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Research advances on the association of nicotinic acetylcholine receptor-related genes and their polymorphisms with lung cancer

LI Yixuan, ZHOU Jing, ZHANG Jing, XIAO Sha

School of Public Health, Heinz Mehlhorn Academician Workstation, Hainan Medical University, Haikou, Hainan 571199, China

Corresponding author: XIAO Sha, E-mail:xiaosha4226@126.com

Abstract: Lung cancer is one of the malignant solid tumor types with the highest morbidity and mortality globally. In recent years, the survival of lung cancer has improved, but its prognosis and five-year survival are still poor. Risk factors of lung cancer include smoking, environmental pollution, occupational factors and chronic obstructive pulmonary diseases. Nicotinic acetylcholine receptors (nAChRs) have various forms and are widely involved in physiological, pathological and pharmacological processes of the body. Nicotine, one of the main components in tobacco, can be mediated by nAChRs after entering the human body. It is found that different subtypes of nAChRs have single nucleotide polymorphisms (SNPs), which can affect their functions. Genome-wide association study (GWAS), as an epidemiological research strategy, can better mine SNPs sites that are closely related to cancer occurrence, and then make it possible to find targets and drugs closely related to cancer occurrence and development. Based on the relevant research results at home and abroad, this paper systematically expounds the global prevalence of lung cancer and the relationship between nAChRs related gene SNPs and their function, and lung cancer, in order to provide a reference basis for accurate prevention and treatment of lung cancer.

Keywords: Lung cancer; Nicotinic acetylcholine receptor; Smoking; Single nucleotide polymorphisms; Genetic susceptibility
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Lung cancer is a global health problem with high morbidity and mortality worldwide. Early screening and precise preventive treatment of lung cancer has become important research topics in oncology. As an epidemiological research strategy, genome-wide association study (GWAS) can better explore the single nucleotide polymorphisms (SNPs) closely related to cancer development. This may lead to the discovery of therapeutic targets and drugs closely associated with cancer development. In this paper, we reviewed the epidemiological status of lung cancer, the functions of nicotinic acetylcholine receptors (nAChRs)-related genes involved in tobacco smoking, and the relationship between SNPs in nAChRs and lung cancer, as well as genetic susceptibility to lung cancer.

1 Prevalence of Lung Cancer

1.1 Incidence and mortality of lung cancer

Lung cancer is one of the most common malignant tumors in the world, with high morbidity and mortality. It is also the leading cause of cancer deaths in men [1]. Globally, lung cancer ranks first among the causes of cancer deaths, with approximately 2 million new cases and 1.76 million deaths each year. About half of the new cases occur in the Asian region [2]. In 2020, the incidence and mortality of lung cancer ranked first in men, while the incidence ranked third and the mortality ranked second in women. The 5-year survival rate was only 10% to 20% in most lung cancer patients, which in Japan (33%), Israel (27%) and South Korea (25%) was relatively high [3].

The latest cancer database in China showed that lung cancer was the most common cancer among men in China, accounting for about 21.8% of the total number of male cancers. The incidence and mortality of lung cancer in China were higher than those in the world. It was expected that the number of lung cancer patients will continue to increase in the next decade, and China will face a heavy burden of cancer [4]. In recent years, the incidence and mortality of lung cancer in China was higher in the central and eastern regions than that in the western region, and which was significantly higher in men than women. Moreover, the disparity in lung cancer incidence and mortality rates between urban and rural areas has been gradually decreasing. Lung cancer has a poor prognosis among all cancers, with a 5-year survival rate of 19.7% and a median survival time of less than 2 years [5]. Domestic and international cancer statistics revealed that the incidence and mortality rates of the same type of lung cancer vary among different races, ages, and geographic locations. Therefore, early screening, accurate prevention, and treatment of lung cancer will help reduce its incidence and mortality [6].

1.2 Risk factors for lung cancer

Risk factors for lung cancer include tobacco use, occupational exposure, air pollution, family history, radiation exposure, and chronic lung disease. The development of lung cancer was closely related to

tobacco use. According to the 2018 Global Adult Tobacco Survey of the Chinese Centre for Disease Control and Prevention (CDC), there were 308 million adult smokers in China, and as many as 732 million Chinese residents were passively exposed to secondhand smoke [7]. At present, studies at home and abroad still agree that the most important risk factor for lung cancer is smoking, and exposure to secondhand smoke can also lead to lung cancer. Occupational exposure, air pollution, and other problems are highlighted. Occupational factors include polycyclic aromatic hydrocarbons, asbestos, arsenic, and some forms of silica and chromium, hydrogen, chromium, and so on. Complex and new air pollutants in the atmosphere, particulate matter in the atmosphere, as well as ozone, pollutants emitted from indoor decoration materials, and fumes from cooking may adversely affect the cardiopulmonary system [8]. Certain lung diseases and a genetic history of tumors may also increase the risk of lung cancer, such as chronic obstructive pulmonary disease (COPD). Unhealthy psychological factors and dietary habits may also be risk factors for lung cancer to some extent.

