Quercetin inhibition of tumor invasion via suppressing PKC delta/ERK/AP-1-dependent matrix metalloproteinase-9 activation in breast carcinoma cells.

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摘要

Abstract

Quercetin (3,5,7,3',4'-tetrahydroxyflavone; QUE) has been shown to possess several beneficial biological activities including anti-tumor, anti-inflammation, and antioxidant properties; however, the effects of QUE in preventing invasion by breast carcinoma cells are still undefined. Increases in the protein, mRNA, and enzyme activity levels of matrix metalloproteinase-9 (MMP-9) were observed in 12-O-tetradecanoylphorbol-13-acetate (TPA)-treated MCF-7 cells, and these were blocked by QUE, but not by quercitrin (QUI) or rutin (RUT). A translocation of protein kinase C (PKC) from the cytosol to the membrane followed by activation of ERK and c-Jun/AP-1 by TPA was demonstrated, and TPA-induced MMP-9 activation and migration were inhibited by the pan PKC inhibitor, GF109203X (GF), the specific PKC inhibitor, rottlerin (Rot), an ERK inhibitor (PD98059), and an AP-1 inhibitor (curcumin). Application of QUE significantly suppressed TPA-induced activation of the PKC/ERK/AP-1 signaling cascade. To elucidate the importance of OH substitutions to QUE's inhibition of tumor migration, several structurally related flavones of QUE including 3',4'-diOH, 3',4'-diOCH3, 3,5,7-triOH, 3,4',4'-triOH, 3,3',4'-triOCH3, luteolin, and fisetin were used. Results suggested that OH groups at both C3' and C4' play central roles in QUE's inhibition of TPA-induced MMP-9 activation and migration, and an additional OH at C3, C5, or C7 may increase the inhibitory potency of the 3',4'-diOH flavone against TPA-induced MMP-9 activity and migration. The anti-tumor invasion and migration effects of breast carcinoma cells induced by QUE with the structure-activity relationship analysis were identified.