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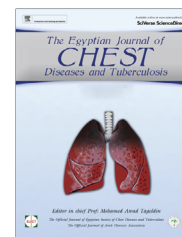

ORIGINAL ARTICLE

Association between environmental tobacco smoke exposure and lung cancer susceptibility: Modification by antioxidant enzymes genetic polymorphisms

Wafa Ashour [a,*], **Mona Fathy** [b], **Mai Hamed** [b], **Omnia Youssif** [b], **Nahla Fawzy** [b]

[a] *Chest Diseases Department, Faculty of Medicine, Cairo University, Egypt*
[b] *Clinical and Chemical Pathology Department, Faculty of Medicine, Cairo University, Egypt*

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KEYWORDS

Environmental tobacco smoke;
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Abstract *Background:* Environmental tobacco smoke (ETS) is the primary etiological factor of lung cancer. However, only 10–15% of smokers develop lung cancer, suggesting genetic role in modifying individual susceptibility to lung cancer. Antioxidant enzyme functional genetic polymorphisms should be considered.

Aim of the work: The present study aimed to evaluate the role of antioxidant enzyme activity and genetic polymorphisms in modifying the susceptibility to lung cancer among individuals exposed to ETS.

Subjects and methods: A total of 150 male subjects were divided into three groups: 50 lung cancer patients, 50 chronic smokers and 50 passive smokers. Genotyping of mEH exon 3 (Tyr^{113}Hist) and exon 4 ($Hist^{139}$Arg) polymorphisms was done by PCR–RFLP technique. MnSOD (Val^{16}Ala) polymorphism was detected by Real time-TaqMan assay. Erythrocyte MnSOD activity was measured spectrophotometrically.

Results: ETS exposed individuals (both active and passive smokers) who carried His allele of mEH exon3 have 2.9-folds increased risk of lung cancer (***OR* 2.9 *P* < 0.001**). Also ETS exposed carriers of Arg allele of mEH exon 4 have 2.1-folds higher risk to lung cancer (***OR* 2.1 *P* = 0.024**). However no association between MnSOD Val^{16}Ala polymorphism and lung cancer was detected among ETS (***OR* 1.6 *P* = 0.147**), although lung cancer group had significantly lower MnSOD activity than chronic or passive smokers groups (***P* = 0.03**).

Conclusion: Exons 3 and 4 polymorphisms of the mEH gene may contribute to lung cancer susceptibility through disturbed antioxidant balance. However, this was not the case with MnSOD Val^{16}Ala SNP. Antioxidant enzymes may modulate the influence of ETS exposure on lung cancer risk.

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* Corresponding author. Tel.: +20 1223382517.
E-mail address: wafaaashur@yahoo.com (W. Ashour).

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Introduction

Environmental tobacco smoke (ETS) refers to the exposure of a non-smoker to the smoke produced from cigarettes consumed by another person. It is also called second-hand smoke, passive smoking or involuntary smoking [1]. Exposure to tobacco smoke, either by active or passive smoking, is the primary etiologic factor responsible for lung cancer. Long-term tobacco smoke exposure was found to cause 80–90% of lung cancers worldwide [2]. Although most of lung cancer patients are smokers or ex-smokers, in fact many of them are also non-smokers and only 10–15% of smokers may develop lung cancer in their lifetime, suggesting that environmental factors (mainly tobacco smoke) interact with multiple polymorphic genes to influence cancer susceptibility [3,4].

Mild oxidative stress occurs on a daily basis and is a key factor in maintaining homeostasis. However, strong, acute, or chronic oxidative stress disrupts this delicate homeostasis and causes oxidative damage to lipids, proteins and nucleic acid molecules leading to increased vulnerability to malignant diseases [5].

Microsomal epoxide hydrolase (mEH), a phase II metabolic enzyme, catalyzes the hydrolysis of epoxides from polycyclic aromatic hydrocarbons and aromatic amines of cigarette smoke [6]. Although this hydrolysis is generally a detoxification reaction as less reactive and more water soluble dihydrodioles are produced, in case of some hydrocarbons such as benzo(α)pyrene, present in tobacco smoke, more highly reactive and mutagenic compounds are generated. Thus mEH exhibits a dual role of procarcinogen detoxification and activation depending on the substrate [7,8]. In the coding region of mEH gene, two common polymorphisms are characterized within exons 3 and 4. In exon 3, a T > C transition resulting in Tyr113His substitution, is associated with 40-50% decrease in the in vitro activity of mEH, and thus this allelic conversion has been referred to as the "slow" allele. The second variant is characterized by an A > G transition in exon 4 causing His139Arg substitution, and is associated with 25% increase of enzyme activity. This allele has been called the "fast" allele. The distance between exon 3 and exon 4 is 6696 base pairs [9].

