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Association of interleukin 1 beta (*IL-1β*) polymorphism with mRNA expression and risk of non small cell lung cancer ☆

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ABSTRACT

Introduction: Interleukin 1 beta (*IL- 1β*), a key proinflammatory cytokine encoded by the interleukin 1 beta gene, has been associated with chronic inflammation and plays an important role in lung inflammatory diseases including lung cancer. Elevated levels of Interleukin 1proteins, in particular interleukin 1 beta greatly enhance the intensity of the inflammatory response.

Aim: To study the role of interleukin 1 beta-31C > T and -511 T > C polymorphism in the pathogenesis of non small cell lung cancer (NSCLC).

Materials and methods: One hundred and ninety non small cell lung cancer patients and 200 healthy age, sex, smoking and dwelling matched controls were used for polymorphic analysis by polymerase chain reaction—restriction fragment length polymorphism (PCR-RFLP) followed by sequencing. Normal tissues of 48 histopathologically confirmed non small cell lung cancer patients were taken for mRNA expression analysis. Quantitation of interleukin 1 beta was carried out by quantitative real time PCR.

Result: The T/T genotype of interleukin 1 beta-31 gene was significantly associated with increased risk of NSCLC [(P = 0.001, OR – 2.8 (95%CI 1.52–5.26)]. The interleukin 1 beta −511 T > C does not show any difference between the NSCLC and control group (P = 0.3, OR – 0.72

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(95%CI 0.41–1.28). Quantitative analysis of mRNA showed significant association with interleukin 1 beta T allele as compared to the interleukin 1 beta-31C allele ($P = 0.006$).

Conclusion: We conclude that lung cancer risk genotype interleukin 1 beta-31TT results in increased expression of interleukin 1 beta mRNA in lung cancer patients. Our data suggest that this genotype (IL1β -31TT) in the interleukin 1 beta regulatory region provide a microenvironment with elevated inflammatory stimuli and thus increasing the risk for lung cancer.

Introduction

Lung cancer kills more people annually than the next four cancer types combined, and as many as one billion people may die worldwide from lung cancer this century (Jha, 2009). Tobacco smoking is considered to be the leading cause of lung cancer, with approximately 85% of deaths directly linked to smoking. It has been observed that all smokers did not develop lung cancer but other factors such as individual genetic susceptibility and inflammation may play a role in the development of lung cancer. Chronic inflammation has long been deemed to be an important factor in the pathogenesis of many human cancers, including lung cancer. Many lung cancer pathogens can cause inflammation in the respiratory tract and lung parenchyma. Elevated numbers of inflammatory cells and higher levels of pro-inflammatory cytokines are seen in lung cancer tumor microenvironments and their surrounding stromal tissue (Balkwill and Mantovani, 2001; Takizawa et al., 2000). Many pro inflammatory cytokines have been shown to be involved in the pathogenesis of lung cancer. However, the cellular and molecular mechanisms underlying this relationship are not well elucidated.

Interleukin 1 beta is an important cytokine in regulating the expression of several genes involved in various inflammatory processes (Dinarello, 1996, 2002a). Interleukin 1 beta plays an important role in various inflammatory diseases including lung cancer (Azad et al., 2008; Mayne et al., 1999). Sustained induction of interleukin 1 beta enhances the intensity of the inflammatory response and creates an inflammatory micro-environment in advantage of tumor initiation and/or promotion (Dinarello, 2006). The amount of interleukin 1 beta secreted to the microenvironment is regulated at the messenger RNA (mRNA) level and protein level. The processing of the pro-interleukin 1 beta precursor into active interleukin 1 beta molecules is mediated by the caspase-1 enzyme (Dinarello, 1996; Apte et al., 2006b). Different cell types including lung epithelial cells upon exposure to various chemicals and other environmental agents produce and secrete interleukin 1 beta (Apte et al., 2006a; Dinarello, 1996). It has also been shown that the interleukin 1beta gene may be induced by cigarette smoke in human cells in vitro (Hellermann et al., 2002). The crucial role of interleukin 1 beta in susceptibility to 3-methylcholanthrene-induced carcinogenesis has been recently investigated in interleukin 1 beta knock-out mice. In the mice deficient in interleukin 1 beta, tumours developed slower and in fewer animals than in wild-type mice (Shirakawa et al., 1993; Apte et al., 2006a). Several single-nucleotide polymorphisms (SNPs) such interleukin 1 beta-31C > T (rs1143627), interleukin 1 beta-511 T > C (rs16944), in the promoter region of the gene have been identified. The role of interleukin 1 beta in increasing the risk of lung cancer has been observed. In particular, the interleukin 1 beta-31 C > T polymorphism has been has been examined in several association studies. Some studies have reported an association between this SNP and risk for cancer and inflammatory diseases (Lind et al., 2005; Zienolddiny et al., 2004; Chen et al., 2006a; Haukim et al., 2002; Bidwell et al., 1999). Several studies have shown that both -31C/T and -511 T > C are significantly associated with the increased risk of non small cell lung cancer (Zienolddiny et al., 2004). The interleukin 1 beta-31 C > T is being considered as a potential candidate in regulating the expression of interleukin 1 beta due to the shift from T to C at position -31 that mediates a change from TATAAA to CATA AA and a potential disruption of the TATA box (Wobbe and Struhl, 1990). A study conducted in A549 cells showed that the expression of interleukin 1 beta was higher in cells carrying -31 T allele as compared to the normal wild -31 C allele (Lind et al., 2007) while studies have so far failed to show any functional relevance of -511 SNP to alter gene transcription (Chen et al., 2006b; El Omar et al., 2000).