PPAR 配體抑制肝纖維化作用之機制探討

Study of the inhibitory effects of PPAR ligands on the TGF-beta-induced liver fibrosis.

中文摘要

在大部分因慢性發炎而造成損傷的肝臟疾病中，纖維化是一種結痂反應。肝臟慢性損傷最終會造成細胞外基質(ECM)累積而形成肝纖維化。轉型生長因子-beta 是強效的促纖維生成細胞激素，通常是經由細胞內蛋白 Smad 來傳遞訊號，但是也會經由活化 MAPK 路徑來傳遞其訊號。而結締組織生長因子這個名稱是在 1991 年首次被提出，它的表現無論在時間還是空間上皆與轉型生長因子-beta 有相關性。經過轉型生長因子-beta 處理後結締組織生長因子的 mRNA 及蛋白都會大量表現，體外的實驗中發現結締組織生長因子可以促進纖維母細胞的增生，細胞外基質的產生及結節組織的形成。在許多體內的纖維化部位可以發現結締組織生長因子有大量表現的情形。而 15d-PGJ2 (15-Deoxy-delta-12,14- Prostaglandin J2)是最新發現的前列腺素，已知為過氧化物體增殖物活化受體γ的內生性配體，但 15d-PGJ2 有一些作用可能是不須要過氧化物體增殖物活化受體γ參與的。許多研究指出過氧化物體增殖物活化受體γ配體具有抗發炎的活性，而且也可能有抗纖維化的作用。在本實驗中，我們利用 15d-PGJ2 來抑制經由轉型生長因子-beta 所誘發的結締組織生長因子 mRNA 及蛋白的表現，發現 15d-PGJ2 可以降低 Smad2 的磷酸化及抑制結締組織生長因子 promoter 的活性，而且可以活化 MAPK 這條傳導路徑。

英文摘要

Fibrosis is the liver’s scarring response to injury that occurs in most chronic inflammatory liver diseases. The ultimate result of chronic injury is the accumulation of extracellular matrix (ECM). Transforming growth factor-beta(TGF-beta), the potent profibrogenic cytokine, classically transmits intracellular signaling via Smad proteins. TGF-beta also can induce the activation of the MAPK pathway. The term “connective tissue growth factor”(CTGF) was first coined in 1991. CTGF expression was linked both temporally and spatially to TGF-beta. CTGF mRNA or protein was produced at high levels after treatment with TGF-beta. In vitro, CTGF promotes fibroblast proliferation, matrix production, and granulation tissue formation. In vivo, High levels of CTGF were detected in many fibrotic lesions.

15-Deoxy-delta-12,14-prostaglandin J2 (15d-PGJ2) is the most recently discovered prostaglandin and is recognized as the endogenous ligand for the intranuclear receptor PPAR. But some effects of 15d-PGJ2 are likely to be PPAR independent. Many studies showed that PPAR ligands have anti-inflammatory activities and may have

potential as antifibrotic agents. In this study，we examined the ability of 15d-PGJ2 to block the TGF-beta induced CTGF mRNA and protein expression on Hep-3B cells. We demonstrated that 15d-PGJ2 down-regulated the phosphorylation of Smad2 protein and inhibit the activity of CTGF promoter. 15d-PGJ2 also activated the MAPK pathway.