Available online at www.sciencedirect.com

ScienceDirect

Journal of Genetics and Genomics 42 (2015) 549−561

JGG

REVIEW

Genetic Polymorphism, Telomere Biology and Non-Small Lung Cancer Risk

Rongrong Wei [a], Frank T. DeVilbiss [b], Wanqing Liu [a,*]

[a] *Department of Medicinal Chemistry and Molecular Pharmacology, College of Pharmacy, Purdue University, West Lafayette, IN 47907, USA*
[b] *School of Chemical Engineering, Purdue University, West Lafayette, IN 47907, USA*

Received 12 June 2015; revised 3 August 2015; accepted 10 August 2015
Available online 14 September 2015

ABSTRACT

Recent genome-wide association studies (GWAS) have identified a number of chromosomal regions associated with the risk of lung cancer. Of these regions, single-nucleotide polymorphisms (SNPs), especially rs2736100 located in the telomerase reverse transcriptase (*TERT*) gene show unique and significant association with non-small cell lung cancer (NSCLC) in a few subpopulations including women, nonsmokers, East Asians and those with adenocarcinoma. Recent studies have also linked rs2736100 with a longer telomere length and lung cancer risk. In this review, we seek to summarize the relationship between these factors and to further link the underlying telomere biology to lung cancer etiology. We conclude that genetic alleles combined with environmental (e.g., less-smoking) and physiological factors (gender and age) that confer longer telomere length are strong risk factors for NSCLC. This linkage may be particularly relevant in lung adenocarcinoma driven by epidermal growth factor receptor (*EGFR*) mutations, as these mutations have also been strongly linked to female gender, less-smoking history, adenocarcinoma histology and East Asian ethnicity. By establishing this connection, a strong argument is made for further investigating of the involvement of these entities during the tumorigenesis of NSCLC.

KEYWORDS: Telomere; Non-small cell lung cancer; Cancer risk; Polymorphism; *EGFR* mutations

INTRODUCTION

Lung cancer is one of the most common cancer types worldwide in terms of incidence and mortality. Global statistic data show that lung cancer alone accounts for 13% of all newly diagnosed cancers and is responsible for 18% of all cancer-related deaths (Jemal et al., 2011). Behavioral factors such as tobacco smoking and environmental exposure are well-known risk factors of lung cancer (Clapp et al., 2008). Beyond this, genetic factors also play a crucial role in increasing susceptibility to lung cancer (Lichtenstein et al., 2000). However, the etiology of lung cancer based on different histology types is still largely unknown. It is important to find genetic factors which are essential for carcinogenesis.

The most predominant subtype of lung cancer is non-small cell lung cancer (NSCLC), which accounts for over 85% of all lung cancers (Breathnach et al., 2001) and is further classified into three main subtypes: adenocarcinoma, squamous cell carcinoma, and large-cell carcinoma. The major risk factor of lung cancer is tobacco smoking. Exposure to tobacco accounts for 80%−90% of lung cancer cases. 10%−15% of lung cancer cases occur without tobacco smoking (Tsao, 2007; Thun et al., 2008; Longo et al., 2011). Other risk factors including exposure to asbestos (O'Reilly et al., 2007), radon gas and other forms of air pollution including second-hand smoke are also causes of lung cancer (U.S. Department of Health and Human Services, 2006; Mason et al., 2010). Although tobacco smoking is the major risk factor for lung cancer, genetic diversity also plays a big role in the etiology of lung cancer. A

* Corresponding author. Tel: +1 765 496 6389.
E-mail address: liu781@purdue.edu (W. Liu).

http://dx.doi.org/10.1016/j.jgg.2015.08.005

combination of genetic and environmental factors plays a critical role in determining the cause and development of lung cancer (Jin et al., 2009).

Various studies showed that age, gender and ethnicity affect the incidence of lung cancer as well. Lung cancer does not typically occur before the age of 40 but after, and lung cancer rate increase with age until 70 (Stewart and Kleihues, 2003). Over 30% of males are smokers while only 6% of females smoke (Ng et al., 2014). However, 17% of males with cancer are lung cancer patients and 9% of all female cancer patients have lung cancer (Ferlay et al., 2010). This indicates that a large cohort of female lung cancer patients have a never-smoking history. Moreover, lung cancer with never-smoking history is much more common in females, especially among East Asians and East Asian immigrants (McCredie et al., 1999; Stewart and Kleihues, 2003; McCracken et al., 2007). Evidence indicates that female lung cancer patients with never-smoking history are influenced more by genetic/familial history rather than second-hand smoking or radon gas (Subramanian and Govindan, 2007). Therefore, understanding the interactions between genetic alleles, and physiological and environmental factors involved in lung cancer carcinogenesis is crucial for the early diagnosis, and prevention of lung cancer and also for the development of therapeutic strategies.

