2× TaqMan Universal PCR Master Mix, 0.2 μL of 20× SNP Genotyping Assay, 1.3 μL DNase-free sterile water, and 10 ng genomic DNA. The thermal conditions of real-time PCR were as follows: 95°C for 10 min plus 49 cycles of 92°C for 15 s and 60°C for 1 min. For IL17F rs763780, TaqMan probe real-time PCR was conducted in a total volume of 5 μL reaction mixture containing 2.5 μL of 2× TaqMan Universal PCR Master Mix, 0.25 μL of 20× SNP Genotyping Assay, 1.25 μL DNase-free sterile water, and 10 ng genomic DNA. The thermal conditions of real-time PCR were as follows: 95°C for 10 min plus 59 cycles of 92°C for 15 s and 60°C for 1 min.

2.3. DNA Sequencing Analysis. About 10% of the samples were randomly selected to perform the repeated assays, and the results were 100% concordant. The genotypes were confirmed by DNA sequencing analysis (BigDye Terminator v3.1 Cycle Sequencing Kits; Applied Biosystems, Foster City, CA, USA). For SNP rs2275913, the following primers were used: forward 5′-ATTTCTGCCCCTCCCATTTT-3′ and reverse 5′-CAGAAGGCATGCAGTTTTT-3′. For SNP rs763780, the following primers were used: forward 5′-GGCACCAGCATTGGTAAAGG-3′ and reverse 5′-GCTGAACATGCTGAGGAA-3′.

2.4. Statistical Analysis. The genotype and allele frequencies of SNPs rs2275913 and rs763780 were calculated by direct count, and Hardy-Weinberg equilibrium was evaluated by chi-square test. Odds ratio (OR) and 95% confidence intervals (CIs) were calculated using logistic regression. Statistical analyses were performed with SPSS for Windows software package version 13.0 (SPSS Inc., Chicago, IL, USA). The differences were regarded significant if P value was less than 0.05. The study power was calculated using the Quanto 1.1.1 program (http://hydra.usc.edu/gxe/).

3. Results

3.1. Definition of Genotypes of SNP Loci rs2275913 (IL-17A) and rs763780 (IL-17F). SNPs loci rs2275913 (IL17A) and rs763780 (IL17F) were analyzed using TaqMan probe real-time PCR. At the end of real-time PCR, the genotype of sample was distinguished on the basis of fluorescent dye; the allelic A probe for rs2275913 and allelic C probe for rs763780 were labeled with the fluorescent VIC dye and the others with the fluorescent FAM dye.

3.2. Comparison of IL17A and IL17F Polymorphisms between Patients and Controls. Polymorphisms at the two SNP loci were analyzed in 311 cervical cancer patients and 463 control subjects. Genotype distribution of these two polymorphisms in our cases and control subjects was consistent with the Hardy-Weinberg equilibrium. The genotype and allele frequencies of the two SNPs are summarized in Table 1. For SNP rs2275913, AA homozygous carriers had a significantly increased risk for cervical cancer compared with GG homozygous carriers in a codominant model (P = 0.008, OR = 1.72, 95% CI, 1.15–2.57). Subjects carrying AA homozygote of rs2275913 had a significantly increased risk for cervical cancer compared with that with allele G (AG/GG genotype) in a recessive model (P = 0.015, OR = 1.55, 95% CI, 1.09–2.20). Comparison of allelic frequency revealed a significant higher frequency of allele A in cervical cancer patient group in comparison to controls (47.3% versus 40.5%). To estimate the association between the A allele and cervical cancer, OR and 95% CI were calculated, and the results suggested that allele A is significantly associated with cervical cancer (P = 0.008, OR = 1.32; 95% CI, 1.07–1.62). The genotype and allele frequencies of locus rs763780 (IL-17F) did not show significant difference between cervical cancer patients and controls.

