The Association of Genetic Polymorphisms of *TNFα*, *TNF-R1*, and *TNF-R2* and Lung Cancer Chemotherapy Response

Yi Zheng[1,2,3], Ji-Ye Yin[1,2], Ying Wang[1,2], Xiang-Ping Li[1,2], Juan Chen[1,2], Chen-Yue Qian[1,2], Xiao-Ke Wen[3], Wei Zhang[1,2], Hong-Hao Zhou[1,2] and Zhao-Qian Liu[1,2,*]

[1] *Department of Clinical Pharmacology, Xiangya Hospital, Central South University, Changsha 410008, P. R. China*

[2] *Institute of Clinical Pharmacology, Central South University, Hunan Key Laboratory of Pharmacogenetics, Changsha 410078, P. R. China*

[3] *Department of Pharmacy, The Maternal and Child Health of Hunan Province, Changsha 410078, P. R. China*

Abstract: Platinum-based therapy is commonly used for the treatment of lung cancer and has been widely accepted by clinicians, but the chemotherapy responses differ greatly among individuals. TNFα/TNF-R1/R2 signal pathway can trigger the extrinsic pathway of apoptosis after DNA damage was caused by platinum-based treatment. The aim of this study was to investigate the association of *TNFα* -308 A/G, *TNF-R1* -383A>C, -609T>G and *TNF-R2* +676 T>G and the response of platinum-based chemotherapy in 313 Chinese advanced-stage non-small-cell lung cancer (NSCLC) patients. MassARRAY was used to detect these four SNPs in three apoptosis-related genes. *TNFα* -308 A/G was significantly correlated with better clinical benefit. Patients carrying A allele tended to have a favorable prognosis after treated with platinum-based chemotherapy (P=0.043, OR=0.488, 95%CI=0.244-0.979). The patients with CA genotype have significantly reduced risk of platinum resistance compared with wild-type homozygotes CC genotype (P=0.025, OR=0.447, 95% CI=0.220-0.906). No association was found in other polymorphisms. In conclusion, our data suggest that *TNFα* -308 A/G polymorphism may serve as the indicator of platinum-based chemotherapy response in NSCLC patients.

Keywords: TNFα, TNF-R1, TNF-R2, chemotherapy response, genetic polymorphism, lung cancer.

INTRODUCTION

Globally, the incidence and mortality of lung cancer rank the first above other cancers and about 1.3 million people die each year of lung cancer on average [1]. According to the pathology classification, lung cancer can be divided into small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), in which NSCLC accounts for the most, approximately 80% [2]. Due to the lack of early symptoms and specific biomarkers, two-thirds of the patients were diagnosed at late stage III or IV with poor physical condition, loss of surgical indications, and can only rely on drugs or radiation therapy to prolong life and release physical burden. The 5-year survival rate of lung cancer is very low, about 15% and ten year survival rate is only 5% or so [3].

The current treatment plan for advanced NSCLC is platinum-based therapy, mainly the cisplatin or carboplatin plus another cytotoxic drug, in which platinum play the pivotal role [4]. Upon entering a cell, all platinum agents become aquatic, inclined to bond with nucleophilic molecules within the cell, such as DNA, RNA, and proteins, forming adducts which then induce the activation of apoptosis signaling pathways [5]. Clinical observations have discovered that the response rate of platinum vary greatly among individuals even with the same dose and same chemotherapy regimens. Many factors contribute to this variability in which DNA repair pathway exert the biggest effect, as platinum mainly play the cytotoxic role by causing the DNA damage [6, 7]. Apart from DNA repair pathway, other important proteins in apoptosis signaling pathways may also have certain impact on the efficacy, toxicity and prognosis of patients treating with platinum agents [8, 9].

Apoptosis is responsible for the deletion of tumor cells and may affect the response of platinum treatment. Tumor necrosis factor α (TNFα), the most effective cytokine ever discovered, have direct cytotoxic effect in many kinds of tumor cells, and can cause the blood vessel damage and ischemic necrosis. What’s more, it can induce and enhance the cytotoxic effects of NK cells and macrophages. TNFα can trigger the extrinsic pathway of apoptosis by bonding with death receptors which belongs to the TNF receptor superfamily in response of the cellular stress and DNA

---

*Address correspondence to this author at the Department of Clinical Pharmacology, Xiangya Hospital, Central South University, Changsha 410008, P. R. China; Institute of Clinical Pharmacology, Central South University; Hunan Key Laboratory of Pharmacogenetics, Changsha 410078, P. R. China; Tel: +86 731 84805380; Fax: +86 731 82354476;
E-mail: liuzhaoqian63@126.com

ISSN: 1929-2260 / E-ISSN: 1929-2279/14

damage caused by cisplatin [10]. Studies have indicated that TNFα can enhance the cytotoxicity effect of cisplatin on human ovarian carcinoma cells *in vitro* [11, 12].

