Dihydroxyphenylethanol, a product from olive oil, reduces colon cancer growth by enhancing EGFR degradation

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2-(3,4-dihydroxyphenil)ethanol (DPE), a polyphenol of extra-virgin olive oil, has showed various properties, including antioxidant, anti-inflammatory and anticancer effects. We have previously demonstrated that DPE inhibits the *in vitro* growth of colon tumor cells and reduces the growth of human colon cancer HT-29 xenografts *in vivo* thought the anti-inflammatory and anti-angiogenic pathway (downregulation of HIF-1alpha/mPGEs-1/VEGF) (Terzuoli et al, 2010). Epidermal growth factor receptor (EGFR) activates signal transduction pathways involved in colon cancer progression. Its overexpression and activation are associated with poor prognosis of colon cancer patients.

This study demonstrates that DPE significantly downregulates EGFR expression in human colorectal adenocarcinoma cells HT-29, CaCo2 and WiDr, and in HT-29 mouse xenografts. DPE accelerates EGFR degradation by reducing its half-life. Specifically, DPE induces EGFR ubiquitination which is mediated by the phosphorylation at pY1045, the docking site where Cbl binds, thereby enabling receptor ubiquitination and degradation. Pre-treatment with either the lysosomal inhibitor chloroquine or the proteosomal inhibitor MG132 blocks DPE–induced downregulation of EGFR. Tumor growth and EGFR expression levels are decreased by DPE treatment in HT-29 xenograft model, and in colon cancer cells DPE-mediated downregulation of EGFR reduces cell proliferation.

We conclude that DPE promotes downregulation of EGFR expression via lysosomal and proteasomal degradation activated by DPE-induced EGFR phosphorylation at pY1045, increased Cbl activity, and, as a consequence, EGFR ubiquitination.

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