3.3. Analysis of IL17A and IL17F Polymorphisms and Clinicopathologic Features of Cervical Cancer. To determine whether the polymorphisms of the two loci were associated with certain clinicopathologic features, we performed stratified analyses for genotype distribution and allelic frequency in cervical cancer patients with different age, clinical stage,
Table 1: Genotype and allele distribution of two single-nucleotide polymorphism loci in cervical squamous cell carcinoma patients and controls.

| Genotype | Patients (%) | Controls (%) | P value | OR (95% CI) |
|----------|--------------|--------------|---------|-------------|
|          | N = 311      | N = 463      |         |             |
| rs2275913|              |              |         |             |
| GG       | 93 (29.9)    | 168 (36.3)   | Ref     |             |
| AA       | 76 (24.4)    | 80 (17.3)    | 0.008   | 1.72 (1.15–2.57) |
| AG       | 142 (45.7)   | 215 (46.4)   | 0.295   | 1.19 (0.86–1.67) |
| AA       | 76 (24.4)    | 80 (17.3)    | 0.015   | 1.55 (1.09–2.20) |
| GG/AG    | 235 (75.6)   | 383 (82.7)   |         |             |
| Allele   |              |              |         |             |
| A        | 294 (47.3)   | 375 (40.5)   | 0.008   | 1.32 (1.07–1.62) |
| G        | 328 (52.7)   | 551 (59.5)   |         |             |
| rs763780 |              |              |         |             |
| TT       | 222 (71.4)   | 332 (71.7)   | Ref     |             |
| CC       | 4 (1.3)      | 5 (1.1)      | 0.445   | 0.61 (0.16–2.29) |
| CT       | 85 (27.3)    | 126 (27.2)   | 0.957   | 1.01 (0.73–1.39) |
| TT       | 222 (71.4)   | 332 (71.7)   | 0.922   | 1.02 (0.74–1.40) |
| CC/CT    | 89 (28.6)    | 131 (28.3)   |         |             |
| Allele   |              |              |         |             |
| C        | 93 (15.0)    | 136 (14.7)   | 0.886   | 1.02 (0.77–1.36) |
| T        | 529 (85.0)   | 790 (85.3)   |         |             |

Values with P < 0.05 are shown in bold.

N: number; OR: odds ratio; CI: confidence interval.

tumor differentiation, lymph node metastasis, parametrial invasion, and peritumor intravascular cancer emboli. The frequencies of genotype and allele of rs2275913 locus were significantly different between patient groups with high clinical stage and peritumor intravascular cancer emboli (Table 2). A significantly higher frequency of allele A was observed in patients with high clinical stage and positive peritumor intravascular cancer emboli. The results revealed that A allele was associated with high clinical stage (P = 0.022, OR = 1.46, 95% CI, 1.06–2.01) and peritumor intravascular cancer emboli (P = 0.006, OR = 1.57, 95% CI, 1.14–2.71). The genotype and allele frequencies of rs763780 did not relate to patient clinical characteristics (Table 3).

Collectively, these results indicated that allele A of rs2275913 locus was not only associated with the susceptibility of cervical cancer (Table 1) but also the high clinical stage and positive peritumor intravascular cancer emboli of cervical cancer.

4. Discussion

In the present study, we found that the rs2275913 of IL17A was correlated to the risk of cervical cancer. The homozygous AA genotype and the A allele of the rs2275913 were more frequent in cervical cancer patients. No significant association between rs763780 of IL17F gene polymorphism and risk of cervical cancer was observed.

Both IL17A and IL17F are located in 6p12. Highly similar amino acid sequence is found between IL-17A and -17F among the IL-17 family and IL-17A and -17F share similar functions in terms of their ability to induce chemokines that is crucial in neutrophil recruitment as well as activation. IL-17 can induce multiple proinflammatory mediators, including chemokines, cytokines, and metalloproteinases, from epithelial and fibroblast cells. Increasing evidence shows that IL-17 and IL-17-producing cells play important role in the pathogenesis of various diseases, even tumors [20].

The function of IL-17 is well defined in the pathogenesis of many diseases, but its role in the tumors is still under debate. Kato et al. found that in murine tumor models, IL-17 was an angiogenic factor, and it could promote tumor growth. The proangiogenic functions of IL-17 have also been reported by several studies [21–23]. Numasaki et al. indicated that the role of IL-17 in angiogenesis was achieved through the stimulation of vascular endothelial cell migration and regulation of a series of proangiogenic factors [24]. On the contrary, some studies indicated that IL-17 could slow or suppress tumor development and reinforce tumor-specific cytotoxic responses. Benchetrit et al. found that the growth of tumors was inhibited by IL-17 [25]. Another study also showed that tumor-specific antitumor immunity could be induced by the Meth-A cells transfected with the hIL-17 gene [26].

