Myricetin inhibits matrix metalloproteinase 2 protein expression and enzyme activity in colorectal carcinoma cells.

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Abstract

Colorectal carcinoma is a leading cause of human mortality due to its high metastatic ability. Because the activation of matrix metalloproteinases (MMP) is a key factor in the metastatic process, agents with the ability to inhibit MMP activity have potential in the treatment of colorectal carcinoma. In the present study, among 36 flavonoids examined, myricetin was found to be the most potent inhibitor of MMP-2 enzyme activity in COLO 205 cells (IC50 = 7.82 micromol/L). Myricetin inhibition of MMP-2 enzyme activity was also found in the human colorectal carcinoma cell lines COLO 320HSR, COLO 320DM, HT 29, and COLO 205-X (IC50 = 11.18, 11.56, 13.25, and 23.51 micromol/L, respectively). In contrast, no inhibitory effect of MMP-2 protein expression or enzyme activity was observed in myricitrin (myricetin-3-rhamnoside)-treated cells. In 12-O-tetradecanoylphorbol-13-acetate (TPA)-stimulated COLO 205 cells, an increase in MMP-2 protein expression and enzyme activity, as well as of protein kinase C (PKC) alpha protein translocation, extracellular signal-regulated kinase (ERK) 1/2 protein phosphorylation, and c-Jun protein expression was observed. ERK inhibitor (PD98059) and PKC inhibitors (GF-109203X and H-7), but not p38 inhibitor (SB203580) or c-jun-NH2-kinase inhibitor (SP600125), significantly inhibited TPA-induced MMP-2 protein expression, with reduced ERK phosphorylation and c-Jun protein expression. Addition of myricetin but not myricitrin suppressed TPA-induced MMP-2 protein expression in COLO 205 cells by blocking the TPA-induced events, including translocation of PKCalpha from cytosol to membrane, phosphorylation of ERK1/2 protein, and induction of c-Jun protein expression. Addition of PD98059 or GF-109203X significantly enhanced the inhibitory effect of myricetin on MMP-2 enzyme activity induced by TPA. Furthermore, myricetin, but not myricitrin, suppressed TPA-induced invasion of COLO 205 cells in an in vitro invasion assay using Engelbreth-Holm-Swarm sarcoma tumor extract Matrigel-coated Transwells. Results of the present study indicate that myricetin significantly blocked both endogenous and TPA-induced MMP-2 enzyme activity by inhibiting its protein expression and enzyme activity. The blockade involved suppression of PKC translocation, ERK phosphorylation, and c-Jun protein expression.