Notoginsenoside R1 targets PPAR-γ to inhibit Hepatic Stellate Cell activation and ameliorates liver fibrosis

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Abstract

Background: Hepatic fibrosis, a common pathological process that occurs in end-stage liver diseases, is a serious public health problem and lacks effective therapy. Notoginsenoside R1 (NR1) is a small molecule derived from the traditional Chinese medicine Sanqi, exhibiting great potential in treating diverse metabolic disorders. Here we aimed to enquired the role of NR1 in liver fibrosis and its underlying mechanism in hepatoprotective effects. Methods: We investigated the anti-fibrosis effects of NR1 using CCl₄-induced mouse mode of liver fibrosis as well as TGF-β₁-activated JS-1, LX-2 cells and primary hepatic stellate cells. Cell samples treated by NR1 were collected for transcriptomic profiling analysis. PPAR-γ mediated TGF-β₁/Smads signaling was examined using PPAR-γ selective inhibitors and agonists intervention, immunofluorescence staining and western blot analysis. Additionally, we designed and studied the binding of NR1 to PPAR-γ using molecular docking. Results: NR1 obviously attenuated liver histological damage, reduced serum ALT, AST levels, and decreased liver fibrogenesis markers in mouse mode. Mechanistically, NR1 elevated the levels of PPAR-γ, and decreased TGF-β₁, p-Smad2/3 expression. The TGF-β₁/Smads signaling pathway and fibrotic phenotype were altered in JS-1 cells after using PPAR-γ selective inhibitors and agonists respectively, confirming PPAR-γ played a pivotal protection role by NR1 from liver fibrosis. Further molecular docking indicated NR1 had a strong binding with PPAR-γ of minimum free energy of -7.1 kcal/mol. Conclusions: NR1 mitigated liver fibrosis and hepatic stellate cell activation by promoting PPAR-γ-mediated TGF-β₁/Smads signalling pathways. NR1 may be a potential candidate compound for reliving liver fibrosis.

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Weeks
0 1 9 13

CCl4 5ml/kg
(three times a week)

NR1, 10 or 40mg/kg
(four times a week)

Sacrificed and Evaluation

CCl4 for 8 weeks
NR1 for 4 weeks

A

B

C

D

E

F

G

H

I

J
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