TNFSF15 promoter polymorphisms increase the susceptibility to small cell lung cancer: a case-control study

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Abstract

Background: Tumor necrosis factor superfamily member 15 (TNFSF15) is closely related to tumorigenesis and development. This study aimed to investigate the correlations between TNFSF15 polymorphisms and genetic susceptibility to lung cancer.

Methods: This case-control study included 209 small cell lung cancer patients (SCLC), 340 non-small cell lung cancer patients (NSCLC) and 460 health controls. TNFSF15 –638 A > G and –358 T > C polymorphisms were genotyped by polymerase chain reaction-restrictive fragment length polymorphism (PCR-RFLP) analysis. Odds ratio (OR) and 95% confidence interval (95% CI) were estimated by unconditional logistic regression.

Results: Our results showed that subjects carrying the TNFSF15–638GG genotype or -358CC genotype were more likely to develop SCLC (–638GG, OR = 1.84, 95% CI = 1.13–2.99; -358CC, OR = 2.44, 95% CI = 1.46–4.06), but not NSCLC (P > 0.05). In stratified analysis, –638GG genotype was related to SCLC among males (OR = 1.95, 95% CI = 1.09–3.45, P = 0.023) and older patients (OR = 2.93, 95% CI = 1.44–8.68, P = 0.006). However, -358CC genotype was associated with SCLC among females (OR = 8.42, 95% CI = 2.22–31.89, P = 0.002) and older subjects with OR (95%CI) of 11.04 (3.57–34.15) (P < 0.001). Moreover, TNFSF15 –358CC was linked with a higher risk of SCLC among non-smokers (OR = 2.54, 95% CI = 1.20–5.35, P = 0.015) but not among smokers (OR = 1.88, 95% CI = 0.92–3.84, P = 0.086).

Conclusion: These findings highlight the importance of TNFSF15 polymorphisms in the development of SCLC.

Keywords: TNFSF15, Lung cancer, Single nucleotide polymorphism, Cancer susceptibility

Background

Lung cancer is one of the most common malignant tumors worldwide and the first leading cause of cancer-related mortality in China [1, 2]. According to World Health Organization, lung cancer is divided into two main types: non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), of which NSCLC accounts for almost 85% of lung cancer cases [3]. Epidemiological studies have identified several risk factors for lung cancer, such as tobacco smoking, atmospheric pollution and occupational environment challenge [4]. However, many individuals who have been exposed to these risk factors do not get lung cancer during lifetime, so genetic factor is likely play an important role.

The initiation and progression of cancer are closely linked to inflammation and angiogenesis [5, 6]. As one of potent mediators of inflammation, the tumor necrosis factor (TNF) family plays an important role in the process of immunoregulation and further contributes to cancer development [7]. Tumor necrosis factor superfamily 15 (TNFSF15), also known as vascular endothelial growth inhibitor (VEGI), belongs to the TNF ligand family, which negatively regulates angiogenesis [8]. By stimulating T cell, TNFSF15 is involved in the modulation of inflammation [9, 10]. Studies have shown that over-expression of TNFSF15 inhibits tumor growth in various cancers

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whereas reduced expression of TNFSF15 is associated with poor prognosis in cancer patients [11–15].

Single nucleotide polymorphisms (SNPs) in regulatory region of a gene can influence the gene expression and further contribute to the development of various cancers [16–19]. In our previous study, we identified two SNPs (−638A > G and -358 T > C) in the TNFSF15 promoter by direct sequencing, and found that -358 T > C variant changed the transcriptional activity of TNFSF15 and was significantly associated with the susceptibility to gastric adenocarcinoma [20]. In the present study, we tested if these two variants in the TNFSF15 promoter region contributed to the risk of developing lung cancer by performing a case-control study in a Chinese population.

Methods
Study population
This case-control study consisted of 209 SCLC patients, 340 NSCLC patients and 460 healthy controls (Table 1). The 549 cases were collected from Tangshan Gongren Hospital and Tangshan Renmin Hospital affiliated to North China University of Science and Technology in China from 2012 to 2016. None of the patients were treated with any radiotherapy or chemotherapy before blood sampling. All subjects were unrelated ethnic Han Chinese. Control individuals without a history of any cancer were recruited from the same region and frequency-matched to cases according to gender and age. This study was approved by Institutional Review Board of North China University of Science and Technology, and written informed consents were obtained from all participants of their own free will.