There are two kinds of TNF receptors: TNF-R1 (Tumor necrosis factor-receptor Ⅰ, TNF-R1) and TNF-R2 (Tumor necrosis factor-receptor 2, TNF-R2), in which TNF-R1 is closely related with cell apoptosis [13]. Most of the cells express TNF-R1 in its surface, while TNF-R2 was restricted to immune cells. TNF-R1 is widely located in nucleated cells and have death domain in regions inside the cells which can bind with TNF receptor-associated death domain (TRADD) to activate caspases and NF-κB, thus triggering the transcription of inflammatory cytokines and chemokines [14]. TNF-R2 mainly expressed in lymphocytes with no death domain inside the cells, but it can induce apoptosis and the activating of NF-κB through TNF receptor-associated factor 2 (TRAF2), even with low concentration [15].

Several single nucleotide polymorphisms have been identified in *TNFα*, *TNF-R1*, and *TNF-R2* genes and some of them may contribute to discrepancy in protein levels [16-18]. Therefore, we guess the polymorphisms in those three genes may influence the clinical outcome of NSCLC patients treated with platinum therapy. In this study, we aimed to investigate the association of polymorphisms in *TNFα*, *TNF-R1* and *TNF-R2* and platinum-based chemotherapy response in advanced NSCLC patients.

MATERIALS AND METHODS

Study Subjects

Patients were recruited from the Xiangya Hospital and Hunan Province Tumor Hospital from 2012 to 2013 year in Changsha, Hunan, China. All the patients were histologically diagnosed to be III-IV NSCLC (including lung adenocarcinoma, lung squamous carcinoma, gland scale cancer, etc) with measurable lesions confirmed by CT scan. Eastern Cooperative Oncology Group (ECOG) performance status of patients was all between 0-2. Required laboratory values for inclusion were neutrophil count≥1.5×109/L, platelet count≥100× 109/L, serum creatinine ≤1.5×upper limit normal, estimated creatinine clearance≥60 mL/min, alanine amino-transferase (ALT) and aspartate aminotransferase (AST)≤1.5×upper limit normal; no recent myocardial infarction and no active congestive heart failure or cardiac arrhyth-mia requiring medical treatment.

Those people who have history of malignancy, accepted the surgery or radiation therapy before, used other chemical treatment other than platinum drugs or have uncontrolled infectious disease or other serious medical or psychological factors that might hamper their adherence to the treatment schedule were excluded.

The study protocol has been approved by the Ethics Committee of Xiangya School of Medicine, Central South University with a registration number of CTXY-110008-1. The clinical research admission was approved by Chinese Clinical Trial Registry and the registration number is ChiCTR-RNC-12002892 (http://www. chictr.org/usercenter/project/edit.aspx?proj=4039). All the patients signed written informed consent before they participated in this study.

Treatment and Clinical Assessments

All the patients enrolled in the study were given first-line platinum-based chemotherapy. The combinations regime are as follows: DDP 75 mg/m^2 or CBP (AUC)=5 mg/ml Day 1, NVB 25 mg/m^2, Day 1, 8. DDP 75 mg/m^2 or CBP (AUC)=5 mg/ml Day 1, GEM 250 mg/m^2 Day 1, 8. DDP 75 mg/m^2 or CBP (AUC)=5 mg/ml Day 1, TAX 175 mg/m^2 Day 1. DDP 75 mg/m^2 or CBP(AUC)=5 mg/ml Day 1, PEM 500 mg/m^2 Day 1. DDP 75 mg/m^2 or CBP(AUC)=5 mg/ml Day 1, DOC 75 mg/m^2 Day 1. All chemotherapeutic drugs were administered i.v. and all the patients were treated for two to six cycles.

After the first two cycles of chemotherapy, response of all the patients was assessed according to the RECIST guideline (version 1.1) for solid tumors by professional clinicians. Complete response (CR) or partial response (PR) are regarded as being sensitive to platinum agents, while resistance to platinum agents include progressive disease (PD) or stable disease (SD).

SNPs Selection

NCBI dbSNPs database are used to screen key SNPs. The main principles include: 1 SNPs that have been demonstrated to be of biological significance, influence gene expression or associated with disease risk or survival according to the articles search ed from PubMed website. 2 SNPs located at 50 flaking regions (5’FR), 5’-untranslated regions (5’-UTRs), coding regions, or 3’-UTRs according to NCBI dbSNPs that may have potentially functional significance. 3 Common polymorphisms (minor allele frequency, MAF

> 0.05 in Chinese). 1 If multiple SNPs are in close linkage disequilibrium (LD)($r^2 \geq 0.80$), only one of them was selected as representative.