The functional influence of the rs2275913 that located in the IL17A promoter region on IL-17 production in peripheral blood mononuclear cells (PBMCs) is still unclear. Chen et al. investigated PBMCs from 27 healthy subjects and found that the SNP rs2275913 did not affect IL-17 expression level [27]. However, Espinoza et al. reported that the 197A allele-positive (AG/AA genotypes) PBMCs secreted more IL-17 than the 197A allele-negative (GG genotype) cells [28]. Although the impact of SNP rs2275913 on IL-17 production
Table 2: Analysis of patient characteristics and polymorphism of locus rs2275913.

| Characteristics                           | Total number | Genotype | P value | Allele | P value | OR (95% CI) |
|-------------------------------------------|--------------|----------|---------|--------|---------|-------------|
|                                           | N = 311      |          |         |        |         |             |
| **Age**                                   |              |          |         |        |         |             |
| ≤45 year                                  | 200          | AA: 51   | 25 (25.5) | 47 (42.4) | 54 (27.0) | 197 (49.3) | 97 (43.7) | 0.324 | 0.184 | 1.25 (0.90–1.74) |
| >45 year                                  | 111          | AG: 25   | 47 (42.4) | 39 (35.1) | 54 (27.0) | 203 (50.7) | 125 (56.3) | 0.184 | 1.25 (0.90–1.74) |
| **Clinical stage**                        |              |          |         |        |         |             |
| I                                         | 135          | AA: 20   | 47 (35.1) | 42 (31.1) | 73 (54.1) | Ref         | 113 (41.9) | 157 (58.1) | 0.002 | 1.46 (1.06–2.01) |
| II                                        | 169          | AG: 53   | 67 (39.6) | 49 (29.0) | 73 (44.1) | 173 (51.2) | 165 (48.8) | 0.022 | 2.03 (0.69–6.04) |
| III                                       | 7            | GG: 3    | 2 (28.6)  | 2 (28.6)  | 2 (28.6)  | 8 (57.1)   | 6 (42.9)   | 0.198 | 0.193 |             |
| **Tumor differentiation**                 |              |          |         |        |         |             |
| Poor                                      | 251          | AA: 59   | 118 (47.0) | 74 (29.5) | 236 (47.0) | 266 (53.0) | 0.588 | 0.795 | 0.95 (0.64–1.41) |
| Well-moderate                             | 60           | AG: 17   | 24 (40.0) | 19 (31.7) | 58 (48.3) | 62 (51.7)   | Ref         | 173 (51.2) | 165 (48.8) | 0.002 | 1.46 (1.06–2.01) |
| **Lymph node status**                     |              |          |         |        |         |             |
| Positive                                  | 55           | AA: 20   | 40 (36.4) | 15 (27.2) | 7 (13.5)  | 60 (54.5) | 50 (45.5) | 0.070 | 0.70 (0.46–1.06) |
| Negative                                  | 256          | AG: 56   | 122 (47.6) | 78 (30.5) | 234 (45.7) | 278 (54.3) | 0.070 | 0.70 (0.46–1.06) |
| **Parametrical invasion**                 |              |          |         |        |         |             |
| Positive                                  | 95           | AA: 25   | 48 (50.5) | 23 (24.2) | 96 (50.5) | 94 (49.5) | 0.328 | 0.820 | 1.21 (0.86–1.70) |
| Negative                                  | 216          | AG: 52   | 94 (43.5) | 70 (32.4) | 198 (45.8) | 234 (54.2) | 0.328 | 0.820 | 1.21 (0.86–1.70) |
| **Peritumor intravascular cancer emboli** |              |          |         |        |         |             |
| Positive                                  | 121          | AA: 43   | 45 (37.2) | 33 (27.3) | 131 (54.1) | 111 (45.9) | 0.001 | 0.006 | 1.57 (1.14–2.71) |
| Negative                                  | 190          | AG: 33   | 97 (51.1) | 60 (31.6) | 163 (42.9) | 217 (57.1) | 0.001 | 0.006 | 1.57 (1.14–2.71) |

N corresponds to the number of individuals.

