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Original Article

Genetic polymorphisms of *IL-6* and *IL-10* genes correlate with lung cancer in never-smoking Han population in China

Ying-Min Zhang, Yi-Min Mao, Yu-Xia Sun

Department of respiration, The First Affiliated Hospital of Henan University of Science and Technology, Luoyang 471003, China

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Abstract: Lung cancer is one of the most common cancers in the world, especially in China. It is believed that genetic polymorphisms played a role in cancer susceptibility. Here we investigated the association of interleukin-6 (*IL*-6) and interleukin-10 (*IL*-10) gene polymorphisms with the susceptibility of lung cancer in never-smoking Chinese Han population. In this study, we performed a case-control study including 330 cases of never-smoking lung cancer patients and 336 cancer-free never-smoking controls in Chinese Han population. We used polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method to identify gene polymorphisms, and then verified by sequencing method. The results indicated that the four single nucleotide polymorphisms (*IL*-6 -1363T/G and -572G/C, *IL*-10 -819T/C and -592A/C) were genotyped by PCR-RFLP and confirmed by sequencing, and we found that the allelic frequencies of G in *IL*-6 -1363T/G, C in *IL*-10 -819T/C and C in *IL*-10 -592A/C were significantly increased in lung cancer patients, by comparing with the control group. However, there was no significant difference in the distribution of the IL-6 572G/C polymorphisms between patients and controls. In conclusion, the *IL*-6 -1363T/G, *IL*-10 -819T/C and *IL*-10 -592A/C polymorphisms are closely related to genetic susceptibility to lung cancer in never-smoking Chinese Han population, and these genetic variants might be used as molecular markers for detecting lung cancer susceptibility.

Keywords: Lung cancer, *IL*-6 gene, *IL*-10 gene, single-nucleotide polymorphisms, cancer susceptibility

Introduction

Lung cancer is a very common and growing health problem, which causes high morbidity and mortality in the world, especially in China. According to the recent studies, more than one million deaths are caused by lung cancer worldwide [1, 2], and the incidence and mortality rate has increased rapidly. Take Chinese as an example, the overall five-year survival rate is lower than 15%, and the mortality number is estimated to exceed one million by 2025 [3, 4]. Many environmental and occupational factors, such as exposure to tobacco smoke as well as other exogenous carcinogens, are clearly related to the development of lung cancer [5]. However, only 11% of tobacco smokers ultimately develop lung cancer, and many genetic factors have been suggested to modulate the pathogenesis of lung cancer [6].

Although smoking is the principal risk factor for lung cancer, many common gene variants have been recently identified to involve in the lung cancer tumorigenesis and development [7-10]. Identification of genes involved in the occurrence and development of lung cancer could contribute to further understanding of the underlying mechanisms, and even a very important additional appropriate prevention strategies and targeted treatments for reducing lung cancer burden [5]. Chronic inflammation is likely to be closely related to the development of lung cancer. As reported based on the genetic and molecular studies, many inflammatory markers such as cytokines showed differential expressions and gene polymorphisms in lung tumor tissues and in peripheral blood [11, 12]. Cytokines are important mediators involved in the inflammatory response. More and more studies demonstrated that human lung cancer

Table 1. Primer pairs, PCR and CRS-PCR analysis for *IL-6* and *IL-10* gene

SNP	Primer sequence	Tm (°C)	PCR Products (bp)	Restriction enzyme	Genotype (bp)	References
IL-6 -1363T/G	5'-CGGGTCCTGAAATGTTAT-3'	59	222	*Tag I*	G: 156, 66	[21, 30]
	5'-GTTGTCCCTCCAGTCTCC-3'				C: 222	
IL-6 -572G/C	5'-CTCCTCTAAGTGGGCTGAAG-3'	56	212	*BsrB I*	G: 139, 73	[21, 30]
	5'-GTTGTCCCTCCAGTCTCC-3'				C: 212	
IL-10 -819T/C	5'-TCATTCTATGTGCTGGAGATGG-3'	59	209	*Msl I*	C: 116, 93	[31, 32]
	5'-TGGGGGAAGTGGGTAAGAGT-5				T: 209	
IL-10 -592A/C	5'-GGTGAGCACTACCTGACTAGC-3'	58	412	*Rsa I*	A: 236, 176	[31, 32]
	5'-CCTAGGTCACAGTGACGTGG-3'				C: 412	