2 Function of nAChRs

2.1 nAChRs

Nicotinic acetylcholine receptors, abbreviated as nAChRs, belong to the Cys-loop superfamily. Mammalian nicotinic receptors are composed of five subunits that resemble a cylindrical pentameric structure. Each subunit contains an N-terminal extracellular structure used for ligand binding. These receptors can be divided into two major subtypes: nicotinic neural (N1) and nicotinic muscle (N2). There are two main subtypes of nicotinic receptors [9]: N1 receptors are primarily found in the postsynaptic membrane of autonomic ganglia and the central nervous system, while N2 receptors are mainly distributed in the endplate membrane of the neuromuscular junction. nAChRs consist of extracellular domains, transmembrane domains, and intracellular domains. The extracellular domain is folded along the N-terminal α-helix to form a β-sandwich structure containing 10 β-sheets. The transmembrane domain consists of four α-helices (TM1-TM4) arranged in a pseudorhombic bundle, with TM1 and TM3 forming an intermediate circle that stabilizes the inner helix bundle formed by TM2 helices through extensive intra- and inter-subunit interactions. The TM4 helices form a looser outer circle on the periphery of the TM domain. The intracellular domain consists of three components. The extracellular domain is composed of four α-helices (TM1-TM4) and is arranged in a pseudo rhombic bundle. TM4 helices form a looser outer circle at the periphery of the TM structural domain. The intracellular structural domain is the large cytoplasmic region between TM3 and TM4 consisting of two structured helices, MX and MA [10].

The nicotinic receptor family consists of 17 subunits (α1-α10, β1-β4, γ, δ and ε), and the subunits that have been demonstrated to be involved in the formation of nAChRs in mammals are nine α (CHRNA2-CHRNA10) subunits, three β (CHRNB2-CHRNB4) subunits, one γ (CHRNG) subunit, one δ (CHRND) subunit and one ε (CHRNE) subunit. The human nAChRs subunits α2-α7, α9 and α10 are mainly encoded by eight genes, CHRNA2, CHRNA3, CHRNA4, CHRNA5, CHRNA6, CHRNA7, CHRNA9 and CHRNA10, and the nAChRs subunits β2-β4 are mainly encoded by CHRNB2, CHRNB3, CHRNB4 encoding. Among them, CHRNA2 is located at 8p21.2, CHRNA4 is located at 20q13.2, CHRNB2 is located at 1q21.3, CHRNA3-CHRNA5-CHRNB4 is a cluster of genes located at 15q25.1, the CHRNB3-CHRNA6 gene region is located at 8p11, CHRNA7 is located at 15q13.3, CHRNA9 is located at 4p15.1, and *CHRNA*10 is located at 11p15.5 [11].

2.2 Function of nAChRs

The variety of nAChRs and their complex biosynthesis, transport, and biological functions, as well as the regulation of these processes by nAChRs cofactor molecules, result in different constituent subunits of various types of nAChRs. nAChRs are expressed on the surface of all mammalian cells. There is a wide distribution of nAChRs in tissues such as the brain, muscle, lymphocytes, and cochlear hair cells, which mediate physiological functions such as cognition, muscle contraction, immune regulation and sound discrimination, respectively. Koukouli et al. [12] demonstrated that the β2 subunit of nAChRs had an effect on higher-order cognitive processes, as well as mediating sleep and anesthesia. As a central regulator, nAChRs can also be expressed in human cancer cells and tumor microenvironment (TME), to participate in the proliferation and metastasis of cancer cells [13].

nAChRs, as ion channel receptors, have been implicated in various pathological processes. Numerous studies have demonstrated the role of nAChR polymorphisms in various diseases, including tobacco addiction, deafness, psychiatric disorders, and cardiovascular diseases [14]. The addictive effects of nicotine and the key mechanisms of tobacco addiction are closely related to the effects mediated by nAChRs. After nicotine is ingested into the body, it binds to nAChRs, causing the activation of receptors present throughout the nervous system and the opening of ion channels. This stimulation leads to the release of dopamine, resulting in dependence [15]. Additionally, nicotine has been found to potentially promote tumor progression and correlate with metastasis in lung cancer through receptor activation. Previous studies have confirmed the existence of the acetylcholine autocrine pathway in lung cancer. This pathway involves the synthesis of acetylcholine from choline and acetyl coenzyme A, which is facilitated by choline acetyltransferase (ChAT). The synthesized acetylcholine is then transported and secreted to the extracellular area through the vesicular acetylcholine transporter (VAChT). In the extracellular area,

acetylcholine binds to the acetylcholine receptor on the cell membrane, thereby regulating the proliferation of tumor cells [16].