DNA Extraction and Genotyping

Approximately 5 ml peripheral venous blood was collected from each patient and genomic DNA was extracted using Genomic DNA Purification Kit (Promega, USA). Genotyping was accomplished by Sequenom Mass Array Genotype Platform (Sequenom, San Diego, California, USA). Detailed procedures were described in our previous report [19].

Statistical Analyses

Chi-square test was used to compare demographic and epidemiological features with response of

Table 1: The Basic Clinical Characteristics of Lung Cancer Patients

Stratification of patients	Total (n%)	Response		P#
		CR+PR (n%)	SD+PD (n%)	
All patients	313	100(31.9)	213(68.1)	
Age				0.592
≤55	134(42.8)	45(45.0)	89(41.8)	
>55	179(57.2)	55(55.0)	124(58.2)	
Smoking status				0.801
Never	140(44.7)	44(44.0)	96(45.1)	
Ever	173(55.3)	56(56.0)	117(54.9)	
Gender				0.665
Male	233(74.4)	76(76.0)	157(73.7)	
Female	80(25.6)	24(24.0)	56(21.3)	
ECOG				0.926
0-1	330(95.8)	96(96.0)	204(95.7)	
2	13(4.2)	4(4.0)	9(4.2)	
Histologic type				0.007
Adenocarcinoma	162(51.7)	56(56.0)	71(33.3)	
Squamous cell	127(40.5)	37(37.0)	125(58.7)	
Adenosquamous	9(2.9)	4(4.0)	5(2.3)	
Others*	15(4.8)	3(3.0)	12(5.6)	
Platinum-based drug				0.248
Cisplatin	251(80.2)	84(84.0)	167(78.4)	
Carboplatin	62(19.8)	16(16.0)	46(21.6)	
Chemotherapy regimen				0.006
Platinum- gemcitabine	163(52.1)	68(68.0)	95(44.6)	
Platinum- pemetrexed	114(36.4)	24(24.0)	90(42.2)	
Platinum-paclitaxel	21(6.7)	6(6.0)	14(6.5)	
Platinum-docetaxel	13(4.1)	2(2.0)	11(5.1)	
Platinum- navelbine	2(0.6)	0(0.0)	2(0.9)	
TNM stage				0.086
IIIA/IIIB	73(23.3)	29(29.0)	43(20.2)	
IV	240(76.7)	71(71.0)	170(79.8)	

*Others represent the large cell, bronchioalveolar, mixed cell, and undifferentiated NSCLC.
#P value represent response group compared with non-response group using χ^2 with 2 df or Fisher's exact test.

platinum-based therapy. The Hardy–Weinberg equilibrium assumption of those 4 SNPs was assessed by chi-square test. The unconditioned Logistic regression analysis was used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs). Multivariate analysis was done to find whether clinical characteristics were considered as covariates when we assessed the relationship between genetic polymorphism and chemosensitivity. Significance was set at 5% and all reported values are two-tailed. All analyses were performed with the SPSS software package, version 17.0 (SPSS Inc, Chicago, IL) and PLINK version 1.07 (Cambridge, MA, USA).

RESULTS

The Clinical Characteristics of all Scubjects

Totally 313 patients with cytologically or histologically confirmed NSCLC were recruited in this study. The basic characteristics of those patients were summarized in Table **1**. 100 patients were sensitive to platinum therapy. The overall response rate was 31.9%. The 213 patients (68.1%) were resistant to platinum therapy.

Median age was 55 years (range 21–75), with 134 subjects (42.8%) older than 55 years. 179 subjects (57.2%) younger than 55 years. 173 patients (55.3%) were smokers and 173 patients (55.3%) were nonsmokers. Overall, 233 patients (74.4%) were male. All the patients were in advanced stage, in which 240 patients (76.7%) were at stage IV, 73 patients (16.7%) were at stage IIIA or IIIB. All the patients were inoperable advanced NSCLC. Most patients (95.8%) have well physical condition (EGFR：0-1) and they have received platinum-based therapy, including cisplatin and carboplatin. 163 patients (52.1%) received platinum-gemcitabine regimens; 114 patients (36.4%) received platinum-pemetrexed regimens, 21 patients (6.7%) received platinum-paclitaxel regimens; 13 patients (4.1%) received platinum-docetaxel regimens; 2 patients (0.6%) received platinum- navelbine regimens. 251 patients (80.2%) received cisplatin-based therapy while 62 patients(19.8%) received carboplatin-based therapy.

