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• 計畫中文名稱	PI3K/Akt 在 Thrombin 誘導人類肺部上皮細胞前發炎物質釋放所扮演的角色
• 計畫英文名稱	Role of the PI3K/Akt in Thrombin-Induced Proinflammatory Mediator Release in Human Lung Epithelial Cells
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• 中文摘要	我們先前的研究發現 thrombin 可經由活化 protease-activated receptor 1 (PAR1)的訊息傳 遞徑活化 protein kinase C α (PKCα)使得 nuclear factor-κB (NF-κB)的活化，最後促使 interleukin-8 (IL-8)的表現及肺部的發炎反應。本計劃將探討在 A549 肺部上皮細胞中， PI3K/Akt 在 thrombin 誘導前發炎物質如 IL-8 的表現中所扮演的角色。LY 294002 (PI3K 選擇性抑制劑) 及 Akt inh (Akt 選擇性抑制劑)抑制 thrombin 誘導 IL-8 的釋放。當細胞給予 LY 294002 及 Akt inh 二者皆可抑制 thrombin 誘導 IL-8-luciferase 的活性。A549 細胞給予 thrombin 可依時間依賴誘導 Akt 磷酸化在 Ser473 的位置及 Akt 激的活性。相同地，TRAP1 及 TRAP4 也可以誘導 Akt 磷酸化在 Ser473 的位置，但是 TRAP3 卻。當細胞給予 LY 294002 可抑制 thrombin 誘導 Akt 激的活化。當細胞給予 LY 294002、Akt inh 及 Akt DN 皆可抑制 thrombin 誘導 IKK α/β 的磷酸化或是 IKKα/β 激的活性。再者，LY 294002 及 Akt DN 也可抑制 thrombin 誘導 κB-luciferase 的活化。經由以上的結果顯示，在 A549 細胞中， thrombin 可能經由活化 PI3K/Akt 的訊息傳遞徑活化 IKK α/β 使得 NF-κB 活化，最後再促 使 IL-8 的表現及釋放。
• 英文摘要	Our previously study has been shown that thrombin activates the protease-activated receptor 1 (PAR1) signaling pathway to activates protein kinase C.alpha. (PKC.alpha.), which in turn initiates nuclear factor-？eB (NF-？eB) activation, and finally induces IL-8 expression and lung inflammation. This study investigated the signaling pathway involved in PI3K/Akt in proinflammatory mediator such as IL-8 expression caused by thrombin in A549 lung epithelial cells. LY 294002 (a selective PI3K inhibitor) and Akt inh (a selective Akt inhibitor) inhibited thrombin-induced IL-8 release. IL-8-luciferase activity caused by thrombin was separately attenuated by LY 294002 and dominant negative mutant Akt (Akt DN). Treatment of A549 cells with thrombin caused time-dependent phosphorylation of Akt at Ser 473 and Akt activity. Similarly, TRAP1, and TRAP4 but not TRAP3 induced phosphorylation of Akt at Ser 473. Treatment of A549 cells with a LY 294002 inhibited thrombin-induced Akt kinase activity. Treatment of A549 cells with LY 294002, Akt inhibitor, and Akt DN all inhibited thrombin-induced IKK .alpha./.beta. phosphorylation or IKK .alpha./.beta. kinase activity. Furthermore, LY 294002 and Akt DN also inhibited thrombin-induced increase in NF-？eB-luciferase activity. These results indicate that thrombin activates the PI3K/Akt signaling

pathway to activate IKK .alpha./.beta., which in turn initiates NF- ? eB activation, and ultimately induces IL-8 expression and release in A549 cells.