Polymorphisms in nAChRs genes are also associated with lung cancer development. α7-nAChR is the most studied nAChR, encoded by *CHRNA7*, whose N-terminus binds to a variety of selective antagonists. α7-nAChR is widely expressed in the central and immune systems, involved in the regulation of inflammatory responses and neural-immunomodulation effect. Nicotine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) are carcinogenic components of tobacco, and α7-nAChR, as a specific binding site for nicotine and NNK, involved in the key pathway mediating tobacco-induced lung cancer carcinogenesis [17-18]. Additionally, another study found a significant correlation between variants of *CHRNA3, CHRNA5*, and *CHRNB4* and nicotine, cocaine, and alcohol dependence [19]. In mammals, the α3β4 nAChRs mutant phenotype is a potential new target for diseases such as nicotine addiction, cancer, obesity, and hypertension. nAChRs in the brain's dopamine circuits are also involved in aversive responses to nicotine and nicotine-induced negative affective states [20]. As nAChRs play important roles in normal physiological functions and pathological processes, nAChRs have also become important targets for the treatment and prevention of certain diseases. α7 and α4β2 nAChRs have been shown to improve memory impairment in Alzheimer's disease, and α5 nAChRs may provide a precise drug for the treatment of nicotine addiction, and studies targeting these sites are expected to lead to the identification of new targets for lung cancer. Related studies are expected to find a breakthrough in targeted therapy for lung cancer [21-22].

3 Correlation between nAChRs gene polymorphisms and lung cancer

3.1 Genetic polymorphism

Genetic polymorphism refers to the alteration of DNA molecules or certain sites of genes, resulting in a different primary structure of DNA. This alteration forms polymorphism, which is considered an individual genetic marker at the molecular level. DNA polymorphism includes fragment length polymorphism (FLP), repeat sequence polymorphism (RSP), and single nucleotide polymorphism (SNP), among others [23]. FLP is a DNA fragment length polymorphism caused by changes in restriction endonuclease sites due to deletions, duplications and insertions of individual bases; RSP is mainly manifested as the copy number of repeated sequences, and RSP is mainly manifested as the copy number of repeated sequences. It manifests as variation in the copy number of repeated sequences; and SNP refers to DNA sequence polymorphisms at the genomic level caused by changes in individual nucleotides, such as base transitions, inversions, insertions, and deletions in four forms [24].

3.2 nAChRs genetic polymorphism

SNP loci have been reported in almost every subtype of nicotinic receptors, such as rs1051730, rs16969968, rs6474412, rs7329797, and rs6819385. It has been demonstrated that genetic variants in the *CHRNA*3-*CHRNA*5-*CHRNB*4 gene cluster are closely associated with tobacco addiction, which affects the genetic susceptibility to lung cancer. Carriers of the T allele located at the rs1051730 locus of the *CHRNA*3 gene have a 1.83-fold increase in the risk of lung cancer. Additionally, carriers of the A allele located in the rs16969968 locus of the *CHRNA*5 gene, specifically in the European Region, have a 1.30-fold increased risk of lung cancer [25-26]; it has been suggested that the desensitizing role of the α4 receptor in mediating the response to NNK may contribute to the development of adenocarcinomas of small airway epithelial cell origin in females [27]. SNPs in the region of the CHRNB3 gene have been associated with the development of lung cancer, with the carrier of the T allele at locus rs6474412 leading to a 1.12-fold increase, and also leading to the development of psoriasis [28]; another study found that three SNPs in the genes *CHRNA*2, *CHRNA*4, and *CHRNB*2 were associated with the rare epilepsy syndrome autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE). In one study, it was mentioned that the *CHRNA*2 mutation affects nAChR receptor function, the *CHRNA*4 mutation down-regulates nAChR receptor function, and the *CHRNB*2 mutation up-regulates nAChR receptor function [29-30]. Additionally, the mutation at the rs892413 locus of *CHRNA*6 may contribute to the co-morbidity of cigarette smoking and alcohol abuse, and alcohol may regulate the binding of nicotine to nAChRs [31]. Furthermore, *CHRNA*7 gene SNPs are also associated with a variety of psychiatric disorders, affecting the responsiveness of Alzheimer's disease medication and correlating with tobacco addiction and oral precancerous lesions, and correlating with tobacco addiction, oral precancerous lesions, and lung carcinogenesis [32], *CHRNA*9 gene SNPs are closely associated with the development of breast and lung cancers. Patients carrying the G allele at the rs7329797 locus are at a 1.8-fold increased risk of breast cancer, and individuals carrying the AA genotype at locus rs6819385 have a 1.61-fold increased risk of squamous lung cancer [33-34]. On the other hand, *CHRNA*10 is closely associated with ear diseases and breast cancer.

