探討 **Biochanin A** 及 **Hesperitin** 藥物對於內生性 **CBF1** 所媒介的 **Notch** 訊息路徑之調控作用

Effects of the biochanin A and hesperitin on the control of endogenous CBF1-dependent Notch signal pathway

中文摘要

Notch 蛋白是一個穿膜受體，結構上具有高度的保留性，與其 ligands 進行特異性結合後，被活化的 Notch 受體藉由 CBF1 所媒介與非 CBF1 媒介的兩種路徑將訊息傳遞下去。過去的研究指出，Notch 訊息傳導在許多細胞發展中扮演著重要的角色，包含「維持幹細胞不分化」、「決定細胞命運」，「癌化作用」與「抑制腫瘤生成」的能力。本實驗室先前構築了帶有四個野生型 CBF1-response elements 的 luciferase 報導質體 (pCBF1-RE-Luc)，轉染此質體到 K562 細胞建立成一個穩定的 K562/CBF1-RE-Luc 細胞株。藉由報導基因分析，可評估不同藥物對於細胞中內生性 Notch 訊息傳導路徑的影響，本實驗室發現 biochanin A 與 hesperitin 可以活化內生性 Notch 訊息傳導路徑。
本論文的研究得知結果顯示，biochanin A 與 hesperitin 可活化 K562 細胞的內生性 Notch 訊息傳導，並且這些活化現象都具有劑量與時間依賴效應。但是，然而這兩種藥物對於 K562 細胞中內生性 Notch1 mRNA 表現與細胞週期的分布並沒有明顯的影響。在生物功能方面，biochanin A 與 hesperitin 可能經由 Notch 訊息傳導的活化，抑制了 K562 細胞群落的形成，除此之外，這兩種藥物均明顯促進 K562 細胞往紅血球分化。biochanin A 與 hesperitin 對於 CBF1 所媒介之內生性 Notch 訊息傳導的分子調控機制仍有許多問題尚未釐清，需要更多的實驗與研究來討論。

英文摘要

Notch signaling involves in a wide variety of cellular processes including the maintenance of stem cell, specification of cell fate, oncogenesis, and tumor suppression. Notch signal pathway regulates downstream targets through both CBF1-dependent and –-independent pathways. Previously, the luciferase reporter plasmid containing four copies of CBF1-response elements in front of promoter was constructed. This reporter plasmid was transfected into K562 cells to establish a signal cell-derived stable clones which constitutively express luciferase reporter gene regulated by endogenous CBF1-dependent Notch signaling. By reporter gene assay, it was found that both biochanin A and hesperitin activated the activity of CBF1-dependent reporter gene.
In the present study, biochanin A and hesperitin were shown to activate endogenous

CBF1-dependent Notch signaling via both time- and dose-dependent manners. However, there was no significant effect on the expression of Notch1 mRNA and cell cycle progression in K562 cells after the treatment with biochanin A and hesperitin. In the biological functionaddition, both biochanin A and hesperitin might inhibited the colony -formation forming ability of K562 cells through up-regulated Notch signaling. Besides,The treatment with biochanin A and hesperitin enhanced the erythroid-differentiation of K562 cells. It is important to investigate Tthe molecular mechanisms of biochanin A and hesperitin to regulate the endogenous CBF1-dependent Notch signaling will be further investigated.