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Thymoquinone inhibits growth of human medulloblastoma cells by inducing oxidative stress and caspase-dependent apoptosis while suppressing NF-κB signaling and IL-8 expression (Article)

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Abstract

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Medulloblastoma (MB) is the most common malignant brain tumor of childhood. The transcription factor NF-κB is overexpressed in human MB and is a critical factor for MB tumor growth. NF-κB is known to regulate the expression of interleukin-8 (IL-8), the chemokine that enhances cancer cell growth and resistance to chemotherapy. We have recently shown that thymoquinone (TQ) suppresses growth of hepatocellular carcinoma cells in part by inhibiting NF-κB signaling. Here we sought to extend these studies in MB cells and show that TQ suppresses growth of MB cells in a dose- and time-dependent manner, causes G2M cell cycle arrest, and induces apoptosis. TQ significantly increased generation of reactive oxygen species (ROS), while pretreatment of MB cells with the ROS scavenger N-acetylcysteine (NAC) abrogated TQ-induced cell death and apoptosis, suggesting that TQ-induced cell death and apoptosis are oxidative stress-mediated. TQ inhibitory effects were associated with inhibition of NF-κB and altered expression of its downstream effectors IL-8 and its receptors, the anti-apoptotic Bcl-2, Bcl-xL, X-IAP, and FLIP, as well as the pro-apoptotic TRAIL-R1, caspase-8, caspase-9, Bcl-xS, and cytochrome c. TQ-triggered apoptosis was substantiated by up-regulation of the executioner caspase-3 and caspase-7, as well as cleavage of the death substrate poly(ADP-ribose)polymerase. Interestingly, pretreatment of MB cells with NAC or the pan-caspase inhibitor zVAD-fmk abrogated TQ-induced apoptosis, loss of cyclin B1 and NF-κB activity, suggesting that these TQ-mediated effects are oxidative stress- and caspase-dependent. These findings reveal that TQ induces both extrinsic and intrinsic pathways of apoptosis in MB cells, and suggest its potential usefulness in the treatment of MB. © 2016, Springer Science+Business Media New York.

Reaxys Database Information

View Compounds

Author keywords

Apoptosis Cancer Daoy cells Medulloblastoma NF-κB Thymoquinone

Indexed keywords

EMTREE drug terms: Bcl xS protein caspase caspase 3 caspase 7 caspase 8 caspase 9 cell DNA cyclin B1 cytochrome c death receptor 4 immunoglobulin enhancer binding protein interleukin 8 messenger RNA nicotinamide adenine dinucleotide adenosine diphosphate ribosyltransferase protein bcl 2 protein bcl xl reactive oxygen metabolite thymoquinone unclassified drug X linked inhibitor of apoptosis benzoquinone derivative caspase IL8 protein, human immunoglobulin enhancer binding protein interleukin 8 thymoquinone tumor protein

EMTREE medical terms: apoptosis Article cancer cell cancer growth cancer inhibition cell death cell growth cell proliferation cell viability controlled study DNA content down regulation flow cytometry G2 phase cell cycle checkpoint human human cell M phase cell cycle checkpoint medulloblastoma oxidative stress protein depletion protein expression protein phosphorylation signal transduction upregulation apoptosis biosynthesis drug effects gene expression regulation genetics medulloblastoma metabolism oxidative stress pathology signal transduction tumor cell line

MeSH: Apoptosis Benzoquinones Caspases Cell Line, Tumor Gene Expression Regulation, Neoplastic Humans Interleukin-8 Medulloblastoma Neoplasm Proteins NF-kappa B Oxidative Stress Signal Transduction

Chemicals and CAS Registry Numbers:

caspase, 186322-81-6; caspase 3, 169592-56-7; caspase 7, 189258-14-8; caspase 8; caspase 9, 180189-96-2; cytochrome c, 9007-43-6, 9064-84-0; interleukin 8, 114308-91-7; nicotinamide adenine dinucleotide adenosine diphosphate ribosyltransferase, 58319-92-9; protein bcl 2, 219306-68-0; protein bcl xl, 151033-38-4; thymoquinone, 490-91-5; X linked inhibitor of apoptosis, 391965-84-7;

Benzoquinones; Caspases; IL8 protein, human; Interleukin-8; Neoplasm Proteins; NF-kappa B; thymoquinone

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