Table 1 Frequency distribution of select characteristics

| Variables               | NSCLC Case (n = 340) | Controls (n = 460) | P value* | SCLC Case (n = 209) | Controls (n = 460) | P value* |
|-------------------------|----------------------|--------------------|----------|--------------------|--------------------|----------|
| Gender                  |                       |                    |          |                    |                    |          |
| Male                    | 237 (69.7)            | 336 (73.0)         | 0.301    | 154 (73.7)         | 336 (73.0)         | 0.862    |
| Female                  | 103 (30.3)            | 124 (27.0)         |          | 55 (26.3)          | 124 (27.0)         |          |
| Age                     | 0.139                 |                    |          | 0.151              |                    |          |
| <60                     | 187 (55.0)            | 277 (60.2)         |          | 138 (66.0)         | 277 (60.2)         |          |
| ≥ 60                    | 153 (45.0)            | 183 (39.8)         |          | 71 (34.0)          | 183 (39.8)         |          |
| Range                   | 27–84                 | 18–84              |          | 30–92              | 18–84              |          |
| Median                  | 58 (56.2)             | 55                 |          | 55                 | 56.2               |          |
| Smoking status          | 0.252                 |                    |          | 0.431              |                    |          |
| Non-smoker              | 187 (55.0)            | 233 (50.7)         |          | 99 (47.8)          | 233 (50.7)         |          |
| Smoker                  | 153 (45.0)            | 227 (49.3)         |          | 110 (52.2)         | 227 (49.3)         |          |
| Pack year of smoking    | < 0.001               |                    |          | < 0.001            |                    |          |
| <30                     | 59 (38.6)             | 153 (67.4)         |          | 37 (33.7)          | 153 (67.4)         |          |
| ≥ 30                    | 94 (61.4)             | 74 (32.6)          |          | 73 (66.4)          | 74 (32.6)          |          |

*Two-sided χ² test

TNFSF15 genotyping
Genomic DNA was extracted from peripheral blood from all participants using TIANamp Blood DNA Kit (TIANGEN, Beijing, China), according to the manufacturer’s instructions. PCR-restriction fragment length polymorphism (PCR-RFLP) analysis were applied for TNFSF15 genotyping. The PCR primer pairs for −638A > G (rs7848647) were 5′-AGT CAC CTC GAT CTG TGG CCTC-3′ and 5′-AAT CAC GGC TTG GAG TTG TAA CCTC-3′. The target DNA fragment containing −358 T > C (rs6478109) was amplified with primer pairs, −358 -PF (5′-AAA TGT GAT TTC CGT TTC CCCA-3′) and −358 -PR (5′- AAT ATA CCT GTT CCC TGC ACTG -3′). Briefly, PCR was performed using 6 μL reaction mixture containing 10 ng DNA, 0.1 μM each primer, and 1 × Taq PCR StarMix with loading dye (Genstar, Beijing, USA). The PCR thermal cycling condition consists of an initial denaturation step at 94 °C for 3 min, followed by 30 cycles of 94 °C for 40 s, 58 °C for 30 s and 72 °C for 15 s, and then a final extension step at 72 °C for 3 min. PCR products for TNFSF15−638A > G (114 bp) and -358 T > C (123 bp) were digested by Rsa I and Bcc I (New England BioLabs, Inc., Beverly, USA) and separated on 3% agarose gel. The genotypes revealed by PCR-RFLP were further confirmed by DNA sequencing (Fig. 1). To ensure the quality control, approximately 10% of the samples were randomly selected for re-genotyping and all results were in 100% concordance.

Statistical analysis
Quanto program was used to calculate the power of the sample size for this case-control study. The power
estimation was performed, which indicated that our sample size is sufficient for the case-control study. Differences of basic characteristics in cases and control subjects were compared using the $\chi^2$ test. Pearson goodness-of-fit $\chi^2$ test was performed to test whether the distribution of genotypes in the control group was in accordance with Hardy-Weinberg Equilibrium (HWE). Odd ratios (ORs) and 95% Confidence interval (CI) were calculated by unconditional logistic regression model to evaluate the association of $\text{TNFSF15}$ genetic variations with the susceptibility to lung cancer. The smoking status of pack-years was determined as an indicator of the cumulative cigarette dose level (pack-years cigarettes per day/20 × years smoked). Light and heavy smokers were categorized by using 30 as the cut-off point [21]. Older and younger subjects were sub-grouped by using 60 as the cut-off point (https://www.who.int). All statistical calculations were performed using SPSS version 23.0 (SPSS Inc., Chicago, IL).

