• 計畫中文名稱	SMRT 及 HDAC3 在癌症進展過程扮演互斥而多樣性的角色 (I)		
• 計畫英文名稱	Antagonistic Pleiotropic Effects of SMRT and HDAC3 on Cancer Progression (I)		
• 系統編號	PC9611-0054	• 研究性質	基礎研究
• 計畫編號	NSC96-2321-B038-004	• 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	9611 ~ 9707
• 執行機構	臺北醫學大學醫學系		
• 年度	96 年	• 研究經費	810 千元
• 研究領域	基礎醫學類		
• 研究人員	蔡坤志,吳志雄		
• 中文關鍵字	--		
• 英文關鍵字	--		
• 中文摘要	愈來愈多的證據顯示外遺傳 (Epigenetic) 的變化，包括 DNA 甲基化 (Methylation)、組織蛋白 (Histone) 修飾以及染色質 (Chromatin) 重組等，在惡性腫瘤的 發生以及演化上扮演樞紐的地位。其中組織蛋白藉由組織蛋白乙醯基轉移脢 (Histone acetyltransferase) 及去乙醯基脢 (Histone deacetylase) 的動態性修飾代表染色質重組及 基因表現調控的主要方式之一。我們最近發現一個重要的外遺傳調控蛋白，SMRT (Silencing mediator for retinoic acid and thyroid hormone receptor)，是人類乳癌多重抗藥性 表現型的關鍵致因，此一現象仰賴著與其結合的去乙醯基脢 Histone deacetylase 3 (HDAC3) 的活性。運用基因表現剖析 (Gene expression profiling)，我們進一步發現 SMRT 另外並調節許多與癌細胞侵犯 (Invasion) 及轉移 (Metastasis) 過程扮演重要地位 的基因之表現，意味著 SMRT 有著先前未被發現的功能, 此一功能是與其在細胞抗藥性 的地位有所區別的。有關於 SMRT 抑制癌細胞被藥物殺死卻同時抑制其侵犯及轉移的能 力的發現讓我們提出 SMRT 對癌症的進展具有互斥而多樣性 (Antagonistic pleiotropic) 影響的可能性。爲探討此一可能，在此一初期的研究計劃中我們將首先以基因及功能性 研究 (Functional study) 的方法研究 SMRT 在體外實驗中對癌細胞侵犯過程所扮演的角 色。我們更將藉由組織陣列 (Tissue array) 的技術系統性的剖析人類原發及轉移癌組織 中 SMRT 或 HDAC3 蛋白的表現模式進一步探討上述發現的臨床意義。在接下來的承接 計劃中我們將以動物實驗驗證上述體外實驗的發現，同時並進一步探討 SMRT 或 HDAC3 在乳癌以外的其他種類人類惡性腫瘤的進展也扮演重要地位。釐清 SMRT 在惡 性腫瘤致病機轉中的多樣性角色將有助於我們對外遺傳控制腫瘤惡性進展 (Malignant progression) 的認識同時並有助於針對此一外遺傳機轉的治療方式的設計。		

• 英文摘要	It is increasingly recognized that epigenetic changes, including DNA methylation, histone modifications and chromatin remodeling, play a pivotal role in the initiation as well as evolution of malignant tumors. Histone modifications elicited by the dynamic actions of histone acetyltransferases (HATs) and histone deacetylases (HDACs) represent one of the major ways whereby chromatin is remodeled and gene transcription is regulated. We have recently shown that an important epigenetic regulator, SMRT (Silencing mediator for retinoic acid and thyroid hormone receptor), is critically involved in the acquisition of multi-drug resistance phenotype of human malignant tumors, such as breast cancers, which is functionally dependent on the nuclear deacetylase activity of its binding partner HDAC3. Using gene expression profiling, we further demonstrated that SMRT also regulates the expressions of many genes involved in the invasion and metastasis of malignant cells, suggesting a previously unidentified function of SMRT which is distinct from its role in cell death resistance. The findings that SMRT mediates death resistance while suppresses invasion of malignant cells raised an interesting possibility that SMRT may have 「antagonistic pleiotropic effects」 on the progression of cancers. To address this possibility, we will, in this start-up project, investigate the role of SMRT in the invasive activity of cancer cells in vitro using genetic (Aim 1) and functional approaches (Aim 2). We will further address the clinical relevance of these findings by tissue array-dependent large-scale profiling of SMRT and HDAC3 expressions in human malignant tumors (Aim 3). In the follow-up project, we will verify the findings from the present project with animal models of tumor progression. Moreover the role of SMRT/HDAC3 in tumor progression will be also tested in other types of human malignancies. Elucidating the pleiotropic roles of SMRT in the pathogenesis of malignant tumors may improve our understandings of epigenetic control of tumor progression and help the design of therapeutic strategies targeting the epigenetic pathway.