Gamma-tocotrienol acts as a BH3 mimetic to induce apoptosis in neuroblastoma SH-SY5Y cells

ABSTRACT

Bcl-2 family proteins are crucial regulators of apoptosis. Both pro- and antiapoptotic members exist, and overexpression of the latter facilitates evasion of apoptosis in many cancer types. Bcl-2 homology domain 3 (BH3) mimetics are small molecule inhibitors of antiapoptotic Bcl-2 family members, and these inhibitors are promising anticancer agents. In this study, we report that gamma-tocotrienol (ɔT3), an isomer of vitamin E, can inhibit Bcl-2 to induce apoptosis. We demonstrate that ɔT3 induces cell death in human neuroblastoma SH-SY5Y cells by depolarising the mitochondrial membrane potential, enabling release of cytochrome c to the cytosol and increasing the activities of caspases-9 and -3. Treatment of cells with inhibitors of Bax or caspase-9 attenuated the cell death induced by ɔT3. Simulated docking analysis suggested that ɔT3 binds at the hydrophobic groove of Bcl-2, while a binding assay showed that ɔT3 competed with a fluorescent probe to bind at the hydrophobic groove. Our data suggest that ɔT3 mimics the action of BH3-only protein by binding to the hydrophobic groove of Bcl-2 and inducing apoptosis via the intrinsic pathway in a Bax- and caspase-9-dependent manner.

Keyword: Gamma-tocotrienol; BH3 mimetic; Neuroblastoma; Bcl-2; Apoptosis; Vitamin E