Adjusted by age, clinical stage, tumor differentiation, lymph node status, parametrical invasion, and peritumor intravascular cancer emboli.

Boldfaced values indicate a significant difference at the 5% level.

is under debate, a lot of studies have demonstrated that the polymorphism do associate with a wide range of human diseases, including acute graft-versus-host disease, rheumatoid arthritis, and ulcerative colitis [16, 17, 28].

There are some reports that demonstrate the influence of polymorphisms of IL17F in the risk for human disorders. Kawaguchi et al. reported that the IL17F 7488T/C (rs763780) variant, which causes a His-to-Arg substitution at aminoacid 161 (H161R), suppresses the expression and/or activity of wild-type IL-17F. In addition, it has been shown that it influences the risk of asthma [29]. The associations between SNP rs763780 of IL17F and several diseases, such as asthma, inflammatory bowel disease, and Crohn’s disease, have also been investigated [17, 30–33]. These two SNPs have also been investigated in the gastric cancer [18] and breast cancer [19].

A study by Shibata et al. found that rs2275913 of IL17A was significantly associated with the development of gastric cancer [18]. In addition, it was demonstrated that rs2275913 in IL17A but not IL17F was associated with the risk of breast cancer [19]. These studies suggest that IL17 gene may play a crucial role in the pathogenesis of tumorigenesis. However, it remains unknown whether genetic polymorphisms in IL17A and IL17F influence the risk of cervical cancer development.

Therefore, we conducted a case-control study to investigate the association between IL17 polymorphisms and the susceptibility of cervical cancer. In the present study, the results showed that the SNP rs2275913 of IL17A, but not the SNP rs763780 of IL17F was associated with the susceptibility of cervical cancer. The frequencies of rs2275913 AA homozygote and A allele were significantly higher in cervical cancer patients than in controls. Stratified results revealed that IL17A polymorphism was significantly associated with positive peritumor intravascular cancer emboli and high clinical stage that are associated with the survival rate of the patients. No association was found between IL17A and IL17F polymorphisms and results of stratified analyses by other clinical characters. Although the expression of IL-17 in several tumors has been detected, including breast, prostate, gastric, and bladder cancer, its function in the context of tumors remains controversial [34]. Increasing evidences showed that IL-17 was involved in tumorigenicity of human cervical cancer. In the plasma of the cervical cancer patients, there was a significant increase in the concentration of the IL-17 [14]. Tartour et al. reported that human cervical cancer cell lines stimulated with recombinant IL-17 could upregulate IL-6 which played important role in the
pathogenesis of cervical cancer and macrophage recruitment at the tumor site, and when transfected with IL-17 cDNA they show significantly higher tumour growth in athymic nude mice [15]. These results indicated the role of IL-17 in promoting tumorigenicity of human cervical cancer.

In conclusion, the current findings indicate that the polymorphism of \textit{IL17A} may influence the susceptibility to cervical cancer in the Chinese population. The pathophysiologic features of cervical cancer may be also affected by the polymorphisms. The investigation might have some limitations. Our study is inherently limited by the study design and relatively small sample size, which weakens our ability to solidify statistic associations. Further studies in different population and with a larger size of samples are needed to identify the association between the \textit{IL17A} and \textit{IL17F} genes and the risk of cervical cancer.

**Acknowledgments**

This work was supported by Ph.D. Program Foundation of Ministry of Education of China (no. 0040215405003) and Program for Changjiang Scholars and Innovative Research Team in University (PCSIRT0935).