Table 2. Characteristics of the lung cancer group and the control group in this study

Characteristics	Lung cancer group (n=330)	The control group (n=336)	*P*-value
Age mean (Range) (years)	50.11±11.72 (30-77)	50.32±10.98 (31-74)	NS
Gender (male/female)	110/220	116/220	NS
In cancer years (Range)	3.72±1.06 (1.2-7.1)	0	$P<0.001^*$
Historical lung cancer (Y/N)[b]	46/324	0/336	$P<0.001^*$

Abbreviations: NS, Not significant; Y/N, Has historical lung cancer/Not has historical lung cancer; *Represents statistically significant.

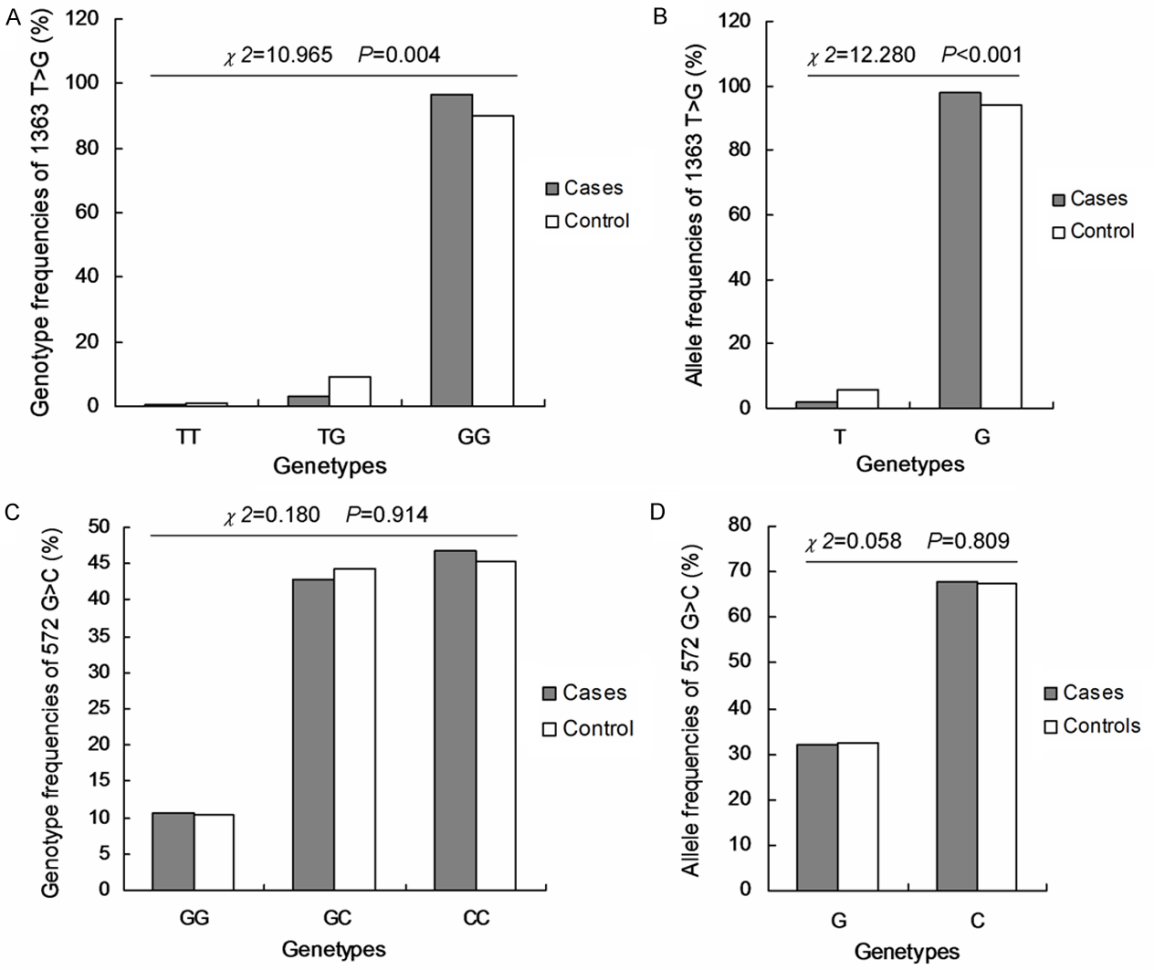

Figure 1. The genotypic frequencies of *IL-6*-1363 T>G and IL6-572 G>C in patients and controls group. A. Genotype frequency of 1363 T>G in patients and controls group. B. Allele frequency of 1363 T>G in patients and controls group. C. Genotype frequency of 572 G>C in patients and controls group. D. Allele frequency of 572 G>C in patients and controls group. The different value of χ^2 and *P* were illustrated in the figures.

