• 系統編號	RN9705-0526		
• 計畫中文名稱	在 NRK49F 腎臟間質纖維母細胞中丹參酮 IIA 抑制高濃度葡萄糖所誘導骨橋素表現的機制		
• 計畫英文名稱	The Inhibitory Effect of Tanshinone IIA on Osteopontin Expression in High Glucose-Stimulated NRK49F Cells		
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• 研究人員	陳作孝 Chen, Tso-Hsiao		
• 中文關鍵字	骨橋素; 血紅素氧合脢-1; 訊息傳遞		
• 英文關鍵字	Osteopontin; Hemeoxygenase-1; Signal transduction; Dipyridamole Ostopontin; Dipyridamole; NR52E tubular epithelial cell; Renal fibrosis		
• 中文摘要	腎臟間質纖維化是腎臟退化最常見的病理特徵，間質纖維化會減少腎小管細胞氧氣的供應，近年來腎臟缺氧導致腎臟纖維化被認爲是慢性腎臟病退化的共通途徑。單側輸尿管結紮是一個研究腎間質纖維化的實驗模型，結紮後造成輸尿管壓力增加，血流減少導致缺氧、骨橋素(Osteopontin)的表現、巨噬細胞的侵入，造成腎臟間質小管的傷害。單側輸尿管結紮後，腎絲球與間質附近會發現血紅素氧合脢-1(HO-1)，如果誘發其表現增加會有保護作用。巨噬細胞的侵入與腎小管細胞骨橋素的表現有關，先天缺乏骨橋素的小鼠會抑制巨噬細胞的侵入，增加細胞凋亡與減低腎臟間質纖維化。最近研究發現骨橋素在發炎與纖維化扮演重要角色，被認可做爲治療的標的。本計劃原擬檢視丹蔘酮(tanshinone)的作用，但因臨床上 dipyridamol 被用來治療腎絲球炎，可以改善蛋白尿和血尿，且可能對腎間質小管病變有保護作用。我們過去的研究發現 dipyridamole 可以藉著抑制 NF-kB 而抑制 LPS 所誘導的 COX-2 基因表現。由於抑制 NF-kB 的藥物(PDTC)被證實可以抑制腎臟病時骨橋素的表現，很可能 dipyridamole 也可以藉著抑制 NF-kB 而抑制骨橋素的表現。由於 dipyridamole 爲常用的藥物，因此先研究 dipyridamole 對腎臟缺氧導致腎臟纖維化的作用。我們以 NRK52E 腎臟小管細胞的實驗顯示，使用氯化鈷 CoCl2 研究不同程度的化學缺氧條件下可以誘導骨橋素的表現，而此一效應可被 dipyridamole 所抑制。		
• 英文摘要	Osteopontin, a secreted phospho-glycoprotein, plays a pivotal role in the progression of interstitial fibrosis in renal ischemia. In the present study, we showed that incubation of renal tubular NR52E cells with cobalt chloride increased osteopontin protein expression		

in a dose- and time- dependent manner. Cobalt chloride induced osteopontin expression was blocked by pretreatment with l-NAC and TTFA suggesting free radical production and electron transport complex II were involved. Pretreatment of cells with dipyridamole (1-10 .mu.M), inhibited the cobalt chloride-induced osteopontin expression and the inhibitory effect was associated with heme oxygenase-1 induction. Because induction of heme oxygenase-1 has been linked to inhibition of renal fibrosis, we tested whether induction of HO-1 modulate osteopontin expression in NR52E cells. In addition, we demonstrated that several agents that exert anti-inflammatory effects inhibited CoCl2-induced osteopontin expression. Among these anti-inflammatory agents, rosiglitazone and dexamethasone did not induce HO-1 expression, whereas celecoxib and tanshinone IIA caused a mark HO-1 expression. Pretreatment of cells with SnPP, a HO-1 inhibitor, or transfection of HO-1 siRNA reversed the inhibition due to dipyridamole, suggesting HO-1 is linked to the inhibition of CoCl2-induced osteopontin expression by dipyridamole. Incubation of cells with CO releasing molecule, tricarbonyldichloro-ruthenium (II) dimmer, mimicked dipyridamole's inhibitory effect on osteopontin expression. Pretreatment of cells with CO scavenging agent, hemoglobin, abolished the inhibition of cobalt chloride-induced osteopontin expression by dipyridamole. Taken together, these data suggest that dipyridamole may inhibit osteopontin expression through HO-1 induction. Increased HO-1 may catalyze the conversion of heme into CO, which in turn suppresses CoCl2-induced osteopontin expression. Our data suggest that HO-1 inducers may serve as therapeutic agents in the treatment of renal fibrosis.