GENETIC RISK FACTORS FOR NSCLC

Genome-wide association studies (GWASs)

GWAS is a population-level examination to identify genetic alleles associated with disease status or clinical phenotypes throughout the entire genome, rather than focusing on a specific gene. GWAS is based on a large sample size and independent replications. Since 2005, GWAS has been widely used in discovering risk alleles for various cancers in human populations. A cornucopia of GWAS focuses on lung cancer in particular. These studies have identified a number of factors that are significantly correlated with the onset and progression of lung cancer.

Table 1 summarizes the single-nucleotide polymorphisms (SNPs) in different genetic loci related to the susceptibility of NSCLC. Of the 20 GWAS studies in NSCLC, a total of 28 SNPs have been significantly associated with NSCLC risk, among which three major susceptible loci in the human genome are related to lung cancer risk. Loci 15q24-25 (Amos et al., 2008; Hung et al., 2008; Thorgeirsson et al., 2008; Wu et al., 2009), 5p15 (McKay et al., 2008; Rafnar et al., 2009; Zienolddiny et al., 2009), and 6p21 (Wang et al., 2008; Zienolddiny et al., 2009) are consistently associated with lung cancer in multiple populations. Interestingly, some of these loci have been associated with lung cancer risk only in specific ethnic groups. For instance, the 15p24-25 locus harboring nicotinic acetylcholine receptor subunit genes *CHRNA3*, *CHRNA4*, and *CHRNB5*, is only associated with lung cancer risk in Caucasians. These nicotinic acetylcholine receptor subunits are related to nicotine dependence in smokers. While present in Caucasian populations, no association between nicotinic acetylcholine receptor-encoding loci and lung cancer has been found in Asian patients. This may be partly due to the low frequency of the minor allele of these particular SNPs in East Asian populations (Shiraishi et al., 2009; Wu et al., 2009). Loci 5p15 and 6p21 have been associated with lung cancer in both East Asian (e.g., Chinese, Korean and Japanese) (Jin et al., 2009; Kohno et al., 2010; Yoon et al., 2010; Bae et al., 2012; Lan et al., 2012; Ke et al., 2013; Lu et al., 2013) and Caucasian populations (Wang et al., 2008; Zienolddiny et al., 2009; Truong et al., 2010). Beyond these three well-established loci, other regions including 3q28-29, 13q12.12, 22q12.2 and 18p11.22 have also been found to be associated with lung cancer particularly in Asian populations (Yoon et al., 2010; Hu et al., 2011; Ahn et al., 2012; Lan et al., 2012; Hu et al., 2014).

Two genes encoding telomerase reverse transcriptase (TERT) and cleft lip and palate transmembrane protein 1-like protein (CLPTM1L) located in the 5p15 locus have received the most attention and are deemed to mediate observed genotype-phenotype correlations. Of all 20 GWAS-identified SNPs, rs402710 in the *CLPTM1L* gene was identified in eight studies in both Caucasian and Asian populations, rs401681 (in *CLPTM1L* gene) was identified in five studies, while rs2736100 in the *TERT* gene was identified in 13 studies. Interestingly, the rs2736100 locus was also associated with increased risk for common cancers in many other organs, including bladder, colorectal, pancreatic cancers and glioma (Shete et al., 2009; Gago-Dominguez et al., 2011; Kinnersley et al., 2012; Campa et al., 2015), suggesting that this locus is involved in genetic susceptibility to cancer in general.

Association between *TERT* polymorphism and lung cancer

Beyond the association with lung cancer as a combined phenotype, *TERT* polymorphisms are specifically associated with a few subtypes of lung cancer. These subtypes include lung adenocarcinoma, lung cancers in women, lung cancers related to East Asian ethnicity and lung cancers related to nonsmokers. Table 2 lists studies relating the rs2736100 to each of these subpopulations.

Lung adenocarcinoma

About 50% of lung cancers are adenocarcinomas and the incidence of adenocarcinomas is increasing (Jee et al., 1998; Janssen-Heijnen and Coebergh, 2003; Liam et al., 2006; Toyoda et al., 2008; Lortet-Tieulent et al., 2014). Although all major histological types of lung cancer are associated with tobacco smoking, adenocarcinoma is the most common type in never smokers (Subramanian and Govindan, 2007; Stewart and Wild, 2014). Published data have reported that *TERT* polymorphism rs2736100 C allele is associated with an increased risk of NSCLC. A case-control study has revealed that genotype frequencies of both AC and CC were significantly elevated with NSCLC (OR = 1.18; 95% CI, 1.01−1.39; $P = 0.040$ and OR = 1.46; 95% CI, 1.19−1.78; $P < 0.001$, respectively) (Wang et al., 2014). Notably, the association was