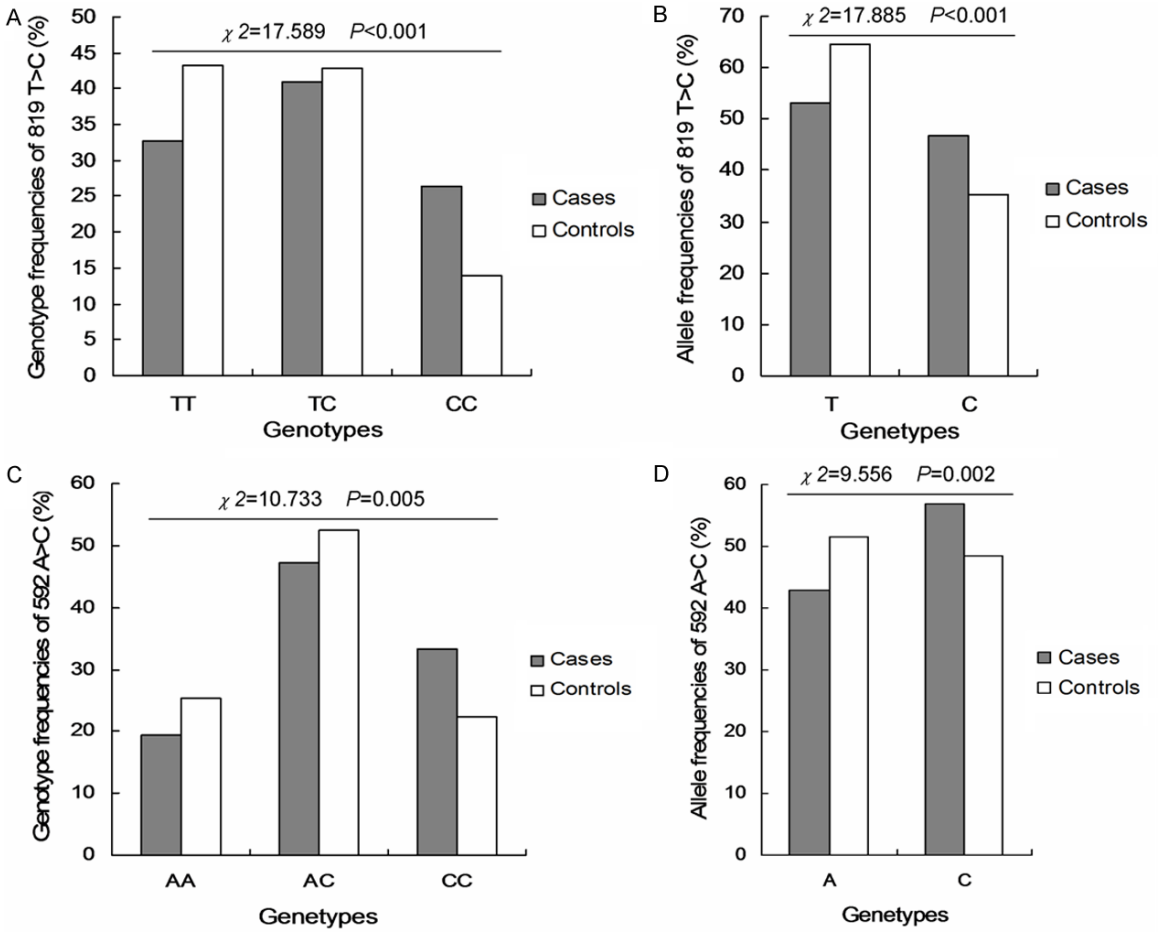

Figure 2. The genotypic frequencies of *IL-10*-819 T>C and IL-10-592 A>C in patients and controls group. A. Genotype frequency of 819 T>C in patients and controls group. B. Allele frequency of 819 T>C in patients and controls group. C. Genotype frequency of 592 A>C in patients and controls group. D. Allele frequency of 592 A>C in patients and controls group. The different value of χ^2 and *P* were illustrated in the figures.

