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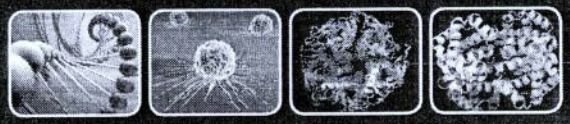

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Parthenolide induces EGF receptor phosphorylation and superoxide anion production in MDA-MB231 breast cancer cells.

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The sesquiterpene lactone parthenolide (PN) has recently attracted considerable attention because of its anti-cancer activity in several cancer cell type. We recently provided evidence that PN exerted a marked cytotoxic effect on MDA-MB231 cells, a triple-negative breast cancer cell line. This effect was induced by the production of reactive oxygen species (ROS). Here we investigate about the role of EGFR activation in the mechanism of PN effect exerted on MDA-MB231 cells. Our results demonstrated that PN promoted phosphorylation of EGF receptor at Tyr1173, an event which was observed already at 1h of incubation with 25 μM PN and reached a peak at 8-16 h. This effect seemed to be a consequence of ROS production, because N-acetylcysteine, a powerful ROS scavenger, prevented the increment of phospho-EGFR level. In addition fluorescence analysis performed by using dihydroethidium demonstrated that PN stimulated the production of superoxide anion already at 2-3h of incubation. This production further increased prolonging the time of treatment with PN, reaching a peak at 8-16 h. This effect was markedly reduced by apocynin, a well known NADPH oxidase (NOX) inhibitor, suggesting that superoxide anion production was determined by NOX activity. The finding that AG1478, an EGFR kinase inhibitor, blocked both EGFR phosphorylation as well as superoxide anion production strongly suggested that phosphorylation of EGFR can be responsible for the activation of NOX with the consequent production of superoxide anion. Thus, we can conclude that PN, through the production of ROS, could stimulate EGFR phosphorylation and this causes stimulation of NOX and production of superoxide anion.

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