IGF-I plus E2 induces proliferation via activation of ROS-dependent ERKs and JNKs in human breast carcinoma cells

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摘要

Abstract

Induction of 17beta-estradiol (E2) and insulin-like growth factor-I (IGF-I) has been detected in breast carcinoma, however the interaction between E2 and IGF-I in the proliferation of breast carcinoma cells is still unclear. In the present study, we found that IGF-I enhances the E2-induced proliferation in MCF-7 human breast carcinoma cells in accordance with stimulation of colony formation via a soft agar assay. Activation of insulin receptor substrate-1 (IRS-1) protein and extracellular signal-related kinases (ERKs) and c-Jun N-terminal kinases (JNKs), but not p38 mitogen-activated protein kinase (MAPK), via phosphorylation induction was detected in MCF-7 cells treated with IGF-I plus E2 (E2/IGF-I). E2/IGF-I-induced proliferation was blocked by chemical inhibitors of ERKs (PD98059) and JNKs (SP600125). An increase in the expression of c-Jun protein was detected in E2/IGF-I-treated MCF-7 cells, and this was inhibited by PD98059 and SP600125. Transfection of the dominant negative MEKK and JNK plasmids significantly reduced E2/IGF-I-induced proliferation with suppression of c-Jun protein expression. An increase in peroxide production was detected in E2/IGF-I-treated cells, and N-acetyl-L-cysteine (NAC) and Tiron (TIR) addition significantly inhibited E2/IGF-I-induced cell proliferation with blocking of the phosphorylation of ERKs and JNKs, and the expression of c-Jun protein. Additionally, 3-OH flavone, baicalein, and quercetin showed effective inhibitory activities against E2/IGF-I-induced proliferation through suppressing proliferative events such as phosphorylation of IRS-1, ERKs, and JNKs proteins, and induction of c-Jun protein and colony formation. These results indicate that IGF-I interacts with E2 to promote the proliferation of breast carcinoma cells via ROS-dependent MAPK activation and c-Jun protein expression. The structure-related inhibition of E2/IGF-I-induced proliferative events by flavonoids is elucidated. J. Cell. Physiol. 212:666-674, 2007. (c) 2007 Wiley-Liss, Inc.