3-OH flavone inhibition of epidermal growth factor-induced proliferaton through blocking prostaglandin E2 production.

沈杏娟;陳彥州
Shen SC;Ko CH;Hsu KC;Chen YC

Abstract

Epidermal growth factor (EGF) has been shown to induce proliferation in cells, however, the role of prostaglandin E2 (PGE2) plays in EGF-induced proliferation in still unclear. EGF and PGE2 showed proliferation responses in epidermoid carcinoma cell A431 by MTT and [3H] thymidine incorporation assay. Activation of the EGF receptor and extracellular signal-regulated protein kinases (ERK1/2), but not p38 and JNK, appeared 10 min after EGF treatment, whereas total amounts of ERK1/2, p38 and JNK remained unchanged in A431 cells, accompanied by induction of COX-2 and PGE2 production. PD98059, a specific ERK1/2 inhibitor, inhibited EGF-induced proliferation with concomitant decreases in ERK1/2 phosphorylation and COX-2/PGE2 induction. Nonsteroid anti-inflammatory drugs (NSAIDs) such as aspirin and diclofenac, a COX activity inhibitor, inhibited EGF-induced proliferation by blocking PGE2 production. The addition of PGE2 reversed the inhibitory effects of PD98059, aspirin, and diclofenac on EGF-induced proliferation. This suggests that COX-2/PGE2 activation involves in EGF-induced proliferation and locates at the downstream of ERK1/2 activation. Furthermore, the natural product, 3-OH flavone, showed the most-potent inhibitory activity on EGF-induced proliferation among 9 structurally-related compounds, and suppression of EGF receptor phosphorylation, ERK1/2 phosphorylation, and COX-2/PGE2 production by 3-OH flavone was identified. PGE2 addition attenuates the inhibitory activity of 3-OH flavone on EGF-induced proliferation by MTT assay and colony formation by soft agar assay. Additionally, 3-OH flavone also showed more-specific inhibition on EGFthan on fetal bovine serum (FBS)-induced proliferation in A431 cells. Results of our present study provide evidence to demonstrate that PGE2 is an important downstream molecule in EGF-induced proliferation, and 3-OH flavone, which inhibits PGE2 production by blocking MAPK cascade, might reserve potential for development as an anti-cancer drug.