Genotyping and Hardy–Weinberg Equilibrium (HWB) Analysis

The results of genotyping, HWB analysis, and detailed information of *TNF-α*, *TNF-R1* and *TNF-R2* genes were listed in Table **2**. The genotyping rates of all the SNPs were all over 95%. These SNPs were all under the Hardy–Weinberg equilibrium ($P > 0.05$).

Association of Polymorphisms in *TNFα*, *TNF-R1,* and *TNF-R2* and Platinum-Based Chemotherapy Response in NSCLC Patients

Logistic regression analysis showed that *TNFα* -308 A/G is significantly correlated with better clinical benefit (Table **3**). Patients carrying -308 A allele had a favorable prognosis after the treatment of platinum-based chemotherapy (P=0.043, OR=0.488, 95% CI=0.244-0.979). The carriers with CA genotype significantly reduced the risk of platinum resistance compared with wild-type homozygotes CC genotype (P=0.025, OR=0.447, 95% CI=0.220-0.906). In addition, there was no significant association of platinum-based chemotherapy efficacy and other SNP polymorphisms.

Several subsets were selected for stratified examination: aged ≤55 years, aged >55 years, women, men, smokers, nonsmokers, stage IIIA-B or stage IV, histologic type of adenocarcinoma or squamouscell carcinoma, patients receiving platinum-gemcitabine, or platinum-paclitaxel, patients receiving cisplatin-based therapy or carboplatin-based therapy. Further stratification analysis showed that the protective effect of *TNFα*-308 A/G polymorphism is better in population of aged >55 years (*P*=0.004), women (*P*=0.027), never-smokers (*P*=0.012), adenocarcinoma (*P*=0.027), and NSCLC patients receiving cisplatin-based chemotherapy (*P*=0.044).

Table 2: The Genotyping and Hardy-Weinberg Balance Analysis of *TNF-α*, *TNF-R1*, and *TNF-R2* Polymorphisms

Gene	SNP	Location in gene region	Base Change	Call Rate	MAF	HWE
TNF-α	rs1800629	-308 A/G	G/A	99.4%	0.067	0.6387
TNF-R1	rs2234649	-383A>C	A/C	99.7%	0.083	0.7080
	rs4149570	-609T>G	T/G	96.5%	0.458	0. 5608
TNF-R2	rs1061622	+676 T>G	T/G	99.4%	0.172	0.5487

Table 3: Association of *TNF-α*, *TNF-R1*, and *TNF-R2* Polymorphisms and Platinum-Based Chemotherapy Response in NSCLC Patients

Genotypes	Response		Adjusted OR (95% CI)^a	P^a
	CR+PR n (%)	SD+PD n (%)		
TNF-α -308 A/G				
GG	80(80.8)	191(90.1)	1.000(reference)	
GA	19(19.2)	19(9.0)	0.447(0.220-0.906)	0.025
AA	0(0.0)	2(0.9)	-	-
GA+AA			0.488(0.244-0.979)	0.043
GG+GA vs AA			-	-
TNF-R1 -383A>C				
AA	80(80.0)	181(85.4)	1.000(reference)	
CA	19(19.0)	31(14.6)	0.646(0.345-1.208)	0.171
CC	1(1.0)	0(0.0)	-	-
CA+AA			0.686(0.358-1.313)	0.255
AA+CA vs CC				-
TNF-R1 -609T>G				
TT	27(28.4)	58(28.3)	1.000(reference)	
GT	52(54.7)	103(50.2)	1.073(0.594-1.938)	0.815
GG	16(16.8)	44(21.5)	1.317(0.612-2.834)	0.482
GT+GG			1.132(0.644-1.990)	0.666
TT+GTvs GG			1.258(0.647-2.447,)	0.499
TNF-R2 +676 T>G				
TT	72(72.7)	139(65.6)	1.000(reference)	
GT	26(26.3)	67(31.6)	1.360(0.779-2.375)	0.279
GG	1(1.0)	6(2.8)	2.928(0.318-27.001)	0.343
GG+GT			1.417(0.819-2.450)	0.212
TT+GT vs GG			2.678(0.292-24.540)	0.384

^{a}Adjusted for Chemotherapy regimen and histological of lung cancer.

DISCUSSION

In the present study, we found that *TNFα* -308 A/G polymorphism is significantly associated with efficacy of platinum-based chemotherapy and it may serve as the indicators of platinum-based chemotherapy response in NSCLC cancer patients. Additionally, our results showed that patients carrying *TNFα*-308 A/G A allele have a favorable prognosis.