**Results**

Demographic and clinical characteristics of lung cancer cases and controls

Demographic and clinical characteristics of lung cancer cases and controls are shown in Table 1. There was no significant difference in gender, age and smoking status between NSCLC or SCLC cases and healthy controls ($P > 0.05$). In terms of the amount of smoking, the significant difference was showed between lung cancer group and control group ($P < 0.001$ for NSCLC and $P < 0.001$ for SCLC). The proportion of heavy smokers in SCLC and NSCLC patients (66.4 and 61.4%) was significantly higher than that in healthy controls (32.6%).

Association of $\text{TNFSF15}$ variants with the risk of lung cancer

Tables 2 and 3 present the genotypes of $\text{TNFSF15}$–638A > G and -358 T > C variants in lung cancer patients and controls. Genotype distributions of $\text{TNFSF15}$–638A > G and -358 T > C in controls were conformed to be in the Hardy-Weinberg equilibrium (HWE) ($P = 0.32$ and $P = 0.78$, respectively). We used unconditional logistic regression to assess the association of $\text{TNFSF15}$ SNPs with the risk of lung cancer. For the $\text{TNFSF15}$–638A > G polymorphism, we found that GG genotype carriers had a significantly elevated risk for developing SCLC ($\text{OR} = 1.84$, 95% CI = 1.13–2.99), but not for developing NSCLC ($\text{OR} = 1.11$, 95% CI = 0.74–1.67), in comparison to those with AA genotype. For the $\text{TNFSF15}$ -358 T > C variant, our data showed that CC genotype and CT genotype were associated with a higher risk of SCLC ($\text{OR} = 2.44$, 95% CI = 1.46–4.06; OR = 2.00, 95% CI = 1.26–3.19) as compared to TT genotype. However, we did not find that the $\text{TNFSF15}$ -358 T > C polymorphism was associated with the susceptibility to NSCLC with an OR (95% CI) of 1.45 (0.96–2.11) in CT carriers and an OR (95% CI) of 1.24 (0.86–1.76) in CC carriers, respectively.
Table 2 Genotype frequencies of TNFSF15 polymorphisms and their association with SCLC

| Genotype | Patients(n = 340) | Controls(n = 460) | OR (95% CI) | P value |
|----------|------------------|------------------|-------------|---------|
|          | No (%)           | No (%)           |             |         |
| -638 A > G |                  |                  |             |         |
| AA       | 39 (11.8)        | 122 (26.5)       |             |         |
| AG       | 112 (33.5)       | 240 (52.2)       | 1.46 (0.95–2.23) | 0.084  |
| GG       | 58 (17.1)        | 98 (21.3)        | 1.84 (1.13–2.99) | 0.014  |
| -358 T > C |                  |                  |             |         |
| TT       | 29 (8.5)         | 116 (25.2)       |             |         |
| CT       | 114 (33.5)       | 233 (50.7)       | 2.00 (1.26–3.19) | 0.004  |
| CC       | 66 (19.4)        | 111 (24.1)       | 2.44 (1.46–4.06) | 0.001  |

*Adjusted for age, gender, and smoking status

Stratification analysis of the TNFSF15 polymorphism and the risk of SCLC

To evaluate the effect of smoking status and non-modifiable risk factors (age and gender) on the association of TNFSF15 –638A > G with the risk of SCLC, we performed stratification analysis (Table 4). When stratified by gender, the TNFSF15 –638GG genotype was associated with an increased risk of SCLC among females (OR = 2.44, 95% CI = 1.46–4.06, P = 0.001), but not among males. Age stratification analysis showed that there was a correlation between the CC genotype and the risk of SCLC (OR = 1.09, 95% CI = 1.44–3.57, P = 0.000) among elders when compared to TT carriers, but not among youngers. In addition, the CC genotype increased the risk of lung cancer among non-smokers (OR = 2.54, 95% CI = 1.20–5.35, P = 0.015) compared with the TT genotype.

