尿苷雙磷酸葡萄糖醛酸基轉移酶 1A7(UGT1A7)基因型與肺癌之關聯研究

The Correlation between UDP-Glucuronosyltransferase 1A7 (UGT1A7) Genotypes and Lung Cancer

中文摘要

肺癌是台灣地區癌症死亡原因之首。活化的致癌物質在體內使得某些重要致癌基因發生突變而失去正常調控， 最終形成肺癌。UGT1A7 (UDP-glucuronosyltransferases1A7) 分布於人體肝臟外的組織，負責許多肺癌致癌物質的代謝解毒。UGT1A7 具有基因多型性，許多研究顯示帶有基因變異的 UGT1A7 酵素代謝能力較野生型酵素差，因此被認為是造成癌症的可能危險因子。本研究的目的在於探討 UGT1A7 基因多型性與台灣族群中肺癌的關係。此外，由於肺癌相關致癌基因 KRAS 之突變與抽菸高度相關，我們也進一步假設 UGT1A7 基因多型會與發生此突變的風險有關。本研究收納 210 位肺癌病人及 210 位依性別年齡配對之健康對照組，以 PCR-RFLP 方法分析其 UGT1A7 基因多型性，另外可取得腫瘤組織 DNA 的病人亦同時檢測 KRAS 基因 codon 12 與 13 位置的突變。結果發現 Intermediate-activity (UGT1A7*1/*2, UGT1A7*1/*3, UGT1A7*1/*4, UGT1A7*2/*2, UGT1A7*2/*3)和 Low-activity (UGT1A7*3/*3, UGT1A7*4/*4) 兩種代謝能力較低之 UGT1A7 基因表現型為肺癌的可能危險因子，危險對比值分別為 1.799, 95% CI:1.178-2.748, p=0.006 及 3.333, 95% CI: 1.192-9.322, p=0.032。此增加之罹癌風險在男性有顯著統計學上差異，但在女性則無此發現。另外，上述代謝能力較低之 UGT1A7 基因表現型與 EGFR 原型之肺癌相關，而與帶有 EGFR 突變之肺癌無關。本研究中並未發現 UGT1A7 基因多型性與 KRAS 基因突變的發生具有顯著之相關性。本研究結果顯示代謝能力較低之 UGT1A7 基因表現型為肺癌的可能危險因子。未來應進一步研究受此酵素能力缺損影響的易感族群及其腫瘤上的分子特徵，並且探索其他可能造成致癌基因突變的危險因子，以期對肺癌致病機轉能有更深的認識。

英文摘要

Lung cancer is the leading cause of cancer deaths in Taiwan. The carcinogenesis process involves activated carcinogens which lead to mutations of crucial oncogenes resulting in tumor development. UGT1A7 (UDP-glucuronosyltransferases1A7) is an important extrahepatic enzyme that detoxifies a variety of lung carcinogens. Genetic polymorphisms in UGT1A7 were shown to have decreased catalytic activity

when compared to the wild-type protein and therefore implicated as a cancer risk factor. The purpose of this study was to investigate the association between genetic polymorphisms of UGT1A7 gene and lung cancer in the Taiwanese population. In addition, since KRAS mutation is highly associated with tobacco smoking, we further hypothesized that UGT1A7 polymorphisms might be correlated with the risk of developing this mutation.

The 210 lung cancer patients and 210 healthy individuals enrolled in this matched case-control study were genotyped for UGT1A7 polymorphisms using PCR-RFLP method. Tumor tissues available from 150 patients were also tested for KRAS codon 12 and 13 mutations. Predicted intermediate-activity UGT1A7 genotypes (UGT1A7*1/*2, UGT1A7*1/*3, UGT1A7*1/*4, UGT1A7*2/*2, UGT1A7*2/*3) and low-activity UGT1A7 genotypes (UGT1A7*3/*3, UGT1A7*4/*4) were both significantly correlated with lung cancer risk ($p=0.006$, odds ratio (OR): 1.799, 95% confidence interval (CI): 1.178-2.748 and $p=0.032$, OR: 3.333, 95% CI: 1.192-9.322, respectively). Interestingly, the risks were significant in males but not in females. Besides, those lower-activity UGT1A7 genotypes were significantly associated with lung cancer with wild-type EGFR but not with those with EGFR mutations. Of the 150 patients screened for KRAS mutations, 26 (17.3%) patients were identified. However, no association was found between UGT1A7 polymorphisms and the incidence of KRAS mutation.

These results suggest that there is a potential role of UGT1A7 polymorphisms as a potential risk factor for lung cancer. Further studies are warranted to find out specific clinical characteristics and tumor biomarkers on these susceptible indivisuals. Moreover, it is also important to discover other risk factors that predispose patients to form lung cancer-related oncogenic mutations.