3.3 Association study of nAChRs gene polymorphisms with genetic susceptibility to lung cancer

Tobacco smoking and betel nut chewing, as considered adverse environmental and lifestyle factors, may up-regulate the pro-cancer effects and down-regulate the cancer inhibitory effects of nAChRs. The interaction between the two induces and accelerates the formation of lung cancer. Nicotine, the main component of tobacco, is an agonist of nAChRs, which can be transmitted in the

brain through nAChRs. The signal transduction mechanism of nAChRs plays a role in the signaling pathway of lung cancer, promoting the progression of lung cancer and generating resistance to treatment. Inhibition of nAChRs in vivo can reduce tumor growth [35].

3.3.1 *CHRNA*3-*CHRNA*5-*CHRNB*4 gene cluster polymorphisms

The association of *CHRNA*3-*CHRNA*5-*CHRNB*4 gene cluster polymorphisms with lung cancer has been extensively studied in the last 20 years. Yang et al. [36] conducted a meta-analysis and showed that C*HRNA*3 rs1051730, rs578776, rs6495309, rs938682 and *CHRNA*5 rs16969968, rs58888 were associated with lung cancer, and the rs1051730 polymorphism affected the development of non-small cell lung cancer and nicotine dependence in Iranian populations. A meta-analysis of 32 studies showed that the risk of lung cancer in individuals carrying rs1051730 (G>A), rs16969968 (G>A), rs8034191 (T>C) was significantly higher than that in individuals carrying rs1051730 (G>A), rs16969968 (G>A), rs8034191 (T>C), and rs8034191 (T>A). Additionally, individuals carrying rs8034191 (T>C) had a significantly increased risk of lung cancer [37]. In Caucasians, the risk of lung cancer was 1.519-fold higher in the A genotype pure carriers of the rs1051730 locus than in carriers of the other two genotypes, and in Asian populations, the risk of lung cancer was 1.580-fold higher in the A allele carriers than in the C allele carriers of the rs3743037 locus.

3.3.2 Other nAChRs gene polymorphisms

Studies have reported that polymorphisms at the rs2229959 and rs1044396 loci of the *CHRNA*4 gene were associated with nicotine dependence. Gu et al. [38] detected rs1044396, rs2229959 and rs2236196 polymorphisms in 240 lung cancer patients, and found that lung cancer patients carrying rs1044396 AA genotype had the highest proportion of successful smoking cessation (7.7%), indicating that patients with this genotype were more likely to quit smoking after diagnosis. α7-nAChR is highly expressed in squamous-cell carcinoma (SCC), pulmonary adenocarcinomas (PAC), and non-small cell lung cancer (NSCLC). Pal et al. [39] examined the expression levels of *CHRNA*7 in surgical tumor samples from 46 NSCLC patients, and showed that *CHRNA*7 was positively correlated with programmed cell death protein-1 (PD-L1) (P=0.058) and dopamine receptors 2 (DRD2) (P=0.028 8), suggesting that both PD-L1 and DRD2 play important roles in cancer development and progression. Wang et al. [34] examined *CHRNA*9 rs56159866, rs6819385, rs55998310, and rs182073550 polymorphisms in the blood of 500 NSCLC patients and 500 healthy controls, found that individuals carrying the A allele at the rs6819385 locus had a 1.37-fold increased risk of developing NSCLC.

4 Summary and prospects

Among global public health problems, the burden of chronic non-communicable diseases, such as tumors, is increasing year by year. Lung cancer is one of the major causes of the increasing burden of tumors. From early family-based linkage analysis to the current genomic level, the study of tumor genetic susceptibility loci has become a hot area in the research of the interaction between tumor genetics and the environment. GWAS, as a more efficient epidemiological research strategy, can better uncover SNP loci that are closely related to the development of cancers, which, in turn, promotes the development of human genomics and can make it possible to search for targets and drugs closely related to cancer development, thus promoting the development of pharmacogenomics. Additionally, combining SNP loci with traditional lung cancer risk prediction models, while considering the effects of gene-gene and gene-environment interactions, can significantly enhance the efficacy of lung cancer risk prediction. Therefore, the application of lung cancer prevention and research strategies to the screening of high-risk populations, combined with new epidemiological research methods, can provide a reliable strategy for the precise prevention and treatment of lung cancer.

