Flavanones structure-related inhibition on TPA-induced tumor promotion through suppression of extracellular signal-regulated protein kinases: involvement of prostaglandin E2 in anti-promotive process.

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摘要

Abstract

Biological functions of flavanones have been studied extensively, however, the structure-related activities of flavanones on 12-o-tetradecanoylphorbol 13-acetate (TPA)-induced promotive effects are still unclear. In this study, flavanone, 2'-OH flavanone, 4'-OH flavanone, 6-OH flavanone showed the most significant dose-dependent inhibition on TPA-induced proliferative effects among eight tested flavanones in NIH3T3 cells. TPA-induced mitogen activated protein kinases (MAPK) phosphorylation, ornithine decarboxylase (ODC), c-Jun, and cyclooxygenase 2 (COX-2) protein expressions in a time-dependent manner, and the maximal inductive time point is at 1 h for MAPK phosphorylation and 6 h for others. Flavanone, 2'-OH flavanone, 4'-OH flavanone, 6-OH flavanone showed the dose-dependent inhibition on TPA-stimulated MAPK phosphorylation, COX-2, ODC, c-Jun protein expressions. Induction of, prostaglandin E(2) (PGE(2)) production was detected in TPA-treated NIH3T3 cells, and flavanone, 2'-OH flavanone, 4'-OH flavanone, 6-OH flavanone inhibited significantly PGE(2) production induced by TPA. Addition of PGE(2) reverses the inhibitory activities of flavanone, 2'-OH flavanone, 4'-OH flavanone, 6-OH flavanone on TPA-induced proliferation. And, PD98059, a specific inhibitor of ERKs, inhibited TPA-induced MAPK phosphorylation, accompanied by decreasing COX-2,

c-Jun, and ODC protein expression, and showed dose-dependent inhibition on TPA-induced proliferation in cells. These results demonstrated that PGE(2) is an important mediator in TPA-induced proliferation, and MAPK phosphorylation was located at the upstream of COX-2, c-Jun, and ODC gene expressions in TPA-induced responses. Furthermore, flavanone, 2'-OH flavanone, 4'-OH flavanone, 6-OH flavanone (100 microM) suppressed TPA-induced colony formation associated with blocking MAPK phosphorylation, ODC, c-Jun, and COX-2 proteins expression. And, 1,1-diphenyl-2-picrylhydrazyl (DPPH) assay showed that flavanone, 2'-OH flavanone, 4'-OH flavanone, 6-OH flavanone did not perform potent anti-radical activities among these eight tested compounds. In conclusion, this study provided molecular evidences to demonstrate that flavanone, 2'-OH flavanone, 4'-OH flavanone, 6-OH flavanone were potent inhibitors on TPA-induced responses without notable cytotoxicity through suppression of PGE(2) production; and anti-radical activity of flavanones was not correlated with preventing the occurrence of tumor promotion. We proposed that blocking TPA-induced intracellular signaling responses might be involved in the anti-promotive mechanism of flavanones.