The *TNFα* gene is located on chr 6p21, within the class III region of the major histocompatibility complex, between HLA-B and HLA-DR. TNF-α performs multiple functions in immunity, inflammation, differentiation, apoptosis, and the control of cell proliferation *via* NF-κB through the distinct receptors: TNF-R1 and TNF-R2. Platinum can cause the apoptosis of tumor cells by activating the apoptosis pathway and provide the apoptosis signal which can further cause the binding of TNFα to specific receptors, inducing the recruitment of the signaling proteins, further initiating apoptosis [20].

TNFα -308 A/G polymorphism was the G to A transition , locating at 308 nucleotide upstream of the translation initiation site in the promoter. This variation can elevate the production of TNFα by altering the transcription factor binding site, which is considered to be an important enhancer of transcriptional activation [16, 21]. Recent studies have found this SNP is involved in increased susceptibility to different diseases, including chronic disease such as Alzheimer’s disease [22], Parkinson’s disease [23],

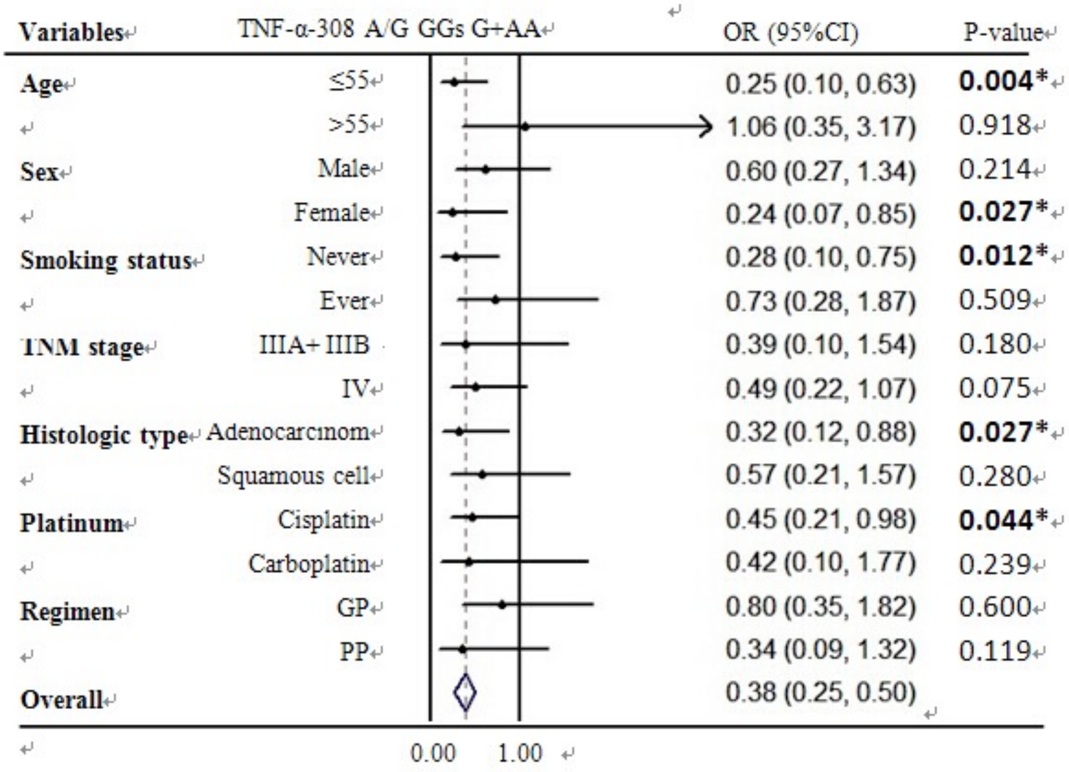

Figure 1: Stratification analysis of association between *TNF-α*-308 A/G polymorphism and platinum-based chemotherapy response in NSCLC patients.

diabetes [24] malignant tumor like breast cancer [25], and Cervical Cancer [26]. In this study, we found that *TNFα* -308 A/G polymorphism was significantly correlated with the preferable effect of platinum-based chemotherapy. We speculate that the A allele elevated the mRNA level, inducing the high concentration of TNFα, which further increased the apoptosis of tumor cell , thus decreasing the risk of resistance to platinum. Moreover, after further stratification analysis, we found that the protective effect of *TNFα* -308 A/G polymorphism is more significant in population of aged >55 years, women, never-smokers, adenocarcinoma, and NSCLC patients receiving cisplatin-based chemotherapy which shows that the protective effect of -308 A/G present in multitude subgroup. Our findings indicate that the increased level of TNFα can modulate the therapeutic effect of platinum agents and TNFα -308 A/G may serve as the indicator of platinum-based chemotherapy response.