Declaration of interest statement

The authors declare that they have no known competing financial interests.

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· 研究进展 ·

烟碱型乙酰胆碱受体相关基因及其多态性与肺癌关联的研究进展

李逸轩，周静，张静，肖莎

海南医学院公共卫生学院 Heinz Mehlhorn 院士工作站，海南 海口 571199

摘要：肺癌是全球发病率和死亡率最高的恶性实体肿瘤类型之一，近年来肺癌生存率有所提升，但其预后及 5 年生存率仍然欠佳。肺癌的危险因素包括吸烟、环境污染、职业因素、慢性阻塞性肺疾病等。烟碱型乙酰胆碱受体（nAChRs）形式多样，且广泛参与机体的生理、病理及药理过程，烟草中主要成分之一——尼古丁进入人体后，可由 nAChRs 介导产生作用。研究发现不同亚型的 nAChRs 存在单核苷酸多态性（SNP），且可对其功能产生影响。全基因组关联研究（GWAS）作为流行病学的研究策略，可更好地挖掘出与癌症发生密切相关的 SNP 位点，进而使寻找与癌症发生发展密切相关的靶标和药物成为可能。基于国内外相关研究成果，本文从肺癌的全球流行情况、nAChRs 相关基因 SNP 及其功能与肺癌的关联研究等进行系统阐述，以期为肺癌的精准预防及治疗提供参考依据。

关键词：肺癌；烟碱型乙酰胆碱受体；吸烟；单核苷酸多态性；遗传易感性

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LI Yixuan, ZHOU Jing, ZHANG Jing, XIAO Sha

School of Public Health, Heinz Mehlhorn Academician Workstation, Hainan Medical University, Haikou, Hainan 571199, China

Corresponding author: XIAO Sha, E-mail: xiaosha4226@126.com

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通信作者：肖莎，E-mail：xiaosha4226@126.com

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肺癌是一个全球性的健康问题,是世界上常见的高发病率、高死亡率的恶性肿瘤之一。肺癌的早期筛查及精准预防、治疗已成为肿瘤学界的重要研究课题。全基因组关联研究(genome-wide association study, GWAS)作为流行病学的研究策略,可更好地发掘与癌症发生密切相关的单核苷酸多态性(SNP)位点,进而可能发现与癌症发生发展密切相关的治疗靶标和药物。本文对肺癌的流行状况、吸烟所涉及的烟碱型乙酰胆碱受体(nicotinic acetylcholine receptors,nAChRs)相关基因的功能、nAChRs 的 SNP 与肺癌以及肺癌的遗传易感性之间关系的研究进展作一综述。

1　肺癌的流行情况

1.1　*肺癌发病率与死亡率*　肺癌为世界上常见的高发病率、高死亡率的恶性肿瘤之一,也是男性癌症死亡的主要原因[1]。肺癌位居全球癌症死因之首,每年约有 200 万新病例和 176 万死亡病例,约有一半的新发病例发生在亚洲地区[2]。2020 年男性肺癌的发病率和死亡率均为第一;女性肺癌的发病率排名第三,死亡率排名第二。大多数肺癌患者确诊后5 年生存率仅 10% 至 20%,而日本(33%)、以色列(27%)和韩国(25%)肺癌患者的 5 年生存率较高[3]。

我国最新的癌症数据显示,肺癌是我国男性最常见的癌症,约占男性癌症总数的 21.8%,且我国肺癌的发病率与死亡率均高于世界水平,预计未来 10 年肺癌患者还会继续增加,我国将面临较重的癌症负担[4]。近年来,我国肺癌发病率和死亡率在中、东部地区较西部地区高,男性明显高于女性。城市和农村之间的肺癌发病率与死亡率差异逐年缩小。肺癌在所有癌症中预后较差,其 5 年生存期仅为 19.7%,且中位生存时间通常少于 2 年[5]。国内外癌症统计数据的比较发现,同类型肺癌的发病率与死亡率在不同种族、年龄和地理位置具有一定的差异。因此肺癌的早期筛查、精准预防与治疗将有助于降低其发病率和死亡率[6]。

