• 系統編號	RN9601-0590
• 計畫中文名稱	酒精誘發肝纖維化機制探討及類黃酮之抑制角色
• 計畫英文名稱	Study on the Mechanisms of Alcohol-Induced Liver Fibrosis--- Inhibitory Role of Flavanones
• 主管機關	行政院國家科學委員會
• 計畫編號	NSC94-2314-B038-060
• 執行機構	臺北醫學大學內科
• 本期期間	9408 ~ 9507
• 報告頁數	5 頁
• 使用語言	中文
• 研究人員	林時宜; 何元順 Lin, Shyr-Yi; Ho, Yuan-Soon
• 中文關鍵字	--
• 英文關鍵字	--
• 中文摘要	癌症是台灣十大死因的第一位，而肝癌(HCC)所造成的死亡人仍是高居第一位，因此如何預防肝癌的發生則成爲相當重要的課題。肝臟纖維化的發生和細胞外基質分子的合成與分解失去平衡有關， collagen 的 cross-linking 增加它對 proteolyticdegradation 的抗性，但過量的 cross-linking 則使組織自我修復的功能喪失。tissuetransglutaminase (tTG) 是一個 Ca2+-dependent 的酵素， 藉由催化 protein-protein 間 cross-linking，而造成纖維化的發生。酒精被認爲是導致肝纖維化的主因，而肝纖維化又是造成肝癌的重要原因，所以我們想研究酒精在人類肝癌細胞株中調控 tTG mRNA 表現的機制。我們初步發現在酒精刺激下只有 Hep3B 細胞被誘發 tTG mRNA 的表現。文獻指出，轉錄因子 NF-κB 參與 tTG 的調控表現。接著我們利用 NF-κB 的抑制劑 TLCK 來研究 tTG 和 NF-κB 間的相關性，我們進一步發現，酒精誘發的 tTG 表現會被 TLCK 所抑制，暗示 NF-κB 參與 tTG 表現的調控。另外，在 Hep3B 細胞中也發現酒精誘發 ERK 磷酸化的情形，並且 NF-κB 的活化被 MEK 的抑制劑--PD98059 所抑制。因此，我們推測酒精是透過 ERK 及 NF-κB 的訊息傳遞路徑來調控 tTG 的表現。Pinocembrin 是富存於蜂膠及蜂蜜中之類黃酮物質，具有抗癌、抗發炎、細胞凋亡、抗血管新生及抗氧化等功效，由於酒精造成纖維化的發生部分可能和氧化壓力大產生自由基有關，所以我們將進一步探討 pinocembrin 是否可以抑制由酒精所誘導的 tTG 表現及活性，並抑制 NF-κB p65subunit 轉位到核裡的能力。另外，也將探討 pinocembrin 否可以抑制酒精所誘發之 ERK 的磷酸化現象。由所得到之結果，希望能有助於了解肝臟纖維之機轉而進一步能達到預防肝臟纖維化的目的。
• 英文摘要	Tissue transglutaminase (tTG) is a Ca2+ dependent enzyme which plays an important role in the stabilization of the extracellular matrix (ECM) and formation of fibrotic lesions by catalysing protein-protein cross-linkage. Increased activity of tTG in an animal cirrhosis model has been

associated with impairment of spontaneous recovery of micronodular cirrhosis of liver. Ethanol has been considered as a significant inducing mediator of the liver fibrosis. In this study, we first investigated the mechanism of how ethanol regulates tTG mRNA expression in HCC cells. We found that only Hep3B cell synthesized tTG mRNA after addition of ethanol. Recent works have shown that transcription factor NF-kappaB was required to regulate tTG expression. In this study, we used the NF-kappaB-specific inhibitor, TLCK, to investigate the correlation between tTG and NF- kappaB and demonstrated that ethanol-induced tTG expression can be suppressed after addition of TLCK, providing evidence that NF-kappaB may participate the regulation in tTG expression. In addition, phosphorylation of ERK was also induced by ethanol in the Hep3B cell, and activation of NF-kappaB can be suppressed by adding MEK inhibitor, PD98059. Therefore, ERK and NF-kappaB are the possible signaling molecules to mediate the tTG activation. Pinocembrin, the most abundant flavanone isolated from various types of propolis and honey, has been considered as a potent antioxidant. Since it has been proposed that ethanol-induced liver fibrosis partially involved increased oxidative stress. We will test whether pinocembrin could suppress ethanol-induced tTG expression and its activity, along with the inhibition of nuclear translocation of NF- kappaB subunit p65. Furthermore, we also want to evaluate 2 whether pinocembrin could also suppress ethanol-induced activation of ERK. Hopefully in the future we could find methods to modulate the liver fibrosis to HCC pathway.