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

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Abstract

Quercetin (QUE; 3,5,7,3',4'-tetrahydroxyflavone) has been shown to possess several beneficial biological activities including antitumor, anti-inflammation and antioxidant properties; however, the effects of QUE in preventing invasion by breast carcinoma cells are still undefined. Increases in the protein, messenger RNA and enzyme activity levels of matrix metalloproteinase (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 or rutin. A translocation of protein kinase C (PKC)delta from the cytosol to the membrane followed by activation of extracellular signal-regulated kinase (ERK) and c-Jun/activator protein-1 (AP-1) by TPA was demonstrated, and TPA-induced MMP-9 activation and migration were inhibited by the pan PKC inhibitor, GF109203X, the specific PKCdelta inhibitor, rottlerin, an ERK inhibitor (PD98059) and an AP-1 inhibitor (curcumin). Application of QUE significantly suppressed TPA-induced activation of the PKCdelta/ERK/AP-1-signaling cascade. To elucidate the importance of hydroxyl (OH) substitutions to QUE's inhibition of tumor migration, several structurally related flavones of QUE including 3',4'-diOH, 3',4'-diOCH(3), 3,5,7-triOH, 3,4',4'-triOH, 3,3',4'-triOCH(3), 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 antitumor invasion and migration effects of breast carcinoma cells induced by QUE with the structure-activity relationship analysis were identified.