1.2　*肺癌危险因素*　肺癌的危险因素包括吸烟、职业接触、空气污染、家族遗传史、辐射暴露和慢性肺部疾病。肺癌的发生发展与烟草的使用情况密切相关,根据中国疾病预防控制中心 2018 年全球成人烟草调查显示,中国成年吸烟者有 3.08 亿人,被动吸入二手烟的中国居民高达 7.32 亿人[7]。目前国内外研究仍一致认为导致肺癌发生的最重要危险因素是吸烟,二手烟的暴露也可致肺癌发生。职业接触、空气污染等问题凸显,其中职业因素包括多环芳烃、石棉、砷以及某些形式的二氧化硅和铬、氡、铬、镉等。大气中复杂的新型空气污染物、大气环境中颗粒物以及臭氧、室内装修材料挥发出的污染物、厨房烹饪时产生的油烟等均可能对心肺系统产生不良影响[8]。某些肺部疾病、肿瘤遗传史也会增加患肺癌的风险,如慢性阻塞性肺疾病(chronic obstructive pulmonary disease, COPD)等,不健康的心理因素和饮食习惯等也在某些程度上成为肺癌的危险因素。

2　nAChRs 的功能

2.1　nAChRs　nAChRs 简称烟碱受体,属于半胱氨酸环受体(Cys-loop)超家族,哺乳动物的烟碱受体是由 5 个亚基组成的类似圆柱体的五聚体结构,每个亚基包含一个 N 端胞外结构用于配体结合,分为神经型烟碱受体(nicotinic neur,N1)和肌肉型烟碱受体(nicotinic muscle,N2)两种主要亚型[9]。N1 型受体主要分布在自主神经节突触后膜以及中枢神经系统;N2 受体则主要分布于神经—骨骼肌接头的终板膜上。nAChRs 包括胞外结构域、跨膜结构域和胞内结构域三个部分。胞外结构域沿 N 端 α 螺旋折叠成包含 10 个 β 片层的 β-夹层结构,跨膜结构域由 4 个 α-螺旋(TM1~TM4)组成,呈伪菱形束排列,TM1 和 TM3 形成中间圆,通过广泛的亚基内和亚基间相互作用来稳定 TM2 螺旋形成的内圆螺旋束,TM4 螺旋在 TM 结构域的外围形成一个更松散的外圆;胞内结构域是 TM3 和 TM4 之间由两个结构化的螺旋 MX 和 MA 组成的大胞质区[10]。

烟碱受体家族由 17 个亚基组成(α1-α10, β1-β4, γ, δ 和 ε),目前已证实哺乳动物参与 nAChRs 形成的亚基分别是:9 个 α(CHRNA2~CHRNA10)亚基、3 个 β(CHRNB2~CHRNB4)亚基、1 个 γ(CHRNG)亚基、1 个 δ(CHRND)亚基以及 1 个 ε(CHRNE)亚基。人类 nAChRs 亚单位 α2~α7、α9 和 α10 主要由八个基因编码,分别为 CHRNA2、CHRNA3、CHRNA4、CHRNA5、CHRNA6、CHRNA7、CHRNA9 和 CHRNA10,nAChRs 亚单位 β2~β4 主要由 CHRNB2、CHRNB3、CHRNB4 编码。其中 CHRNA2 位于 8p21.2,CHRNA4 位于 20q13.2,CHRNB2 位于 1q21.3,CHRNA3-CHRNA5-CHRNB4 是位于 15q25.1 上的基因簇,CHRNB3~CHRNA6 基因区域位于 8p11,CHRNA7 位于 15q13.3,CHRNA9 位于 4p15.1,CHRNA10 位于 11p15.5[11]。

2.2　nAChRs 的功能　nAChRs 种类多样,其生物合成、转运及生物功能复杂,nAChRs 辅助分子对这些过程的调控导致不同类型 nAChRs 的组成亚基不同。nAChRs 在所有哺乳动物细胞表面都可表达,在脑、肌肉、淋巴细胞以及耳蜗毛细胞等组织中都有 nAChRs 的广泛分布,分别介导认知、肌肉收缩、免疫调节和声音辨别等生理功能。Koukouli 等[12]利用转基因小鼠证实了 nAChRs 的 β2 亚基对高阶认知过程存在影响,同时还具有调节睡眠和介导麻醉的功能。nAChRs 作为中枢调节器也可以在人类癌细胞及肿瘤微环境(tumor microenvironment, TME)中表达,参与癌细胞的增殖、转移等过程[13]。

nAChRs 作为离子通道型受体与多种病理过程有关,已有相当一部分研究表明 nAChRs 基因多态性在各类疾病中的作用,包括烟草成瘾、耳聋、精神类疾病、心血管疾病等[14]。比如尼古丁的成瘾作用以及烟草成瘾的关键机制都与 nAChRs 介导的作用密切相关。在尼古丁摄入人体后,与 nAChRs 结合,使存在于整个神经系统中的 nAChRs 受体被激活,离子通道打开后刺激多巴胺释放,从而产生依赖[15]。尼古丁可通过激活受体来促进肿瘤进展,与肺癌的转移存在相关关系。既

