Abstract


Antiproliferative effects of γ-tocotrienol are associated with lipid raft disruption in HER2-positive human breast cancer cells.

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OBJECTIVE: A large percentage of human breast cancers are characterized by excessive or aberrant HER2 activity. Lipid rafts are specialized microdomains within the plasma membrane that are required for HER2 activation and signal transduction. Since the anticancer activity of γ-tocotrienol is associated with suppression in HER2 signaling, studies were conducted to examine the effects of γ-tocotrienol on HER2 activation within the lipid raft microdomain in HER2-positive SKBR3 and BT474 human breast cancer cells.

METHODS AND RESULTS: Treatment with 0-5μM γ-tocotrienol induced a significant dose-dependent inhibition in cancer cell growth after a 5-day culture period, and these growth inhibitory effects were associated with a reduction in HER2 dimerization and phosphorylation (activation). Phosphorylated HER2 was found to be primarily located in the lipid raft microdomain of the plasma membrane in vehicle-treated control groups, whereas γ-tocotrienol treatment significantly inhibited this effect. Assay of plasma membrane subcellular fractions showed that γ-tocotrienol also accumulates exclusively within the lipid raft microdomain. Hydroxypropyl-β-cyclodextrin (HPβCD) is an agent that disrupts lipid raft integrity. Acute exposure to 3mM HPβCD alone had no effect, whereas an acute 24-h exposure to 20μM γ-tocotrienol alone significantly decreased SKBR3 and BT474 cell viability. However, combined treatment with these agents greatly reduced γ-tocotrienol accumulation in the lipid raft microdomain and cytotoxicity.

CONCLUSION: In summary, these findings demonstrate that the anticancer effects of γ-tocotrienol are associated with its accumulation in the lipid raft microdomain and subsequent interference with HER2 dimerization and activation in SKBR3 and BT474 human breast cancer cells.

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