TNF-R1, the major receptor for TNFα, can activate NF-κB, mediate apoptosis, and regulate inflammation. Although we did not find the association between *TNF-R1* -383A>C and -609T>G and clinical response, this two SNPs has been reported to be associated with increased risk of many diseases [27, 28] and clinical outcome [29]. Those two polymorphisms are located in the promoter region of the TNF-R1 and may have effect on transcriptional control. Lee *et al.* [29] found that the *TNF-R1* -609T allele was associated with poor overall survival and disease-free survival in NSCLC patients. Further confirmatory experiment are needed to clarify the effects of those polymorphisms

TNF-R2 is another receptor of TNFα and researches show that it could enhance the function of TNF-R1 in TNF-mediated toxicity [30]. TNF-R2 has a higher binding affinity to TNFα than TNF-R1 [31], but we did not find any association existing in the efficacy of platinum-based chemotherapy. *TNF-R2* +676 T>G is the change of T to G in the exon 6 of TNF-R2 that can cause a functional amino acid substitution at codon196 from methionine (Met) to arginine (Arg) which is supposed to produce a soluble form of TNF-R2, further impairing NF-κB signaling and affecting TNFα induced apoptosis [32]. Based on previous studies, *TNF-R2* +676 T>G are associated with susceptibility and survival of breast cancer patients [33]. Also, Guan *et al.* [34] found *TNF-R2* +676 T>G polymorphism can predicts survival of NSCLC patients treated with platinum-based chemoradiotherapy, in which GG genotype was associated with a significantly better OS of NSCLC. However, our study did not find any association between this SNP and the efficacy of platinum treatment, so the exact biological mechanism underlying this association in our study remains to be investigated.

Our study have several advantages: 1 We systematically studied the association between four SNPs and platinum response through candidate gene strategy, those SNPs are potential functional that can be further analyzed for internal mechanism. 2 All the patients went through strict screening to ensure the homogeneity of population. 3 We include only NSCLC patients so as to eliminate the bias of pathological classification. However, our study inevitably has some limitations: 1 We did not include all the gene variation in *TNFα*, *TNF-R1*, and *TNF-R2*. 2 Chemotherapy regimens are platinum-based combination and heterogeneity is unavoidable. However, we adopted the unconditioned logistic regression to correct the possible confounding factors. 3 We are unable to screen all the genes in apoptosis pathway, as it is a complex process that involves the participation of many other signaling molecules. 4 Although our study are at a relative large sample size, independent samples are still needed for further verification.

In conclusion, our findings showed that the *TNFα* -308 A/G mutant allele is significantly correlated with preferable efficacy. Patients carrying *TNFα* -308 A/G mutant allele have low risk of resistance to platinum-based chemotherapy. This SNP might be a new predictive genetic marker of clinical response of platinum-based chemotherapy.

ACKNOWLEDGEMENTS

We thank all patients who participated in this study, and Bio Miao Biological Technology Co., Ltd. Beijing, China for their technical assistance. We also thank all supported funds from the National High-tech R&D Program of China (863 Program) (2009AA022704, 2012AA02A517), National Natural Science Foundation of China (81173129, 81202595, 81373490), and Program for the Special Scientific Research Foundation of Doctor Disciplines in University of Ministry of Education of China (20110162110034).

CONFLICT OF INTEREST

There are no conflicts of interest.

REFERENCES

[1] Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA: a Cancer Journal for Clinicians 2011; 61(2): 69-90. http://dx.doi.org/10.3322/caac.20107

[2] Patz EF, Jr., Goodman PC, Bepler G. Screening for lung cancer. The New England Journal of Medicine 2000; 343(22): 1627-33. http://dx.doi.org/10.1056/NEJM200011303432208

[3] Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA: A Cancer Journal for Clinicians 2010; 60(5): 277-300. http://dx.doi.org/10.3322/caac.20073

[4] Carbone DP, Minna JD. Chemotherapy for non-small cell lung cancer. BMJ 1995; 311(7010): 889-90. http://dx.doi.org/10.1136/bmj.311.7010.889

[5] Zorbas H, Keppler BK. Cisplatin damage: are DNA repair proteins saviors or traitors to the cell? Chembiochem: a European Journal of Chemical Biology 2005; 6(7): 1157-66. http://dx.doi.org/10.1002/cbic.200400427

[6] Yin JY, Huang Q, Zhao YC, Zhou HH, Liu ZQ. Meta-analysis on pharmacogenetics of platinum-based chemotherapy in non small cell lung cancer (NSCLC) patients. PloS One 2012; 7(6): e38150. http://dx.doi.org/10.1371/journal.pone.0038150

[7] Yin JY, Shen J, Dong ZZ, Huang Q, Zhong MZ, Feng DY, *et al*. Effect of eIF3a on response of lung cancer patients to platinum-based chemotherapy by regulating DNA repair. Clinical cancer research: An Official Journal of the American Association for Cancer Research 2011; 17(13): 4600-9.

