• 系統編號	RN9604-3908
• 計畫中文名稱	以 siRNA 調降 Toll-like 接受器之表達可抑制以 minimally modified LDL 處理之內皮細胞 Monocyte Chemoattractant Protein-1 與 Interle
• 計畫英文名稱	Inhibition of Monocyte Chemoattractant Protein-1 and Interleukin-8 Expression by Down-Regulation of Toll-Like Receptor 4 by siRNA in Minimally Modified LDL Treated Human Endothelial Cells Associated with NF-kB Activity
• 主管機關	行政院國家科學委員會
• 計畫編號	NSC94-2314-B038-068
• 執行機構	臺北醫學大學醫學系
• 本期期間	9408 ~ 9507
• 報告頁數	7 頁
• 使用語言	中文
• 研究人員	胡朝榮 Hu, Chaur-Jong
• 中文關鍵字	粥狀動脈硬化、缺血性中風、慢性發炎反應、低密度脂蛋白、分子機制、固有的免疫反應
• 英文關鍵字	Atheroscleosis, Toll-like receptor 4, MCP-1, IL-8, Adhesion, Migration, siRNA, mmLDL, Endothelial cell, Monocyte
• 中文摘要	腦中風是台灣的第二死亡原因，腦中風的病因相當分歧，目前的趨勢顯示缺血性中風與出血性中風的比例逐年增加，因此缺血性中風應是腦中風最重要的一部份。同樣的，缺血性中風的病因也相當多，其中包括粥狀動脈硬化(大血管疾病)、小洞性中風(小血管疾病)、心因性、凝血病變、血管炎等，及其他不明病因。粥狀動脈硬化可引起腦中風、冠狀動脈疾病、週邊血管阻塞疾病等爲缺血性中風最主要之病因。許多研究指出粥狀動脈硬化是一種慢性發炎反應，在血管內皮細胞受損後，許多發炎介質(cytokines andchemokines)均參與其中；吾人在稍早的研究指出阿司匹林(aspirin)，一種普遍用於缺血性中風預防的藥物，可以抑制發炎介質及單核球對血管內皮細胞的粘黏、穿移。Toll-likereceptor 4 (TLR4)是一種細胞膜上的接受器可啓動固有的免疫反應(innate immuneresponses)，以基因技術移除 TLR4 之老鼠較不會罹患粥狀動脈硬化；在白人族群中 TLR4 之基因多型性, Asp299Gly,被證實與粥狀動脈硬化相關，而吾人的研究指出華人雖很少有 Asp299Gly 基因多型性，但在第一內子的一個基因多型性的確與缺血性中風相關；因此可以推論 TLR4 應在粥狀動脈硬化扮演重要角色。流行病學研究發現高血脂症，特別是高低密度脂蛋白(LDL)爲粥狀動脈硬化之危險因子；最近研究支持脂肪可引起發炎反應，進而引發粥狀動脈硬化。本研究要以 mmLDL 處理血管內皮細胞引發發炎反應，以 siRNA 抑制 TLR4 之表達，並測量多發炎介質及單核球對血管內皮細胞的粘黏、穿移，並探討 NF-kB 在此一路徑之角色，希望可以了解 TLR4 在粥狀動脈硬化的分子機制，未來 TLR4 可作爲治療粥狀動脈硬化的一個標第。目前本研究已經建立 siRNA 抑制 TLR4 表達之系統，未來可應用於功能性之評估。

- 英文摘要

Stroke is the second leading cause of death in Taiwan. The causes of stroke are quite diverse. It's a trend that the ratio of cerebral infarction (CI) and cerebral hemorrhage (CH) is increasing. It implicates that CI plays the most important role in stroke. Many kinds of pathophysilogy are attributed to CI, including atheroscelrosis (large vessel diseases), lacunar infarction (small vessel diseases), cardiogenic origins, coagulopathy, vasculiatis, et al and some of unknown mechanisms. Atherosclerosis resulting in stroke, coronary artery disease (CAD) and peripheral atery occlusion diseases (PAOD) is the major causes of CI. The compelling evidence shows that atherosclerosis is a chronic inflammatory process. Many cytokines and chemokines are involved after endothelial cell damage. In our previous report, we had provided the data the support that Aspirin, the most popular drug for stroke prevention, inhibited monocyte chemoattractant protein-1 (MCP-1) and interleukin-8 (IL-8) expression in TNF-alpha stimulated human umbilical vein endothelial cells. Toll-like receptor 4 (TLR4) is the key 2 receptor for initiating the innate immune responses. Animals without TLR4 were less susceptible to atherosclerosis even taking high cholesterol diet. There is a genetic polymorphism of TLR4 gene, Asp299Gly, associated with atherogenesis among Caucasian populations. In our another recent study, there is very rare Asp299Gly polymorphism in Chinese population but we still found a polymorphism at intron 1 associated with CI. Based on epidemiological researches, hyperlipidemia, especially high low-density-lipoprotein (LDL) strongly contributes to the atherogenesis. The recent studies have raised the mechanism that lipid plays a role in induction of inflammation, which is one of the most important part of atherogenesis. In this study, we will down-regulate the TLR4 expression by siRNA and survey the MCP-1, IL-8 expression at mRNA and protein levels, and then test the effects on monocytes adhesion/migration function in the endothelial cells treated by minimally modified LDL (mmLDL). We also will explore the role of NF-kB in this pathway. Hopefully, we can clarify the molecular mechanism of TLR4 on the atherogenesis and TLR4 might be a target to develop a novel therapy for atherosclerosis.