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Flavonoids activated caspases for apoptosis in human glioblastoma T98G and U87MG cells but not in human normal astrocytes.

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Abstract

BACKGROUND: Human glioblastoma is a deadly brain cancer that continues to defy all current therapeutic strategies. The authors induced apoptosis in human glioblastoma T98G and U87MG cells after treatment with apigenin, (-)-epigallocatechin, (-)-epigallocatechin-3-gallate (EGCG), and **genistein**, which did not induce apoptosis in human normal astrocytes.

METHODS: Induction of apoptosis was examined using Wright staining and ApopTag assay. Production of reactive oxygen species (ROS) and increase in intracellular free Ca²⁺ were measured by fluorescent probes. Analysis of mRNA and Western blotting indicated increases in expression and activities of the stress kinases and cysteine proteases for apoptosis. JC-1 showed changes in mitochondrial membrane potential (DeltaPsi(m)), and use of specific inhibitors confirmed activation of kinases and proteases in apoptosis.

RESULTS: Treatment of glioblastoma cells with apigenin, (-)-epigallocatechin, EGCG, or **genistein** triggered ROS production that induced apoptosis with phosphorylation of p38 mitogen-activated protein kinase (MAPK) and activation of the redox-sensitive c-Jun N-terminal kinase 1 pathway. Pretreatment of cells with ascorbic acid attenuated ROS production and p38 MAPK phosphorylation. Increases in intracellular free Ca²⁺ and activation of caspase-4 indicated involvement of endoplasmic reticulum stress in apoptosis. Other events in apoptosis included overexpression of Bax, loss of DeltaPsi(m), mitochondrial release of cytochrome c and Smac into the cytosol, down-regulation of baculoviral inhibitor-of-apoptosis repeat-containing proteins, and activation of calpain, caspase-9, and caspase-3. (-)-Epigallocatechin and EGCG also induced caspase-8 activity. Apigenin, (-)-epigallocatechin, EGCG, and **genistein** did not induce apoptosis in human normal astrocytes.

CONCLUSIONS: Results strongly suggest that flavonoids are potential therapeutic agents for induction of apoptosis in human glioblastoma cells.

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