risk could be modified by polymorphisms of interleukins, for example, the genetic polymorphism of *IL*-1 beta had influence on the risk of non-small cell lung cancer [13], *IL*-4 -590T/C influenced the susceptibility to non-small cell lung cancer [14], *IL*-8 gene polymorphisms was associated with non-small lung cancer in Tunisia [15], *IL*-18 promoter polymorphisms was associated with lung cancer [16]. Interleukin-6 (IL-6) was a prevalent pro-inflammatory cytokine which plays a central role in regenerative or anti-inflammatory processes [17]. IL-6 has been reported to be the predominant cytokine elevated expressed in lung tumor tissue [18], several single–nucleotide polymorphisms in the *IL*-6 gene have been described to involve in its transcriptional regulation, such as the -174G/C polymorphism [19], the -634C/G polymorphism [20], the -572G/C polymorphism and the -1363G/T polymorphism [21]. Interleukin-10 (IL-10) is another important prevalent cytokine, which influences many aspects of the immune response through having pleiotropic effects in immunoregulation and inflammation [22]. Many previous studies have indicated that many *IL*-10 polymorphisms, especially in the promoter region, were associated with the susceptibility of cancer, especially the lung cancer,

Table 3. Allele frequencies of IL-6 and IL-10 genetic polymorphisms in cases and controls

	Genotype frequencies (%)			Allele frequencies (%)	
IL-6					
1363 T>G	TT	TG	GG	T	G
Cases VS. Controls	OR=0.237, 95% CI (0.026-2.136)			OR=0.335, 95% CI (0.177-0.635)	
572 G>C	GG	GC	CC	G	C
Cases VS. Controls	OR=0.987, 95% CI (0.587-1.659)			OR=0.972, 95% CI (0.773-1.223)	
IL-10					
819 T>C	TT	TC	CC	T	C
Cases VS. Controls	OR=0.402, 95% CI (0.261-0.621)			OR=0.623, 95% CI (0.500-0.776)	
-592 A>C	AA	AC	CC	A	C
Cases VS. Controls	OR=0.513, 95% CI (0.331-0.795)			OR=0.712, 95% CI (0.573-0.883)	

and affected the expression level of IL-10 [11, 23, 24]. Based the results of many recent studies, of the *IL*-10 SNPs, the -1082A/G, -819C/T, -592G/A in the promoter have been confirmed to play important function in immunoregulation and inflammation by functional assays in cell models [11, 25, 26].

Although many polymorphism sites of *IL*-6 and *IL*-10 were suggested to associate with the risk of lung cancer [11, 18, 20, 25, 27, 28], the potential association analysis for *IL*-6 -1363T/G and -572G/C, *IL*-10 -819T/C and -592A/C genetic polymorphism with lung cancer in never-smoking Chinese Han population has not been reported. Thus, in this study, we focused on investigating the distribution of these four SNPs and determining the influence on lung cancer susceptibility in never-smoking Chinese Han population.

Materials and methods

Clinical samples

All the 330 patient specimens were obtained from never-smoking adults diagnosed and/or treated with lung cancer in the First Affiliated Hospital of Henan University of Science and Technology, during June 1, 2010 to May 30, 2013, and all the patients were the Chinese Han people. Accordingly, 336 healthy age-matched never-smoking Chinese Han people who had no history of any lung diseases were enrolled as controls in this study. There was no significant difference regarding age and gender between case and control groups ($P > 0.05$). Patients' data about risk factors were obtained from questionnaires, including living environment conditions, occupation, cancer stage, tumor size and family history of cancer. This study was approved by the local ethics committee, and the informed consent form was obtained by each subject.