[8] Gu S, Wu Q, Zhao X, Wu W, Gao Z, Tan X, *et al*. Association of CASP3 polymorphism with hematologic toxicity in patients with advanced non-small-cell lung carcinoma treated with platinum-based chemotherapy. Cancer Science 2012; 103(8): 1451-9. http://dx.doi.org/10.1111/j.1349-7006.2012.02323.x

[9] Qian J, Gu S, Wu Q, Zhao X, Wu W, Gao Z, *et al*. Association of CASP7 polymorphisms and survival of patients with non-small cell lung cancer with platinum-based chemotherapy treatment. Chest 2012; 142(3): 680-9. http://dx.doi.org/10.1378/chest.11-2522

[10] de Vries EG, Gietema JA, de Jong S. Tumor necrosis factor-related apoptosis-inducing ligand pathway and its therapeutic implications. Clinical cancer research: an Official Journal of the American Association for Cancer Research 2006; 12(8): 2390-3.

[11] Isonishi S, Jekunen AP, Hom DK, Eastman A, Edelstein PS, Thiebaut FB, *et al*. Modulation of cisplatin sensitivity and growth rate of an ovarian carcinoma cell line by bombesin and tumor necrosis factor-alpha. The Journal of Clinical Investigation 1992; 90(4): 1436-42. http://dx.doi.org/10.1172/JCI116010

[12] Isonishi S, Shiotsuka S, Ochiai K, Yasuda M, Terashima Y. Tumor necrosis factor-alpha (TNF alpha) enhances cisplatin cytotoxicity to ovarian carcinoma xenografts. Oncology Reports 1996; 3(6): 1049-53.

[13] Micheau O, Tschopp J. Induction of TNF receptor I-mediated apoptosis *via* two sequential signaling complexes. Cell 2003; 114(2): 181-90. http://dx.doi.org/10.1016/S0092-8674(03)00521-X

[14] Jones SJ, Ledgerwood EC, Prins JB, Galbraith J, Johnson DR, Pober JS, *et al*. TNF recruits TRADD to the plasma membrane but not the trans-Golgi network, the principal subcellular location of TNF-R1. Journal of Immunology 1999; 162(2): 1042-8.

[15] Rothe M, Wong SC, Henzel WJ, Goeddel DV. A novel family of putative signal transducers associated with the cytoplasmic domain of the 75 kDa tumor necrosis factor receptor. Cell 1994; 78(4): 681-92. http://dx.doi.org/10.1016/0092-8674(94)90532-0

[16] Kroeger KM, Carville KS, Abraham LJ. The -308 tumor necrosis factor-alpha promoter polymorphism effects transcription. Molecular Immunology 1997; 34(5): 391-9. http://dx.doi.org/10.1016/S0161-5890(97)00052-7

[17] Sharma S, Sharma A, Kumar S, Sharma SK, Ghosh B. Association of TNF haplotypes with asthma, serum IgE levels, and correlation with serum TNF-alpha levels. American Journal of Respiratory Cell and Molecular Biology 2006; 35(4): 488-95. http://dx.doi.org/10.1165/rcmb.2006-0084OC

[18] Cui G, Wang H, Li R, Zhang L, Li Z, Wang Y, *et al*. Polymorphism of tumor necrosis factor alpha (TNF-alpha) gene promoter, circulating TNF-alpha level, and cardiovascular risk factor for ischemic stroke. Journal of Neuroinflammation 2012; 9: 235. http://dx.doi.org/10.1186/1742-2094-9-235

[19] Wang Y, Yin JY, Li XP, Chen J, Qian CY, Zheng Y, *et al*. The association of transporter genes polymorphisms and lung cancer chemotherapy response. PloS One 2014; 9(3): e91967. http://dx.doi.org/10.1371/journal.pone.0091967

[20] Bodmer JL, Holler N, Reynard S, Vinciguerra P, Schneider P, Juo P, *et al*. TRAIL receptor-2 signals apoptosis through FADD and caspase-8. Nature cell Biology 2000; 2(4): 241-3. http://dx.doi.org/10.1038/35008667

[21] Wilson AG, Symons JA, McDowell TL, McDevitt HO, Duff GW. Effects of a polymorphism in the human tumor necrosis factor alpha promoter on transcriptional activation. Proceedings of the National Academy of Sciences of the United States of America 1997; 94(7): 3195-9. http://dx.doi.org/10.1073/pnas.94.7.3195

[22] Laws SM, Perneczky R, Wagenpfeil S, Muller U, Forstl H, Martins RN, *et al*. TNF polymorphisms in Alzheimer disease and functional implications on CSF beta-amyloid levels. Human Mutation 2005; 26(1): 29-35. http://dx.doi.org/10.1002/humu.20180

