基質金屬蛋白?-2,-9,及其組織抑制劑-1,-2 基因多形性與泌尿道上皮癌之相關研究

Association study on genetic polymorphisms of matrix melloproteinase-2, -9, tissue inhibitor of metalloproteinase-1, -2 and urothelial carcinoma

中文摘要

泌尿道上皮癌中以膀胱癌為最常見的癌症，膀胱癌的研究顯示，基質金屬蛋白酶（matrix melloproteinase, MMPs）家族與腫瘤細胞的增生、血管生成及進展有密切的相關，其中又以 MMP-2 和 MMP-9 的表現與膀胱癌間最有關係。又 MMPs 的活性受到基質金屬蛋白酶組織抑制劑(tissue inhibitor of metalloproteinase, TIMPs)的調控。其中 TIMP-1 及 TIMP-2 分別會與 MMP-9 及 MMP-2 產生特異性的結合，進而抑制其活性。且 MMP-2,9、TIMP-1,2 的表現亦會受到基因多形性的影響。因此，本研究目的在探討 MMP-2,9 及 TIMP-1,2 的基因多形性，是否與罹患泌尿道上皮癌及其臨床病理特徵有關。

本研究為病例對照研究，其中有 402 位為泌尿道上皮癌膀胱癌、腎盂癌及輸尿管癌患者，及 410 位經頻率匹配年齡（±2.5 歲）及性別之對照組個案。利用結構式問卷收集研究對象之基本人口學及相關危險因子之暴露史，以聚合酶連鎖反應（polymerase chain reaction, PCR）增幅 DNA 片段，再用限制片段長度多形性（restriction fragment length polymorphism, RFLP）方法進行基因多形性的判定，之後以多變項邏輯式迴歸（multiple logistic regression）進行各危險因子、基因多形性與罹患膀胱癌的多變項分析。

研究結果顯示在調整其它危險因子後，抽菸及喝酒分別有有 1.9 倍及 2.2 倍的危險性；MMP-9 C-1562T 帶有 CC 基因型者比其他基因型者有較高的罹患泌尿道上皮癌的危險性 OR=1.5（95%CI: 1.1-2.1），而 TIMP-2 G-418C 基因型為 GG 者比其他基因型者有較高的罹患泌尿道上皮癌的危險性 OR=1.8（95%CI: 1.3-2.5），均達統計上顯著意義。在 TIMP-1、MMP-9 基因多形性的合併結果顯示，帶有 3 個以上危險性基因型者，罹患泌尿道上皮癌的危險性達 2.3 倍（95%CI: 1.1-4.5），達統計顯著水準。合併 TIMP-2、MMP-2 基因多形性的結果顯示，帶有 1 個以上危險性基因型者，罹患泌尿道上皮癌的危險性達 1.8 倍（95%CI: 1.3-2.5），達統計上顯著。在基因與抽菸、喝酒的協同作用中發現，有抽菸、有喝酒且帶有 4 個以上危險性基因型數目者罹患泌尿道上皮癌的危險性高達 12.6 倍（95%CI: 3.8-41.3），達統計上顯著。此外，在臨床病理學特徵的分析中，當男性病例組中期別 T3-T4 與 Ta 相較下，帶有 3 個以上危險性基因型者則有 3.5 倍的危險性（95%CI: 1.2-10.2），達統計上顯著；期別 T1-T2 與 Ta 對相較下，帶有 3 個以上危險性基因型者則有 2.5 倍的危險性（95%CI: 1.1-5.6），達統計顯著水準；在男

性病例組中級別 G2 與 G1 相較下，帶有 3 個以上危險性基因型者則有 2.8 倍的危險性（95%CI: 1.0-7.5），達統計上顯著。
根據上述的結果認為，泌尿道上皮癌與 MMP-9 C-1562T 及 TIMP-2 G-418C 基因多形性之間有顯著相關，且在基因與抽菸、喝酒的協同作用下，罹患泌尿道上皮癌的危險性上升；並且癌細胞分化程度、侵襲程度與 TIMP-1,2 及 MMP-2,9 的危險基因型數目愈多有關，因此 TIMP-1,2 及 MMP-2,9 也許可作為泌尿道上皮癌及其預後的腫瘤標記。