Given the known differential effect of mEH alleles in the detoxification of procarcinogens, it has been proposed that these polymorphisms may affect cancer risk [10].

A number of antioxidants enzymes are involved in the scavenging of reactive oxygen species (ROS), including the superoxide dismutase (SOD) family members (Mn, Cu and ZnSOD). Theses enzymes catalyzes the dismutation of superoxide anion ($O_2^{-\bullet}$) to form hydrogen peroxide (H_2O_2), which is further detoxified to water by glutathione peroxidase [11]. MnSOD is the only SOD essential for life, and the major antioxidant in the mitochondria. MnSOD precursor protein is synthesized with a cleavable N-terminal mitochondrial targeting sequence (MTS) which derives the mitochondrial import of MnSOD from the cytoplasm. Genetic polymorphism at codon 16 of MnSOD/MTS leads to substitution of alanine (GCT) for valine (GTT) T > C (Val 16 Ala, rs4880) [12]. This polymorphism was reported to be functional in affecting the transport of the enzyme into mitochondria with the Ala variant accounting for more efficient importation [13]. A number of molecular studies have been conducted to examine the link between MnSOD Val 16 Ala and cancer susceptibility [14–16], but the results remain inconsistent. The aim of the present study is to evaluate the role of mEH and MnSOD enzyme activity and genetic polymorphisms in modifying the susceptibility to lung cancer among individuals exposed to ETS.

Patients and methods

This cross-sectional study was performed in the Chemical Pathology Department in collaboration with the Chest Diseases Department, Kasr Al Aini Faculty of Medicine, Cairo University, from June 2011 until March 2013.

The study was conducted on 150 male subjects with their age ranged between 35 and 70 years, divided into three groups each of 50 subjects as follows: **Group I**: Lung cancer patients diagnosed clinically, radiologically and confirmed by histopathological examination of bronchoscopic or CT guided biopsy. **Group II:** Chronic smokers. They have been smoking for at least 10 years with a minimum of 1 pack/day i.e. (smoking index with a minimum of 10 pack/year). **Group III**: Healthy passive smokers, with no medical history of lung disease (no cough, expectoration or shortness of breath). All subjects were asked about their age, chest symptoms, other co-morbidities, smoking history to calculate smoking index (by multiplying the number of cigarette packs smoked/day by the number of years the person has smoked (pack/year) according to the National Cancer Institute (USA) definition of pack/year [17].

Exclusion criteria

Subjects suffering from other co-morbidities which may lead to oxidative stress such as diabetes, cardiac disorders, severe infections, severe liver and kidney disease are excluded.

Specimen collection and storage

All subjects in this study were informed and verbal consents were taken. Six ml venous blood was withdrawn from all subjects and divided into 3 parts: (a) Two ml was collected in a sterile EDTA vacutainer for DNA extraction. Samples were kept frozen at −20 °C till the time of analysis. (b) Two ml was collected in EDTA containing tube for measurement of erythrocyte MnSOD activity. (c) Two ml was collected on plain tubes, left for 10 min to clot and then centrifuged at 3000 rpm for 5 min, to separate serum for routine laboratory investigations (liver and kidney functions) for the exclusion criteria.

DNA preparation

Extraction of genomic DNA from sterile EDTA anticoagulated blood samples was done using QIAamp DNA blood Mini kit (Qiagen, Hilden, Germany) by silica-gel spin columns [18].

Analysis of mEH gene polymorphisms (exon 3 and exon 4) using Polymerase chain reaction (PCR) followed by Restriction Fragment Length Polymorphism (RFLP) analysis

The PCR-RFLP of extracted genomic DNA was performed as described by Cheng et al. [18]. DNA amplification was performed in Gradient thermal cycler (Professional thermocycler,

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