無機砷代謝酵素之基因多形性與頸動脈粥狀硬化之相關性研究

Association between genetic polymorphisms of arsenic metabolic enzymes and carotid atherosclerosis

中文摘要

動脈粥狀硬化的病理過程是由炎性損傷誘發平滑肌細胞的增生，導致晚期血栓形成與血管的纖維性阻塞。人體暴露於無機砷之後，在無機砷代謝的過程中，體內氧化壓力會隨之增加，進而誘發發炎反應。然而，無機砷代謝酵素的基因多形性會導致個體對於無機砷代謝情形的差異，進而造成對於頸動脈粥狀硬化易感性的不同。因此，本研究主要目的爲探討砷暴露與無機砷代謝酵素嘌呤核苷磷酸化酶(PNP)、穀胱苷肽硫轉移酶 omega(GSTO1,GSTO2)、三價砷甲基化轉移酶(As3MT)的基因多形性對於罹患頸動脈粥狀硬化的獨立及交互作用關係。

本研究對象爲 863 位 40 歲以上參與民國 86 年於蘭陽盆地舉行之健康檢查的民眾，依照醫師判定爲頸動脈粥狀硬化者共 384 人爲個案組，對照組爲 479 人。利用結構式問卷以標準化流程收集研究對象之基本人口學特性並測量其血清生化值。使用聚合酶連鎖反應-限制片段長度基因多形性(Polymerase chain reaction-Restriction fragment length polymorphism, PCR-RFLP)進行基因型的判定。砷暴露及基因多形性對於頸動脈粥狀硬化的獨立及交互作用以邏輯式回歸分析估計。

結果顯示 PNP Gly51Ser 與 Pro57Pro 上帶有危險基因型者會增加罹患頸動脈粥狀硬化的風險(OR=1.3 與 1.6)， PNP 危險單套型者具有 1.5 倍的罹病風險，危險雙套型者則具有 1.6 倍的罹病風險。進一步進行交互作用分析，當飲水砷濃度大於 50ppb 且攜帶危險單套型者，罹病風險是飲水砷濃度小於等於 50ppb 且不具有危險單套型者的 2.3 倍。當累積砷暴露量大於 1.66mg/L*year 者且攜帶危險單套型者，罹病風險是累積砷暴露量小於等於 1.66mg/L*year 且不具有危險單套型者的 2.3 倍。隨著飲水砷濃度或累積砷暴露量且攜帶危險單套型的增加，罹病風險也會隨之提高，達統計顯著意義(P<0.0003)。以上的相關性在不具有糖尿病與高血壓的族群中與罹病關係更爲顯著。

英文摘要

Atherogenesis is a pathophysiological process, which is characterized with the progression from inflammation and smooth muscle cell proliferation to late stage of thrombotic and fibrotic obliterations of the vessels. Level of oxidative stress would increase in human body after long-term exposure to arsenic through drinking well water. However, individual susceptibility to arsenic-induced carotid atherosclerosis were different due to various capability of arsenic metabolism. The aim of this study was to identify the relationship between carotid atherosclerosis and genetic polymorphisms of arsenic related metabolic genes including purine nucleoside

phosphorylase（PNP）, glutathione S-transferase omega（GSTO1, GSTO2）, arsenite methyltransferase （As3MT）.

A total of 863 residents aged equal and greater than 40 years and lived in Lanyan Basin were recruited in this study. Among them, 384 subjects were identified as cases based on physician's diagnosis. All subjects were interviewed by well-trained research assistants to collect questionnaire data including demographic characteristics and serum biochemistry indices. Genetic polymorphisms of PNP, GSTO1, GSTO2 and As3MT were detected by PCR-RFLP. Logistic regression model was used to estimate odds ratio （OR）and 95% confidence interval（CI）of various risk factors of carotid atherosclerosis.

Our results showed that subjects with the T allele of PNP Gly51Ser or Pro57Pro had significantly increased risk of carotid atherosclerosis（OR=1.3 and 1.6）. A significantly increased risk of carotid atherosclerosis was also found in subjects with the risk haplotypes and diplotypes of PNP（OR=1.5 and 1.6）. Those who with risk PNP haplotypes and either had ingested well water contained arsenic level> 50 μg/L or had cumulative arsenic exposure>1.66 mg/L*year would have elevated 2.3-fold risk of carotid atherosclerosis. Dose-response relationships between increased risk haplotypes of PNP and risk of carotid atherosclerosis were observed among subjects with either drank well water contained arsenic level>50μg/L or with cumulative arsenic exposure>1.66 mg/L*year. A highest risk of carotid atherosclerosis was also found in subjects without hypertension and diabetes mellitus.

In conclusion, this study provide the strong evidence that genetic polymorphisms of PNP gene was associated with carotid atherosclerosis. Prominent risk of carotid atherosclerosis were also found among study subjects with risk haplotypes of PNP, high exposure to arsenic and without hypertension and diabetes mellitus.