Discussion

Small-cell lung cancer (SCLC) is a deadly tumor with poor prognosis, which originates from high-grade malignant neuroendocrine cells [22]. Although sensitive to chemotherapy and radiotherapy, SCLC typically recurs rapidly after primary treatment and the five-year survival is only 6% after diagnosis [23]. Platinum-etoposide doublet has been officially approved for clinical use against SCLC [23]; however, few improvement has been made in SCLC treatment in past several years. Since SCLC is known as a stubborn cancer, there is an urgent need for the identification of biomarkers that can act as a potential therapeutic target in SCLC.

Table 3 Genotype frequencies of TNFSF15 polymorphisms and their association with NSCLC

| Genotype | Patients(n = 340) | Controls(n = 460) | OR (95% CI) | P value |
|----------|------------------|------------------|-------------|---------|
|          | No (%)           | No (%)           |             |         |
| -638 A > G |                  |                  |             |         |
| AA       | 90 (26.5)        | 122 (26.5)       |             |         |
| AG       | 171 (50.3)       | 240 (52.2)       | 0.97 (0.69–1.36) | 0.867  |
| GG       | 79 (23.2)        | 98 (21.3)        | 1.11 (0.74–1.67) | 0.605  |
| -358 T > C |                  |                  |             |         |
| TT       | 71 (20.9)        | 116 (25.2)       |             |         |
| CT       | 173 (50.5)       | 233 (50.7)       | 1.24 (0.86–1.76) | 0.248  |
| CC       | 96 (28.2)        | 111 (24.1)       | 1.45 (0.96–2.11) | 0.074  |

*Adjusted for age, gender, and smoking status

Table 4 Association of TNFSF15 –638A > G polymorphism with SCLC risk stratified by selected variables

| Variables | Genotypes (Cases/Controls) | GG/AA model OR (95% CI) | P value |
|-----------|---------------------------|------------------------|---------|
| Gender    |                           | GG AG AA               |         |
| Male      | 42/72 (84/170)            | 1.95 (1.09–3.45)       | 0.023   |
| Female    | 16/26 (28/70)             | 1.41 (0.54–3.70)       | 0.483   |
| Age       |                           |                        |         |
| <60       | 37/62 (71/149)            | 1.28 (0.71–2.34)       | 0.407   |
| ≥ 60      | 21/36 (41/91)             | 2.93 (1.44–8.68)       | 0.006   |
| Smoking status |                  |                        |         |
| Non-smoker | 28/49 (53/124)            | 1.79 (0.88–3.65)       | 0.107   |
| Smoker    | 30/49 (59/116)            | 1.70 (0.86–3.38)       | 0.130   |

Table 5 Association of TNFSF15 –358 T > C polymorphism with SCLC risk stratified by selected variables

| Variables | Genotypes (Cases/Controls) | CC/TT model OR (95% CI) | P value |
|-----------|---------------------------|------------------------|---------|
| Gender    |                           | CC CT TT               |         |
| Male      | 42/85 (86/164)            | 1.66 (0.93–2.95)       | 0.086   |
| Female    | 24/26 (28/69)             | 8.42 (2.22–31.89)      | 0.002   |
| Age       |                           |                        |         |
| <60       | 35/71 (78/146)            | 1.15 (0.62–2.15)       | 0.653   |
| ≥ 60      | 31/40 (36/87)             | 11.04 (3.57–34.15)     | < 0.001 |
| Smoking status |                  |                        |         |
| Non-smoker | 36/55 (51/123)            | 2.54 (1.20–5.35)       | 0.015   |
| Smoker    | 30/56 (63/110)            | 1.88 (0.92–3.84)       | 0.086   |
TNF superfamily members play an important role in cell proliferation, differentiation and apoptosis and are used for clinical treatment, or in clinical trials [24, 25]. TNFSF15, a member of TNF superfamily, is likely to inhibit the growth of tumors by suppressing neovascularization. TNFSF15 inhibits the proliferation of vascular endothelial cells in the G0 and G1 phases of cell cycle, and ultimately inhibits angiogenesis. TNFSF15 gene encodes three splice variants, namely VEGI-174, VEGI-251 and VEGI-192 depending on the number of amino acids included [26]. VEGI-251, also known as TLI1A (TNF-like molecule 1A), is the longest one of the splice variants. The combination of TLI1A and DR3 (Death Receptor 3) activates different signal transduction pathways by inducing NF-kB to activate initial T cell [10] and activating Caspases cascade to promote cell apoptosis [27]. These processes play an important role in the occurrence and development of tumors.

