Buteína (3, 4, 2', 4'-tetrahydroxychalcone) diminui expressão e a função do receptor CXCR4 através da supressão da ativação do NF-kappaB no câncer de mama e pancreático

Butein downregulates chemokine receptor CXCR4 expression and function through suppression of NF-κB activation in breast and pancreatic tumor cells.

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Abstract

The CXC chemokine receptor-4 (CXCR4), a Gi protein-coupled receptor for the ligand CXCL12/stromal cell-derived factor-1α (SDF-1α), is known to be expressed in various tumors. This receptor mediates homing of tumor cells to specific organs that express the ligand CXCL12 for this receptor and plays an important role in tumor growth, invasion, metastasis, and angiogenesis. Thus, a priori, agents that can downregulate CXCR4/CXCL12 signaling cascade have potential against cancer metastasis. In this study, we report the identification of butein (3, 4, 2', 4'-tetrahydroxychalcone) as a novel regulator of CXCR4 expression and function. We found that butein downregulated the expression of CXCR4 in HER2-overexpressing breast cancer cells in a dose- and time-dependent manner. The decrease in CXCR4 expression induced by butein was not cell type-specific as the inhibition also occurred in pancreatic, prostate, multiple myeloma, head and neck, and hepatocellular cancer cell lines. When investigated for the molecular mechanism(s), it was found that the downregulation of CXCR4 was not due to proteolytic degradation but rather to transcriptional regulation as indicated by downregulation of mRNA expression, inhibition of NF-κB activation evident by both DNA binding, and reporter assays, and suppression of chromatin immunoprecipitation activity. Suppression of CXCR4 expression by butein correlated with the inhibition of CXCL12-induced migration and invasion of both breast and pancreatic cancer cells. Overall, our results demonstrate for the first time that butein is a novel inhibitor of CXCR4 expression and thus has a potential in suppressing metastasis of cancer.

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