Journal of Pulmonary & Respiratory Medicine

Mello, J Pulmonar Respirat Med 2011, S:5
DOI: 10.4172/2161-105X.S5-e001

Editorial Open Access

EGF+61 A>G Polymorphisms and Lung Cancer Risk: Future Directions

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Abstract

Purpose: This paper will discuss highlight in EGF+61 A>G genetic polymorphism and NSCLC susceptibility.

Design: Editorial article

Results: Despite controversies results regarding EGF+61 polymorphism and NSCLC risk, recent research showed this association in Portuguese population.

Conclusions: As the same as occurred in colorectal cancer, EGF+61 was demonstrated to be associated with NSCLC risk and in a near future may also serve as predictive biomarkers, but further studies are warranted in order to assess this hypothesis.

Keywords: Lung cancer; EGF; Genetic polymorphism; Biomarkers; Non-small-cell lung cancer

Introduction

Lung cancer accounts more than 1.5 million patients worldwide [1]. It is the leading cancer cause among male, accounting 23% of total cancer cases and 14% of cancer deaths [1]. Non-small-cell lung cancer (NSCLC) comprises approximately 80-85% of lung cancer; and small-cell lung cancer, 15-20%. Adenocarcinoma and squamous cell carcinoma are the most common histological types among NSCLC. To date, many risk factors are associated with lung cancer risk, such as cigar smoking, age, race, gender, randon exposure, wood smoke exposure, environmental and occupational exposure [2]. Genetic influence is a topic that is not completely understandable, but increasing evidence suggests that such factors play important role [3]. Recently, a wide association genome study found that a single nucleotide polymorphism (SNP) at chromosome 13q31.3 was associated with an increased risk of non-small cell lung cancer [4]. Another study also showed that carriers of the most common mutation associated with cystic fibrosis (delta F508) had a decreased incidence of lung cancer compared with controls [5]. Epidermal growth factor (EGF) and its receptor (EGFR) were also demonstrated as a main role in NSCLC carcinogenesis [2]. EGFR tyrosine kinase inhibitors, such as gefitinib [6-8] and erlotinib [2,9,10] showed improved overall survival (OS) and progression free survival (PFS) in NSCLC with EGFR mutation in exon 19 and exon 21 [11]. EGF+61 A>G polymorphisms had been demonstrated to be associated with cancer risk in overall [12,13]. However, results regarding lung cancer risk remains controversies and limited to Asiatic studies [14,15]. Thus, this paper will discuss some highlight concerns regarding EGF+61 A>G polymorphisms and NSCLC susceptibility.

EGF+61 Polymorphism and Lung Cancer

Since last decade, EGF+61 A>G polymorphism has been studied as a risk factor of cancer [12]. The first article published showing this association was concerning malignant melanoma [13]. In this work authors also suggested that it could be biologically explained toward the EGF serum higher expression due to the proximity of +61G locus to a region involved in EGF gene regulation. Furthermore, EGF+61 A>G polymorphism role was determined in several cancer, such as glioma, [16] prostate cancer, [17] hepatocellular carcinoma, [18] colorectal, [19] esophageal squamous cell carcinoma [20] and gastric cancer [21]. However, in lung cancer results remained in controversies and limited to Asian studies [14,15]. Recently, it was showed for the first time in a Portuguese population the association between EGF+61 A>G and EGF+61 G>G genotypes and risk of NSCLC [22]. Nevertheless, this study was in disagreement with Kang et al. [15] that did not reported this association in lung cancer overall. Some concerns could explain those differences in results. First, ethnic divergences may have a role in those divergences. Second, in Kang´s study it was compared influence of allele A and risk of lung cancer, considering AG plus AA genotype versus GG genotype. In the Portuguese study [22] it was compared allele G as risk of NSCLC, considering AG and GG genotype versus AA genotype. This fact may be the most important point in this analysis. According to a recent meta-analysis, [12] presence of G allele is indeed considered as a key point of carcinogenesis steps due to its property of increased serum EGF and therefore stimulate proliferation, angiogenesis, and metastasis [2,12]. This interaction between serum EGF and EGFR is very important in NSCLC framework. It induces tumor aggressiveness towards mainly four pathways: 1) Phospholipase Cγ (PCL-γ); 2) Phosphatidylinositol 3-kinase (PI3K); 3) Signal transducer and activator of transcriptions (STATS); and 4) Ras, Raf, MEK, ERK, MAPK (mitogen-activated protein kinase) [2]. Another Korean study conducted by Lim et al. [14] also showed a slight relationship between EGF+61 A>G polymorphism and lung cancer. However, this study [14] was not statistically strong due to the sample were not in the Hardy-Weinberg equilibrium [12]. Further, in Lim´s study [14] the case and control group was not paired by age and sex. The group with lung cancer was much older (63.5 ±10.6 years) than the healthy control group (45.98±12.19 years), which means that their control group may have less chances to develop lung cancer than the case group due to be younger.

Current and Future Directions

Nowadays, NSCLC molecular tools are very important to take in consideration regarding treatment and management decision [23]. EGFR mutation and echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) fusion are currently the main tools that medical oncologists have in clinical practice in order

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Received July 31, 2012; **Accepted** August 02, 2012; **Published** August 02, 2012

Citation: Mello RAD (2012) EGF+61 A>G Polymorphisms and Lung Cancer Risk: Future Directions. J Pulmonar Respirat Med S5:e001. doi:10.4172/2161-105X.S5-e001

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to improve NSCLC patients care [2]. Nevertheless, researches do not stop in this field. Target therapies against those mainly molecular pathways and novel biomarkers [24] are object of main interest [2,3]. As it occurred in colorectal cancer (CRC), EGF+61 A>G polymorphism was suggested as involved in NSCLC susceptibility. After, it was demonstrated that EGF+61 A>G polymorphisms could serve also as a predictive biomarkers for those CRC patients treated with cetuximab [25]. We believe that this is the key point of EGF+61 A>G polymorphism research in lung cancer context. Firstly, determined EGF+61 A>G polymorphisms with NSCLC susceptibility. Second, test its influence in patient's outcome, assessing where it is possible to serve both as risk either as predictive or prognostic biomarkers. And finally, assess its role in cancer prevention, may be correlating to others risk factors and contributing to creation of nomograms in order to predict cancer risk. This could help in future health public prevention strategies, though many efforts are still warranted to validate those entire issues in others populations.

Statement of Translational Relevance

Recently, Studies in EGF+61 A>G polymorphism field showed its relevance in cancer behavior. EGF+61 genotypes role was determined in several cancers, such as gliomas, gastric and colorectal cancer (CRC). In 2011, it was demonstrated that this polymorphism could also serve as predictive biomarker for CRC patients treated with cetuximab. In lung cancer results remain limited and controversy. Thus, this article will provide a point of view and discuss relevant issues in this framework.

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This article was originally published in a special issue, **Lung Cancer Challenges to the future** handled by Editor(s). Dr. Ramon Andrade de Mello, University of Porto, Portugal

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