基質金屬蛋白酵素-1, -3, -9 基因多形性及其活化態 酵素表現與頸動脈粥狀硬化之相關研究

Association Study on Genetic Polymorphisms and Active Form of Matrix Metalloproteinases-1, -3, -9, and Carotid Atherosclerosis

中文摘要

動脈粥狀硬化是一個牽涉發炎反應和血管重建的緩慢過程，也是腦血管疾病、心血管疾病與周邊血管性疾病的主要次臨床症狀。本研究主要探討基質金屬蛋白酵素-1, -3, -9 (matrix metalloproteinase-1, -3, -9, MMP-1, -3, -9) 的基因多形性及其活化態酵素表現對於頸動脈粥狀硬化的獨立與交互作用之相關。利用國民健康局於民國 92 年到 94 年所補助之「臺北醫學大學文山區中風防治中心先驅性研究計畫」，該計劃於民國 93 年在士林區建立三十歲以上社區居民的追蹤世代，其中 433 位民眾受邀並接受頸部超音波檢查，以此作爲研究樣本，依研究對象頸動脈內中膜層厚度（intimal media thickness, IMT）之中位?0.7 mm 作爲切點，將 IMT ≦ 0.7 mm 者作爲對照組，IMT > 0.7 mm 或頸動脈硬化者爲個案組，藉由動脈粥狀硬化指標進行 MMP-1, -3, -9 之基因型與活化態酵素表現分析。利用標準化問卷與流程收集研究對象之基本人口學資料並抽取禁食後八小時靜脈血測量其生化?。將萃取出的 DNA 利用聚合?連鎖反應（polymerase chain reaction, PCR）與限制片段長度多形性 （restriction fragment length polymorphism, RFLP） 方式來進行各基因型判定；用酵素連結免疫分析法（enzyme-linked immunosorbent assay, ELISA） 方式來進行活化態酵素表現分析。結果顯示年齡、高血壓、脂質異常、肥胖、禁食後血糖、Chol/HDL-C 比值與 LDL/HDL-C 比值爲動脈粥狀硬化的重要預測因子。調整年齡和性別後，對照組與個案組在各生化?有顯著差異。基因型方面，合併 MMP-1, -3, -9 危險基因數後，隨危險基因數的增加，IMT 增厚或頸動脈硬化的危險性提高。表現型方面，Chol/HDL-C 比值低者，MMP-1, -3, -9 隨著濃度的增加其 IMT 增厚或頸動脈硬化的危險性降低。而 MMP-3 則觀察到男性表現量爲女性的兩倍，達統計上顯著差異。

英文摘要

Atherosclerosis is not only a slow process of inflammation and vascular remodeling, but also a major subclinical syndrome of cerebrovascular, heart and peripheral vascular disease. The aim of the study is to investigate the association between genetic polymorphisms and active form of matrix metalloproteinases-1, -3, -9, and carotid atherosclerosis. Residents aged over 30 years old and lived in Shi Lin District were recruited as our population. From them, 433 participants consented and participated in carotid atherosclerosis by Duplex ultrasonography. Based on their medium value of carotid intimal media thickness, 242 subjects with IMT > 0.7 mm or carotid hardness were grouped as carotid atherosclerosis patients. While a total of 190 subjects with IMT $\leqq$ 0.7 mm were recruited as controls. Genetic polymorphisms of matrix metalloproteinases-1, -3, and -9 were detected by PCR and RFLP. Active form of matrix metalloproteinases-1, -3, and -9 enzymes were measured by ELISA. Logistic regression analysis was used to estimate multivariate- adjusted odds ratios and 95% confidence intervals of various risk factors of carotis atherosclerosis.

Our results showed that age, hypertension, dyslipidemia, overweight, obesity, impaired fasting glucose, Chol/HDL ratio, and LDL/HDL ratio are significant risk factors of carotid atherosclerosis. After adjustment for age and gender, significant differences of serum biochemical markers were observed between carotid atherosclerosis patients and controls. The risk of IMT and carotid artery hardness were increased by the number increasing of MMP-1, -3, and -9 risk genotypes. However, the risk of IMT and carotid artery hardness were decreased after the concentration increasing of MMP-1, -3, and -9 among study subjects with low Chol/HDL ratio. An interesting finding in the study was that men had significantly twofold plasma concentrations of MMP-3 than women, showing a significant gender difference.