英文摘要
Background: Urothelial carcinoma (UC) mostly occurs in the bladder and its major risk factor is cigarette smoking. The surrival and recurrence of bladder cancer is dependent on the stage and grade of the initial tumor. For patients who affected with nonmuscle-invasive tumor will have better prognosis than those with muscle-invasive tumor. Matrix melloproteinase(MMPs) plays a critical role for tumor cell proliferation, neovascularization and invasion. Previous studies showed that expression of MMP-2,9 is most significantly association with malignant tumors. However, tissue inhibitor of metalloproteinase(TIMP) inhibits the activity of MMP, that is TIMP-1 binds to inactivate MMP-9, whereas TIMP-2 specifically inhibits MMP-2 activity.Therefore, the specific aim of the study is to investigate the associated between UC and genetic polymorphisms of MMP-2,9 and TIMP-1,2.
Methods: A total of 402 pathologically confirmed UC patients and 410 controls were recruited from Chi Mei Hospital, Chia-yi Christian Hospital and Shin Kong Wu Ho_Su Memorial Hospital. Controls were matched to the cases by age (±2.5 years) and sex. All cases and controls were interviewed during hospital admission by well-trained interviewers using standardized structured questionnaires including demographic variables and other traditional risk factors for UC. Genetic polymorphisms of studied markers were genotyped using a PCR-RFLP assay. Odds ratios (ORs) and 95% confidence interval (CI), obtained from unconditional multiple logistic regression, were used to measure the strength of the association between risk factors and risk of UC.
Results: Cigarette smokers had 1.9-folds risk and alcohol drinkers had 2-folds risk for development of UC after adjustment for age, sex, and educational level. For study subjects who with MMP-9 -1562CC genotype had 1.5-folds risk of UC compared with other genotypes of the marker. When study subjects with TIMP-2 -418GG genotype, we observed a statistically significant increased risk of UC (adjusted OR=1.8, 95%CI: 1.3–2.5). When the combined effects of MMP-9 and TIMP-1 polymorphisms and used MMP-9 -1562CC, MMP-9 279RR+RQ, MMP-9 574PR+PP and TIMP-1 CT+CC as the risk genotypes, a significantly increased risk of UC was

associated with the subjects who carried more than four risk genotypes (adjusted OR=2.3, 95% CI: 1.1-4.5). When the combined effects of MMP-2 and TIMP-2 polymorphisms and used MMP-2 -1306CC and TIMP-2 -418GG as the risk genotypes, a significantly increased risk of UC was associated with the subjects who carried more than two risk genotypes (adjusted OR=1.8, 95% CI: 1.3-2.5). The joint effect with gene, cigarette smoking and alcohol drinking was also examined. The results showed that subjects who had cigarette smoking, alcohol drinking and carried more then five risk genotypes of MMP-2,9 and TIMP-1,2 have 12.6-folds risk for development of UC than those who did not have cigarette smoking, alcohol drinking and also carried less than one risk genotype. Moreover, the male subjects carried more than four risk genotypes of MMP-2,9 and TIMP-1,2 have increased risk of T3-T4 initial tumor than those with less than two risk genotypes of MMP-2,9 and TIMP-1,2 (adjusted OR=3.5, 95% CI: 1.2-10.2). The male subjects carried more than four risk genotypes of MMP-2,9 and TIMP-1,2 have 2.5-folds risk of T1-T2 initial tumor than those with less than two risk genotypes of MMP-2,9 and TIMP-1,2 (95% CI: 1.1-5.6). The male subjects carried more than four risk genotypes of MMP-2,9 and TIMP-1,2 have 2.8-folds risk of G2 initial tumor than those with less than two risk genotypes of MMP-2,9 and TIMP-1,2 (95% CI: 1.0-7.5).

Conclusion: In summary, MMP-9 C-1562T and TIMP-2 G-418C polymorphisms were associated with UC risk. The tumor stage and differentiation grade progressed with the increasing numbers of MMP-2,9 and TIMP-1,2 risk genotypes.