Anti-fibrotic effects of thalidomide on hepatic stellate cells and dimethylnitrosamine-intoxicated rats

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摘要

Abstract

Tumor necrosis factor-alpha (TNF-α) plays a central role in cellular necrosis, apoptosis, organ failure, tissue damage, inflammation and fibrosis. These processes, occurring in liver injury, may lead to cirrhosis. Thalidomide, α-N-phthalidoglutarimide, (C13H10N2)4, has been shown to have immunomodulatory and anti-inflammatory properties, possibly mediated through its anti-TNF-α effect. In this study, we investigated the in vitro and in vivo effects of thalidomide on hepatic fibrosis. A cell line of rat hepatic stellate cells (HSC-T6) was stimulated with transforming growth factor-β1 (TGF-β1) or TNF-α. The inhibitory effects of thalidomide on the NFκB signaling cascade and fibrosis markers including α-smooth muscle actin (α-SMA) and collagen, were assessed. An in vivo therapeutic study was conducted in dimethylnitrosamine (DMN)-treated rats, which were randomly assigned to 1 of 4 groups: vehicle (0.7% carboxyl methyl cellulose, CMC), thalidomide (40 mg/kg), thalidomide (200 mg/kg), or silymarin (50 mg/kg), each given by gavage twice daily for 3 weeks starting after 1 week of DMN administration. Thalidomide (100–800 nM) concentration-dependently inhibited NFκB transcriptional activity induced by TNF-α, including IKKα expression and IκBα phosphorylation in HSC-T6 cells. In addition, thalidomide also suppressed TGF-β1-induced α-SMA expression and collagen deposition in HSC-T6 cells. Fibrosis scores of livers from DMN-treated rats receiving high dose of thalidomide (0.89±0.20) were significantly reduced in comparison with those of DMN-treated rats receiving vehicle (1.56±0.18). Hepatic collagen contents of DMN rats were also significantly reduced by either thalidomide or silymarin treatment. Immunohistochemical double staining results showed that α-SMA- and NFκB-positive cells were decreased in the livers from DMN rats receiving either thalidomide or silymarin treatment. In addition, real-time PCR analysis indicated that hepatic mRNA expressions of TGF-β1, α-SMA, collagen 1α2, TNF-α and iNOS genes were attenuated by thalidomide treatment. In conclusion, our results showed that thalidomide inhibited activation of HSC-T6 cells by TNF-α and ameliorated liver fibrosis in DMN-intoxicated rats.