PCR amplification and genotyping

Genomic DNA was extracted from peripheral venous blood by using the Axygen DNA isolation kit (Axygen, CA), according to the recommended protocol, and then stored at -80°C for analyzed. All polymerase chain reaction (PCR) primers were synthesized by TaKaRa Biotechnology Co., Ltd (Dalian, China) as references listed in **Table 1**, and the theoretical annealing temperature, fragment region, and size were also listed in **Table 1**. All PCRs were carried out in 25 μL of reaction mixture containing 50 ng template DNA, 1×buffer (Tris–HCl 100 mmol/L, pH 8.3; KCl 500 mmol/L), 0.25 μmol/L primers, 2.0 mmol/L $MgCl_2$, 0.25 mmol/L dNTPs and 0.5U rTaq DNA polymerase (Promega, Madison, WI, USA). The PCRs were performed on 94°C for 5 min, followed by 35 cycles of 94°C for 30s, annealing at the corresponding temperature (shown in **Table 1**) for 30s and 72°C for 30s, and a final extension at 72°C for 8 min. All amplified PCR products were preliminary checked by electrophoresis on 2.0% agarose gel and then analyzed under UV light. All SNPs of *IL-6* and *IL-10* gene were genotyped by the created restriction site-polymerase chain (CRS-PCR) method. Aliquots of 5 μL amplified PCR products were digested with 2U selected restriction enzymes (MBI Fermentas, St. Leon-Rot, Germany, **Table 1**) at the corresponding temperatures for 10h following the recommended supplier's manual. Digested

products were separated by 2.5% agarose gel electrophoresis and analyzed under UV light. 10% of random samples were re-analyzed by DNA sequencing method (ABI3730xl DNA Analyzer, Applied Biosystems, Foster City, CA, USA) to make sure concordance with the genotyping results from CRS-PCR.

Statistical analysis

All statistical analyses were performed by using the Statistical Package for Social Sciences software (SPSS, Windows version release 15.0; SPSS Inc.; Chicago, IL, USA). The chi-squared (χ^2) test was utilized to evaluate the Hardy-Weinberg equilibrium in genotypic distributions and clinical characteristics. A level of $P < 0.05$ was considered statistically significant.

Results

Population characteristics

The demographic and clinical characteristics of the study population were summarized in **Table 2**. There were no significant statistical different of age and gender between the lung cancer group and the control group. The age range was 30 to 77 years for the lung cancer group, and 31 to 74 years for the control group. The mean of in cancer year was 3.72±1.06 years for the lung cancer group, while 0 year for the control group. The percentage of those who have historical lung cancer was 13.9% in the lung cancer group, and 0% in the control group.

IL-6 and IL-10 SNPs identification and genotyping

Through CRS-PCR and DNA sequencing, we investigated the -1363T>G, and -572G>C SNPs of *IL-6* and -819T>C, and -592A>C SNPs of *IL-10* gene. The PCR-amplified products were digested with *Tag I* or *Bsr*B I or *Msl I* or *Rsa I* restriction enzyme, and divided into two or three genotypes as shown in **Table 1**.

Genotypic and allelic frequencies

All allelic and genotypic frequencies in the studied populations were investigated. For the -1363 T>G of *IL-6*, the genotypic frequencies of TT, TG and GG were 10.6%, 42.7% and 46.7% in the patients group, and 10.4%, 44.3% and 45.2% in the controls group (**Figure 1A**). And the corresponding allelic frequencies in the patients and controls group were 32.0% and 32.6% for G allele, and 68.0% and 67.4% for C allele, respectively (**Figure 1B**). For the -572G>C of *IL-6*, the genotypic frequencies of GG, GC and CC were 0.3%, 3.3% and 96.4% in the patients group, and 1.2%, 8.9% and 89.9% in the controls group (**Figure 1C**). And the corresponding allelic frequencies in the patients and controls group were 2.0% and 5.7% for T allele, and 98.0% and 94.3% for A allele, respectively (**Figure 1D**). For the -819 T>C of *IL-10*, the genotypic frequencies of TT, TC and CC were 32.7%, 40.9% and 26.4% in the patients group, and 43.2%, 42.9% and 14.0% in the controls group (**Figure 2A**). And the corresponding allelic frequencies in the patients and controls group were 53.2% and 64.6% for T allele, and 46.8% and 35.4% for C allele, respectively (**Figure 2B**). For the -592A>C of *IL-10*, the genotypic frequencies of AA, AC and CC were 19.4%, 47.3% and 33.3% in the patients group, and 25.3%, 52.4% and 22.3% in the controls group (**Figure 2C**). And the corresponding allelic frequencies in the patients and controls group were 43.0% and 51.5% for A allele, and 57.0% and 48.5% for A allele, respectively (**Figure 2D**).