[23] Saiki M, Baker A, Williams-Gray CH, Foltynie T, Goodman RS, Taylor CJ, *et al*. Association of the human leucocyte antigen region with susceptibility to Parkinson's disease. Journal of Neurology, Neurosurgery, and Psychiatry 2010; 81(8): 890-1. http://dx.doi.org/10.1136/jnnp.2008.162883

[24] Bouhaha R, Baroudi T, Ennafaa H, Vaillant E, Abid H, Sassi R, *et al*. Study of TNFalpha -308G/A and IL6 -174G/C polymorphisms in type 2 diabetes and obesity risk in the Tunisian population. Clinical Biochemistry 2010; 43(6): 549-52. http://dx.doi.org/10.1016/j.clinbiochem.2010.01.008

[25] Gaudet MM, Egan KM, Lissowska J, Newcomb PA, Brinton LA, Titus-Ernstoff L, *et al*. Genetic variation in tumor necrosis factor and lymphotoxin-alpha (TNF-LTA) and breast cancer risk. Human Genetics 2007; 121(3-4): 483-90. http://dx.doi.org/10.1007/s00439-006-0315-x

[26] Zidi S, Stayoussef M, Zouidi F, Benali S, Gazouani E, Mezlini A, *et al*. Tumor Necrosis Factor Alpha (-238 / -308) and TNFRII-VNTR (-322) Polymorphisms as Genetic Biomarkers of Susceptibility to Develop Cervical Cancer Among Tunisians. Pathology oncology research: POR 2014.

[27] Corona-Sanchez EG, Munoz-Valle JF, Gonzalez-Lopez L, Sanchez-Hernandez JD, Vazquez-Del Mercado M, Ontiveros-Mercado H, *et al*. -383 A/C tumor necrosis factor receptor 1 polymorphism and ankylosing spondylitis in Mexicans: a preliminary study. Rheumatology International 2012; 32(8): 2565-8. http://dx.doi.org/10.1007/s00296-011-1997-5

[28] Nishimura M, Obayashi H, Mizuta I, Hara H, Adachi T, Ohta M, *et al*. TNF, TNF receptor type 1, and allograft inflammatory factor-1 gene polymorphisms in Japanese patients with type 1 diabetes. Human Immunology 2003; 64(2): 302-9. http://dx.doi.org/10.1016/S0198-8859(02)00799-1

[29] Lee EB, Jeon HS, Yoo SS, Choi YY, Kang HG, Cho S, *et al*. Polymorphisms in apoptosis-related genes and survival of patients with early-stage non-small-cell lung cancer. Annals of Surgical Oncology 2010; 17(10): 2608-18. http://dx.doi.org/10.1245/s10434-010-1082-4

[30] Grell M, Zimmermann G, Gottfried E, Chen CM, Grunwald U, Huang DC, *et al*. Induction of cell death by tumour necrosis factor (TNF) receptor 2, CD40 and CD30: a role for TNF-R1 activation by endogenous membrane-anchored TNF. The EMBO Journal 1999; 18(11): 3034-43. http://dx.doi.org/10.1093/emboj/18.11.3034

[31] Tartaglia LA, Goeddel DV. Two TNF receptors. Immunology Today 1992; 13(5): 151-3. http://dx.doi.org/10.1016/0167-5699(92)90116-O

[32] Till A, Rosenstiel P, Krippner-Heidenreich A, Mascheretti-Croucher S, Croucher PJ, Schafer H, *et al*. The Met-196 -> Arg variation of human tumor necrosis factor receptor 2 (TNFR2) affects TNF-alpha-induced apoptosis by impaired NF-kappaB signaling and target gene expression. The Journal of Biological Chemistry 2005; 280(7): 5994-6004. http://dx.doi.org/10.1074/jbc.M411541200

[33] Mestiri S, Bouaouina N, Ben Ahmed S, Chouchane L. A functional polymorphism of the tumor necrosis factor receptor-II gene associated with the survival and relapse prediction of breast carcinoma. Cytokine 2005; 30(4): 182-7. http://dx.doi.org/10.1016/j.cyto.2005.01.007

[34] Guan X, Liao Z, Ma H, Qian J, Liu Z, Yuan X, *et al*. TNFRSF1B +676 T>G polymorphism predicts survival of non-small cell lung cancer patients treated with chemoradiotherapy. BMC Cancer 2011; 11: 447. http://dx.doi.org/10.1186/1471-2407-11-447

Received on 24-09-2014 Accepted on 06-11-2014 Published on 24-11-2014

DOI: http://dx.doi.org/10.6000/1929-2279.2014.03.04.6