• 計畫中文名稱	研究缺氧及再灌氧傷害對於血管內皮細胞基質金屬蛋白 v-2(MMP-2)調控作用之分子機制		
• 計畫英文名稱	Molecular Mechanism of the Role of Hypoxia/Reoxygenation in Matrix Metalloproteinase-2 Expression in Endothelial Cells		
• 系統編號	PC9706-0929	• 研究性質	基礎研究
• 計畫編號	NSC96-2314-B038-028-MY3	• 研究方式	學術補助
• 主管機關	行政院國家科學委員會	• 研究期間	9708 ~ 9807
• 執行機構	臺北醫學大學內科		
• 年度	97 年	• 研究經費	900 千元
• 研究領域	臨床醫學類		
• 研究人員	陳識中,王寧		
• 中文關鍵字	缺氧及再灌氧 內皮細胞 基質金屬蛋白酵素 訊息傳遞 一氧化氮 活性氧分子 過氧化體增生劑活化受體 活化轉錄因子 3		
• 英文關鍵字	Hypoxia；Reoxygenation；Endothelial Cell；Matrix metalloproteinases；Signal transduction；Nitric oxide；Reactive oxygen species；Peroxisome proliferator-activated receptors；Activating transcription factor 3		
• 中文摘要	血管內壁之內皮細胞(endothelial cells)會受到缺血及再灌注(ischemia/reperfusion; I/R)損傷的影響，而參與許多疾病，諸如心肌梗塞、動脈粥狀硬化、中風及腫瘤轉移，之病理機制。缺氧及再灌氧(hypoxia/reoxygenation; H/R)所造成的傷害可模擬組織缺血及再灌注損傷的狀態。內皮細胞處在缺氧及再灌氧或缺血及再灌注損傷的狀態下會導致血管的新生，其調控機制是藉由一連串細胞內訊息傳遞及相關基因改變而成，包括基質金屬蛋白.-2（matrix metalloproteinase-2；MMP-2）的表現。MMP-2 爲一具有分解細胞外基質與基底膜不同組成的蛋白.。在目前的研究中，缺氧及再灌氧傷害對於內皮細胞內 MMP-2 表現的調控機制尚未十分清楚。我們先前的研究指出，內皮細胞在缺氧狀態下會活化細胞外訊息調控激.（extracellular signal-regulated kinase；ERK）及早期生長因子（early growth response-1；Egr-1）的表現。我們近期的研究更進一步發現缺氧狀態也會活化 c-Jun 氨基末端激.（c-Jun-NH2-terminal kinase；JNK），而 JNK 的活化可能導致活化轉錄因子 3（activating transcription factor 3；ATF3）的表現。缺氧狀態下所誘導的 ATF3 表現可受一氧化氮(nitric oxide; NO)的調控。我們最近的研究亦發現，一氧化氮經由誘導 ATF3，進而抑制內皮細胞的 MMP-2 表現。這些初步的研究結果推測內皮細胞在缺氧狀態下會藉由特定的分子調控機制及細胞內訊息傳遞路徑，進而調節相關基因，諸如 MMP-2，的表現。因此，本研究計畫的主要目的是爲研究內皮細胞在缺氧及再灌氧狀態下，對於 MMP-2 表現的影響及其分子調控機制。計畫中將探討包括 integrins、 Src、 ERK、 JNK、p38、 mitogen-activated protein kinase (MAPK)、phosphatidylinositol 3-kinase (PI3K)/Akt、NO 及 reactive oxygen species (ROS)等，是否參與缺氧及再灌氧對於內皮細胞 MMP-2 表現的調節。此外，針對不同形態的過氧化體增生劑活化受體 (peroxisome proliferator-activated receptor； PPARs: PPAR-α, -δ, -γ)		

	之具專一性促效劑(agonists)及拮抗劑(antagonist)，也將用來研究內皮細胞在缺氧及再灌氧狀態下 MMP-2 的表現是否受 PPAR 相關的訊息傳遞機制所調控。本研究計畫將有助於瞭解血管內皮細在缺氧及再灌氧狀態下，細胞內訊息傳遞、相關基因表現及功能調控的影響，計畫的研究結果或可對於血管在缺氧及再灌氧傷害下，導致損傷的心血管疾病，例如心肌局部缺血及中風等，提供新的治療方向。
• 英文摘要	Vascular endothelial cells (ECs), which form the inner coating of the blood vessel wall, are central participants in the response to ischemic and ensuing reperfusion processes involved in many diseases, including cardiac infarction, atherosclerosis, stroke, and tumor metastasis. Hypoxia and reoxygenation are the main constituents of ischemia/reperfusion conditions. An important consequence of the events of EC ischemia/reperfusion or hypoxia/reoxygenation is angiogenesis, which involves regulation of a number of signaling events and genes, including matrix metalloproteinase-2 (MMP-2), whose product functions as a proteinase to degrade the extracellular matrix components surrounding the endothelium. However, the roles of hypoxia/reoxygenation in MMP-2 expression in ECs and their functional modulations remain unclear. Our previous studies have demonstrated that hypoxia can induce the activation of extracellular signal-regulated kinase (ERK) and expression of early growth response-1 (Egr-1) in ECs. Our recent studies further demonstrated that hypoxic condition can induce activation of c-Jun-NH2-terminal kinase (JNK), which may subsequently induce the expression of activating transcription factor 3 (ATF3) in ECs. This hypoxia-induced ATF3 expression was mediated by nitric oxide (NO). Moreover, our recent study has demonstrated that NO can inhibit the MMP-2 expression via the induction of ATF3 in ECs. These preliminary results suggest a role played by hypoxia in modulating signaling and gene expression in ECs. Thus, the aim of this proposed project is to utilize comprehensive and systemic approaches to elucidate the role of hypoxia/reoxygenation in MMP-2 expression in ECs and their functional modulations. The detailed molecular mechanisms, such as those related to integrins, Src, ERK, JNK, p38 mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase (PI3K)/Akt, NO, and reactive oxygen species (ROS), will be evaluated to elucidate if these signaling pathways are involved in the hypoxia/reoxygenation-mediated MMP-2 expression in ECs. In addition, specific agonists and antagonist of different isoforms of peroxisome proliferator-activated receptors (PPARs: PPAR-α, -δ, -γ) will be used to investigate whether the hypoxia/reoxygenation-modulation of MMP-2 expression in ECs is mediated by the PPAR-related signaling pathways. The proposed work will help to clarify the detailed mechanisms of EC responses to hypoxia and reoxygenation conditions, in terms of signaling induction, gene expression, and cellular function. This better understanding of the detailed mechanisms of EC responses to hypoxia/reoxygenation will provide us new insight into the therapeutic strategies for the treatment of hypoxia/reoxygenation-induced vascular injuries that are frequently encountered in patients suffering from cardiovascular diseases such as myocardial ischemia and stroke.