Association between the IL-6, IL-10 SNPs and lung cancer

Table 3 shows the patients' risk factor characteristics of -1363T>G, and -572G>C SNPs of *IL-6* and -819T>C, and -592A>C SNPs of *IL-10* gene. As for SNPs of *IL-6*, the T-allele of *IL-6* -1363T>G variant genotype is associated with a much lower lung cancer risk than the G-allele variant genotype ($\chi^2 = 10.965$, $P = 0.004$). There is no statistical different of the allelic gene distributions of *IL-6* -572G>C ($\chi^2 = 0.180$, $P = 0.914$). As for SNPs of *IL-10*, the T-allele of *IL-10* -819T>C variant genotype is associated with a much lower lung cancer risk than the C-allele variant genotype ($\chi^2 = 17.589$, $P < 0.001$), and the A-allele of *IL-10* -592A>C variant genotype is associated with a much lower lung cancer risk than the C-allele variant genotype (χ^2=10.733, $P = 0.005$).

Discussion

As a result of complex interactions between environmental and genetic factors, lung cancer evolves with highly variable patterns of genetic

diversity, and cause increasing rate of morbidity and mortality in both developed and developing countries. It is generally accepted that the genetic variants of candidate genes which influence the development of lung cancer play key roles in the pathogenesis of lung cancer. In this case–control study, we analyzed the effects of genetic polymorphisms of the prevalent pro-inflammatory cytokine genes *IL-6* and *IL*-10 on lung cancer susceptibility in never-smoking Chinese Han population. We investigated the possible association of -1363T>G, and -572G>C SNPs of *IL-6* and -819T>C, and -592A>C SNPs of *IL-10* gene on the risk factors of lung cancer. Our data indicated that the distribution of allele and genotype frequencies of *IL*-6 -1363T>G, *IL*-10 -819T>C, and *IL*-10 -592A>C in lung cancer patients were statistical different from lung cancer-free controls ($P < 0.05$, **Table 3**). For more specifically, the T-allele polymorphism of *IL*-6 -1363T>G, the T-allele polymorphism of *IL*-10 -819T>C and the A-allele polymorphism of *IL*-10 -592A>C were associated with significantly decreased lung cancer risk ($\chi^2 = 12.280$, $P < 0.001$; $\chi^2 = 17.885$, $P < 0.001$ and $\chi^2 = 9.556$, $P = 0.002$). While for the *IL*-6 -572G>C, results from our study suggested that no statistically significant differences were found in the distribution of allele and genotype frequencies between the lung cancer patients group and the lung cancer-free group ($\chi^2 = 0.058$, $P = 0.809$). As some research groups showed that the genetic variants of *IL-6* and *IL-10* were associated with the susceptibility of breast cancer and gastric cancer [17, 29-33], our results also suggested that many sites of the genetic variants of *IL-6* and *IL-10* were associated with the susceptibility of lung cancer in never-smoking Chinese Han population. However, as reported by Jiao *et al* [20], not all the reported SNPs sites of *IL-6* have a relevance on the susceptibility of lung cancer. The genetic variants of *IL*-6 -572G>C may not have a correlation on the occurrence and development of lung cancer in never-smoking Chinese Han Population.

Results from this study may suggest a role of cytokine genes polymorphisms in lung cancer development. However, what and how environmental factors induced the cancer-related cytokine genes polymorphisms are still unknown. Further study should confirm the association between *IL-6* -1363T>G, *IL*-10 -819T>C, and *IL*-10 -592A>C or other SNPs of *IL-6* and *IL*-10 and lung cancer risk in larger different populations and elucidate the underlying molecular mechanisms in the lung cancer development.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Yi-Min Mao, Department of respiration, The First Affiliated Hospital of Henan University of Science and Technology, 24 Jing Hua Road, Jianxi District, Luoyang 471003, Henan, China. Tel: +86-379-69823226; Fax: +86-379-69823226; E-mail: maoyimly@yeah.net

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