• 計畫中文名稱	研究 HTm4 和 KAP 的應對關係和對血細胞分化的影響		
• 計畫英文名稱	Study the Interaction between a Hematopoietic Cell-Cycle Regulator HTm4 and KAP and Their Effects on the Differentiation of Hematopoietic Progenitor Cells		
• 系統編號	PC9308-1836	• 研究性質	基礎研究
• 計畫編號	NSC93-2320-B038-032	• 研究方式	學術補助
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• 執行機構	台北醫學院醫學系		
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• 研究領域	基礎醫學類		
• 研究人員	柯順龍		
• 中文關鍵字	--		
• 英文關鍵字	--		
• 中文摘要	血液細胞週期的適當調理對於血液系統保持恆久性的自我還原(Self-renewal)，分化 (differentiation) 和制橫 (homeostasis)上而言是非常重要的。 這個調理的失控是會有巨 大的壞的後遺症譬如自我免疫的失調(autoimmune disorder)，blood dyscrasias，和血細胞 腫瘤等等各種病變.細胞週期調理控制的機制不但是複雜而且是有許多尚未瞭解的地方. 我們最近有發現一個新的蛋白質，HTm4，在血球細胞週期的控制機制上扮演一個非常 重要的角色.我們的實驗顯示 HTm4 和 cyclin-dependent phosphatase (KAP)和 CDK2 形成 一個很重要的複合物那可以參與血細胞週期管理的機制。外加生產(exogenous expression)的 HTm4 會增加 KAP 的活性而導致 CDK2 的去磷化 (dephosphorylation) 和細胞週期在 G0/G1 的中斷此外，我們最近發現調控 HTm4 的表現和造血幹細胞的分化過程密切相 關，這項發現再次凸顯了進一步研究在正常或不正常造血過程和胚胎發育中 HTm4-KAP-CDK2 相互影響的重要性。爲達成此目的，本計畫將設計一系列 in vitro 和 in vivo 的實驗來證實我們的假說，我們推想 HTm4、KAP 和 CDK2 會形成一複合物， 而改變 HTm4 的表現將影響正常造血幹細胞的分裂、分化和細胞週期的變化，在本計畫 所設計的一系列實驗將提供我們足夠的數據來瞭解造血過程，以及造血幹細胞的調控機 制，此結果將有助於臨床上預防、治療造血或免疫失調的病人。 爲達成上述的目的，本計畫有如下五點目標： 一、 決定 HTm4/KAP 複合物和 CDK2 活性的關係。 二、 深入瞭解 HTm4 在細胞循環表現週期和 KAP/ CDK2 複合物的比較與其表現對細 胞循環中止的影響 三、 製造抗 HTm4 抗體 四、 製造細胞不表現的 KAP 的 Ba／F3 的細胞株和 HTm4 外加表現對細胞循環中		

	止的 影響 五、 產生老鼠不表現 HTm4 的鼠種和研究其對 B 細胞分化成長的影響。
• 英文摘要	Regulation of hematopoietic cell cycle progression is critical in controlling the constant self-renewal, differentiation, and homeostasis of the hematopoietic system. Dysregulation of this process has profound consequences, evidenced by the development of autoimmune disorders, blood dyscrasias, and hematologic malignancies with all their associated morbidity and mortality. The complex molecular machinery underlying cell cycle regulation remains ill-defined. We recently described a novel molecule, HTm4, which appears to play a critical role in controlling hematopoietic cell cycle. recently, in the Journal of Clinical Investigation, we showed that HTm4 forms a functionally relevant complex with cyclin-dependent kinase-associated phosphatase (KAP), and CDK2. Exogenous expression of HTm4 stimulates KAP, leading to dephosphorylation of CDK2 and cell cycle arrest at the G0/G1 phase, thus identifying HTm4 as a novel modulator of the hematopoietic G1-S cell cycle transition. Furthermore, we recently found that HTm4 expression is tightly regulated during the differentiation of hematopoietic stems cells. These findings highlight the importance of further elucidating the function of the HTm4-KAP-CDK2 interaction in normal and dysregulated hematopoiesis, as well as during embryogenesis. In order to achieve this goal, we have proposed a series of in vitro and in vivo experiments to be carried out in a murine in vitro system . We hypothesize that HTm4, KAP, and CDK2 form a complex and that altered expression of HTm4 will affect proliferation, differentiation and the cell cycle status of normal hematopoietic stem cells. The proposed investigations will provide data that will contribute to the fundamental understanding of hematopoiesis and hematopoietic stem cell regulation, of clear significance to the prevention and treatment of hematologic and immune disorders. To achieve the stated goals, we propose the following specific aims Specific Aim 1: Studying the regulation of CDK2 activity by KAP/HTm4 complex in murine ystem. Specific Aim 2: Determining the temporal expression of mHTm4 and that of KAP and CDK2 during cell cycle progression, and the ectopic expression of mHTm4 and G0 cell cycle arrest. Specific aim 3: The production of rabbit anti-mHTm4 polyclonal antibodies. Specific Aim 4: The generation of KAP-negative Ba/F3 pro-B cell line and the effect of ectopic expression of mHTm4 on this cell line. Specific Aim 5: The generation of a conditional mHTm4-knock down transgenic mouse.