往研究已证实,肺癌中存在乙酰胆碱自分泌途径:即胆碱和乙酰辅酶 A 在胆碱乙酰转移酶的作用下可以合成乙酰胆碱,进一步经过囊泡型乙酰胆碱转运蛋白转运并分泌至细胞外,在胞外与细胞膜上的乙酰胆碱受体结合,进而调节肿瘤细胞增殖[16]。

nAChRs 基因多态性也与肺癌发生发展存在关联,其中 α7-nAChR 是研究最多的 nAChRs,由 CHRNA7 编码,其 N 端可与多种选择性拮抗剂结合,在中枢系统和免疫系统中广泛表达,参与调节中枢系统炎症反应,并可发挥神经-免疫调节作用。尼古丁、4-N-亚硝基甲基氨-1-(3-吡啶基)丁酮[4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, NNK]均为烟草中致癌成分,α7-nAChR 为尼古丁、NNK 的特异性结合位点,参与构成介导烟草诱导的肺癌发生的关键通路[17-18]。另有研究发现 CHRNA3、CHRNA5、CHRNB4 变异与尼古丁、可卡因和酒精依赖显著相关[19]。在哺乳动物中,α3β4 nAChRs 突变型是尼古丁成瘾、癌症、肥胖和高血压等疾病的潜在新靶点,大脑多巴胺回路中的 nAChRs 也参与对尼古丁的厌恶反应和尼古丁所致的负面情感状态[20]。由于 nAChRs 在正常生理功能和病理过程中均发挥重要作用,nAChRs 也逐渐成为治疗和预防某些疾病的重要靶点,α7 和 α4β2 nAChRs 对阿尔兹海默症的记忆损伤起到一定改善作用,含有 α5 亚基的 nAChRs 可能提供一种靶向治疗尼古丁成瘾的精准药物,针对这些位点进行相关研究有望寻找到肺癌靶向治疗的突破口[21-22]。

3　nAChRs 基因多态性与肺癌的相关性

3.1　基因多态性　基因多态性是指 DNA 分子或基因的某些位点发生改变,使 DNA 的一级结构各不相同,形成多态性,被认为是分子水平上的个体遗传标志。DNA 的多态性包括 DNA 片段长度多态性(fragment length polymorphism,FLP)、DNA 重复序列的多态性(repeat sequence length polymorphism,RSP)和单核苷酸多态性(single nucleotide polymorphism,SNP)等[23]。FLP 是由于单个碱基的缺失、重复和插入所引起限制性内切酶位点变化,导致 DNA 片段长度的变化;RSP 主要表现为重复序列拷贝数的变异;而 SNP 是指在基因组水平上由单个核苷酸改变所导致的 DNA 序列多态性,如碱基转换、颠换、插入、缺失四种形式[24]。

3.2　nAChRs 基因多态性　在烟碱受体的亚型中几乎每种都有 SNP 位点被报道,如 rs1051730、rs16969968、rs6474412、rs7329797、rs6819385 等。研究证明 CHRNA3-CHRNA5-CHRNB4 基因簇的遗传变异与烟草成瘾密切相关,会影响肺癌的遗传易感性,位于 CHRNA3 基因 rs1051730 位点上携带 T 等位基因者患肺癌的风险增高 1.83 倍,位于 CHRNA5 基因 rs16969968 位点上 A 等位基因欧洲地区携带者的患肺癌风险增高 1.30 倍[25-26];有研究表明 α4 受体在介导 NNK 的反应中起到的脱敏作用可能会导致女性患小气道上皮细胞来源的腺癌[27]。CHRNB3 基因区域的 SNP 与肺癌的发生相关,其中 rs6474412 位点携带 T 等位基因会使肺癌的患病风险增高 1.12 倍,还会导致银屑病的发生[28];另有研究发现 CHRNA2、CHRNA4、CHRNB2 这三个基因 SNP 与罕见癫痫综合征常染色体显性额叶癫痫(autosomal dominant nocturnal frontal lobe epilepsy, ADNFLE)有关。多项研究中提到 CHRNA2 突变会影响 nAChR 受体功能,CHRNA4 突变可下调 nAChR 受体功能,CHRNB2 突变则上调 nAChR 受体功能[29-30];CHRNA6 中 rs892413 位点的突变可能会导致吸烟和酗酒共同发病,酒精可能会调节尼古丁与 nAChRs 的结合[31]。CHRNA7 基因 SNP 也与多种精神疾病相关,会影响阿尔茨海默病药物治疗的反应性,与烟草成瘾、口腔癌前病变、肺癌发生相关[32];CHRNA9 基因 SNP 与乳腺癌和肺癌的发生密切相关,rs7329797 位点携带 G 等位基因的患者,其乳腺癌的发生风险增高 1.8 倍,携带 rs6819385 位点 AA 纯合子个体患肺鳞癌的风险增加 1.61 倍[33-34];CHRNA10 则与耳部疾病、乳腺癌等密切相关。