**References**

[1] S. E. Waggoner, “Cervical cancer,” \textit{The Lancet}, vol. 361, no. 9376, pp. 2217–2225, 2003.
[2] A. Hildesheim and S. S. Wang, “Host and viral genetics and risk of cervical cancer: a review,” \textit{Virus Research}, vol. 89, no. 2, pp. 229–240, 2002.
[3] H. Singh, R. Sachan, H. Goel, and B. Mittal, “Genetic variants of interleukin-1RN and interleukin-1β genes and risk of cervical cancer,” \textit{BJOG}, vol. 115, no. 5, pp. 633–638, 2008.
[4] F. A. Castro, K. Haimila, I. Sareneva et al., “Association of HLA-DRB1, interleukin-6 and cyclin D1 polymorphisms with cervical cancer in the Swedish population—a candidate gene approach,” \textit{International Journal of Cancer}, vol. 125, no. 8, pp. 1851–1858, 2009.
[5] X. Chen, S. Han, S. Wang et al., “Interactions of IL-12A and IL-12B polymorphisms on the risk of cervical cancer in Chinese women,” \textit{Clinical Cancer Research}, vol. 15, no. 1, pp. 400–405, 2009.
[6] J. K. Kolls and A. Lindén, “Interleukin-17 family members and inflammation,” \textit{Immunity}, vol. 21, no. 4, pp. 467–476, 2004.
[7] M. Kawaguchi, M. Adachi, N. Oda, F. Kokubu, and S. K. Huang, “IL-17 cytokine family,” \textit{Journal of Allergy and Clinical Immunology}, vol. 114, no. 6, pp. 1263–1273, 2004.
[8] L. I. Rutitzky, I. R. Lopes Da Rosa, and M. I. Stadecker, "Severe CD4 T cell-mediated immunopathology in murine schistosomiasis is dependent on IL-12p40 and correlates with high levels of IL-17," *Journal of Immunology*, vol. 175, no. 6, pp. 3920–3926, 2005.

[9] W. Zou and N. P. Restifo, "TH17 cells in tumour immunity and immunotherapy," *Nature Reviews Immunology*, vol. 10, no. 4, pp. 248–256, 2010.

[10] M. G. Alexandrakis, C. A. Pappa, S. Miyakis et al., "Serum interleukin-17 and its relationship to angiogenic factors in multiple myeloma," *European Journal of Internal Medicine*, vol. 17, no. 6, pp. 412–416, 2006.

[11] T. Kato, H. Furumoto, T. Ogura et al., "Expression of IL-17 mRNA in ovarian cancer," *Biochemical and Biophysical Research Communications*, vol. 282, no. 3, pp. 735–738, 2001.

[12] B. Zhang, G. Rong, H. Wei et al., "The prevalence of Th17 cells in patients with gastric cancer," *Biochemical and Biophysical Research Communications*, vol. 374, no. 3, pp. 533–537, 2008.

[13] X. Zhu, L. A. Mulcahy, R. A. A. Mohammed et al., "IL-17 expression by breast-cancer-associated macrophages: IL-17 promotes invasiveness of breast cancer cell lines," *Breast Cancer Research*, vol. 10, no. 6, article R95, 2008.

[14] Y. Zhang, D. Ma, Y. Zhang et al., "The imbalance of Th17/Treg in patients with uterine cervical cancer," *Clinica Chimica Acta*, vol. 412, no. 11-12, pp. 894–900, 2011.

[15] E. Tartour, E. Fossiez, I. Joyeux et al., "Interleukin 17, a T-cell-derived cytokine, promotes tumorigenicity of human cervical tumors in nude mice," *Cancer Research*, vol. 59, no. 15, pp. 3698–3704, 1999.

[16] G. B. N. Nordang, M. K. Viken, J. E. Hollis-moffatt et al., "Association analysis of the interleukin 17A gene in Caucasian rheumatoid arthritis patients from Norway and New Zealand," *Rheumatology*, vol. 48, no. 4, pp. 367–370, 2009.

[17] T. Arisawa, T. Tahara, T. Shibata et al., "The influence of polymorphisms of interleukin-17A and interleukin-17F genes on the susceptibility to ulcerative colitis," *Journal of Clinical Immunology*, vol. 28, no. 1, pp. 44–49, 2008.

[18] T. Shibata, T. Tahara, I. Hirata, and T. Arisawa, "Genetic polymorphism of interleukin-17A and -17F genes in gastric carcinogenesis," *Human Immunology*, vol. 70, no. 7, pp. 547–551, 2009.

[19] L. Wang, Y. Jiang, Y. Zhang et al., "Association analysis of IL-17A and IL-17F polymorphisms in Chinese han women with breast cancer," *PLoS ONE*, vol. 7, no. 3, Article ID e34400, 2012.