Till now, a few studies have been carried out to demonstrate the association of TNFSF15 polymorphisms with the susceptibility to cancer. In our previous study, we found that TNFSF15–638A > G polymorphism was associated with the development of gastric adenocarcinoma [20]. In another study, authors indicated that TNFSF15 rs6478106 is related to the risk of breast cancer in Chinese Han population [28]. In this study, we explored the association of TNFSF15 variants with the susceptibility to lung cancer and found that -638A > G and -358 T > C variants elevated the risk of SCLC, but not of NSCLC. These findings suggested that the TNFSF15 polymorphisms were involved in the development of various cancer types; however, the specific mechanism is not fully clear. We speculate that the TNFSF15 genetic variation affects the expression of TNFSF15 protein and then controls the downstream signal transduction molecules. These changes affect inflammatory and immune response, and further contribute to the development of cancers. Mattija and Clara found that an intron polymorphism of TNFSF15 (rs6478108) affected the expression level of TNFSF15 and increased NOD2-induced signaling and cytokines through caspase-8–induced IL-1 [29]. In our previous study, we found that the –358 T > C polymorphism eliminates a (NF-Y) binding site and the -358C containing haplotypes had a significantly decreased reporter gene activity in gastric cells [20].

Tobacco smoking is recognized as one of the most important risk factors contributing to lung cancer [30]. Thus, we analyzed the effects of TNFSF15 variants on SCLC by smoking status. Studies have shown a strong association between tobacco exposure and the development of SCLC [31, 32]. Cigarette smoke contains many carcinogenic chemicals such as nicotine and carbon monoxide tar. The complexity of cigarette smoke makes the mechanisms of developing lung cancer even more complicated. At least, tobacco smoking potentially alters the tumor immune microenvironment by creating DNA damage and causing inflammatory response [33, 34]. TNFSF15 is closely related to the inflammatory response. It has been reported that TNFSF15 can directly induce proinflammatory cytokines [35]. Long-term exposure of DNA to the carcinogens in tobacco smoke will lead to a higher mutation load in SCLC [36]. Our present data showed that TNFSF15 -358T > C polymorphism was related to SCLC among non-smokers instead of smokers, which needs more studies to explain. After stratified by smoking status, the sample size is not enough to evaluate the risk of this genetic variant with the risk of SCLC.

Age and gender are considered to be risk factors for tumor development and progression [37]. Our study showed the TNFSF15–638GG genotype elevated the risk of SCLC among males and individuals aged 60 years and older. Whether gender is related to the risk of lung cancer is controversial after taking into account smoking [38–40]. Due to the small size of several subgroups, a further larger-scale study needs to be conducted in order to carefully evaluate these findings.

In the future, it is necessary to evaluate the usability of these polymorphisms as a low-cost NSCLC screening tool for predicting individual lung cancer risk.

Conclusion
Taken together, our results indicated that TNFSF15 promoter polymorphisms might be involved in the development of SCLC.

Abbreviations
NSCL: non-small cell lung cancer; SCLC: small cell lung cancer; TNFSF15: Tumor necrosis factor superfamily member 15

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Availability of data and materials
The datasets used during the current study are available from the corresponding author on reasonable request.

Authors’ contributions
HG and ZN: acquisition, analysis, and interpretation of data; drafting the manuscript. ZZ and HW: data collection and analysis. YX, ZY, AL, ZJ: DNA extraction; acquisition and interpretation of data. XZ: design of the work, analysis and interpretation of data; revision of the article; final approval of the version to be published. All authors read and approved the final manuscript.

Ethics approval and consent to participate
All the study procedures were approved by the Ethics Committee of North China University of Science and Technology (2016134) and written informed consents were obtained from all participants of their own free will.

Taken together, our results indicated that TNFSF15 promoter polymorphisms might be involved in the development of SCLC.

TNFSF15: Tumor necrosis factor superfamily member 15

NSCL: non-small cell lung cancer; SCLC: small cell lung cancer; TNFSF15: Tumor necrosis factor superfamily member 15
Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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