3.3　nAChRs 基因多态性与肺癌遗传易感性的关联研究　吸烟与咀嚼槟榔作为值得研究的不良生活方式,均可能会上调 nAChRs 的促癌作用并下调其抑癌作用,成为肺癌危险因素,二者之间相互作用、诱导加速了肺癌的形成。尼古丁作为烟草的主要成分,是 nAChRs 的激动剂,可通过 nAChRs 在脑中传递,nAChRs 信号转导机制在肺癌信号通路中起作用,促进肺癌进展并且对治疗产生抗性,抑制体内 nAChRs 可降低肿瘤生长[35]。

3.3.1　CHRNA3-CHRNA5-CHRNB4 基因簇多态性　CHRNA3-CHRNA5-CHRNB4 基因簇多态性与肺癌的关联在近 20 年研究中颇多。Yang 等[36]通过 Meta 分析获知 CHRNA3 rs1051730、rs578776、rs6495309、rs938682 和 CHRNA5 rs16969968、rs58888 这 6 个 SNPs 与肺癌发生有关联,其中 rs1051730 多态性在伊朗人群中被证实会影响非小细胞肺癌(non-small cell lung cancer, NSCLC)的发生以及尼古丁的依赖作用。Yi 等[37]在对 32 篇文献的 Meta 分析中得出携带 rs1051730(G>A), rs16969968(G>A), rs8034191(T>C)者患肺癌风险显著增加,在白种人中 rs1051730 位点携带 A 基因型纯合子患肺癌风险较其他两种基因型携带者高 1.519 倍,在亚洲人群中 rs3743037 携带 A 等位基因者较携带 C 等位基因者患肺癌的风险高 1.580 倍的结论。

3.3.2　其他 nAChRs 基因多态性　研究报道 CHRNA4 基因 rs2229959 和 rs1044396 位点多态性与尼古丁依赖相关,Gu 等[38]对 240 例肺癌患者检测了 rs1044396、rs2229959、rs2236196 位点的多态性,结果发现携带 rs1044396 AA 基因型肺癌患者的成功戒烟组比例最高(7.7%),说明这种基因型患者确诊后更容易戒烟。α7-nAChR 在肺鳞状细胞癌(squamous-cell carcinoma, SCC)、肺腺癌(pulmonary adenocarcinomas,PAC)和 NSCLC 中高表达,Pal 等[39]检测了 46 例 NSCLC 患者手术肿瘤样本里 CHRNA7 与程序性细胞死亡配体-1(programmed cell death protein-1, PD-L1)的表达水平($P=0.058$),与多巴胺受体(dopamine receptors, DR)D2 ($P=0.0288$) 呈正相关,说明 PD-L1 与 DRD2 在癌症的发生和进展中均发挥重要作用。Wang 等[34]检测了 500 名 NSCLC 患者和 500 名健康对照者血液中 CHRNA9 rs56159866、rs6819385、rs55998310 和 rs182073550 多态性,发现 rs6819385 位点携带 A 等位基因个体患 NSCLC 的风险

增加1.37 倍。

4　总结和展望

在全球公共卫生问题中,肿瘤等慢性非传染性疾病的负担比重逐年增加,肺癌是造成肿瘤负担加重的重要原因之一。从早期的以家系为基础的连锁分析到目前的基因组水平,肿瘤遗传易感性位点研究成为肿瘤遗传与环境交互作用研究的热点领域。GWAS 作为较高效的流行病学研究策略,可以更好地挖掘出与癌症发生密切相关的 SNP 位点,进而促进人类基因组学的发展,可使寻找与癌症发生发展密切相关的靶标和药物成为可能,从而推动药物基因组学的发展。此外,将 SNP 位点与传统肺癌风险预测模型相结合后,考虑基因-基因和基因-环境交互作用的影响,可显著提高肺癌风险预测的效能。因此,将肺癌防治及研究策略应用于高危人群的筛查,结合新的流行病学研究方法,可为肺癌的精准预防及治疗提供可靠策略。

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