[20] S. Xu and X. Cao, "Interleukin-17 and its expanding biological functions," *Cellular and Molecular Immunology*, vol. 7, no. 3, pp. 164–174, 2010.

[21] M. Numasaki, M. Watanabe, T. Suzuki et al., "IL-17 enhances the net angiogenic activity and in vivo growth of human non-small cell lung cancer in SCID mice through promoting CXCR-2-dependent angiogenesis," *Journal of Immunology*, vol. 175, no. 9, pp. 6177–6189, 2005.

[22] J. P. Zhang, J. Yan, J. Xu et al., "Increased intratumoral IL-17-producing cells correlate with poor survival in hepatocellular carcinoma patients," *Journal of Hepatology*, vol. 50, no. 5, pp. 980–989, 2009.

[23] M. C. Honorati, S. Neri, L. Cattini, and A. Facchini, "Interleukin-17, a regulator of angiogenic factor release by synovial fibroblasts," *Osteoarthritis and Cartilage*, vol. 14, no. 4, pp. 345–352, 2006.

[24] M. Numasaki, J. I. Fukushima, M. Ono et al., "Interleukin-17 promotes angiogenesis and tumor growth," *Blood*, vol. 101, no. 7, pp. 2620–2627, 2003.

[25] F. Benchetrit, A. Ciree, V. Vives et al., "Interleukin-17 inhibits tumor cell growth by means of a T-cell-dependent mechanism," *Blood*, vol. 99, no. 6, pp. 2114–2121, 2002.

[26] N. Hirahara, Y. Nio, S. Sasaki et al., "Inoculation of human interleukin-17 gene-transfected Meth-A fibrosarcoma cells induces T cell-dependent tumor-specific immunity in mice," *Oncology*, vol. 61, no. 1, pp. 79–89, 2001.

[27] J. Chen, Y. Deng, J. Zhao et al., "The polymorphism of IL-17 G-152A was associated with childhood asthma and bacterial colonization of the hypopharynx in bronchiolitis," *Journal of Clinical Immunology*, vol. 30, no. 4, pp. 539–545, 2010.

[28] J. L. Espinoza, A. Takami, K. Nakata et al., "A genetic variant in the IL-17 promoter is functionally associated with acute graft-versus-host disease after unrelated bone marrow transplantation," *PLoS ONE*, vol. 6, no. 10, Article ID e26229, 2011.

[29] M. Kawaguchi, D. Takahashi, N. Hizawa et al., "IL-17F sequence variant (His161Arg) is associated with protection against asthma and antagonizes wild-type IL-17F activity," *Journal of Allergy and Clinical Immunology*, vol. 117, no. 4, pp. 795–801, 2006.

[30] J. Seiederer, I. Elben, J. Diegelmann et al., "Role of the novel Th17 cytokine IL-17F in inflammatory bowel disease (IBD): upregulated colonic IL-17F expression in active Crohn's disease and analysis of the IL17F p.His161Arg polymorphism in IBD," *Inflammatory Bowel Diseases*, vol. 14, no. 4, pp. 437–445, 2008.

[31] C. D. Ramsey, R. Lazarus, C. A. Camargo Jr., S. T. Weiss, and J. C. Celedón, "Polymorphisms in the interleukin 17F gene (IL17F) and asthma," *Genes and Immunity*, vol. 6, no. 3, pp. 236–241, 2005.

[32] B. Chen, Z. Zeng, J. Hou, M. Chen, X. Gao, and P. Hu, "Association of interleukin-17F 7488 single nucleotide polymorphism and inflammatory bowel disease in the Chinese population," *Scandinavian Journal of Gastroenterology*, vol. 44, no. 6, pp. 720–726, 2009.

[33] A. Paradowska-Gorycka, E. Wojtcka-Lukasik, J. Treffler, B. Wojciechowska, J. K. Lacki, and S. Maslinski, "Association between IL-17F gene polymorphisms and susceptibility to and severity of rheumatoid arthritis (RA)," *Scandinavian Journal of Immunology*, vol. 72, no. 2, pp. 134–141, 2010.

[34] E. Maniati, R. Soper, and T. Hagemann, "Up for Mischief IL-17/Th17 in the tumour microenvironment," *Oncogene*, vol. 29, no. 42, pp. 5653–5662, 2010.