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Thymoquinone suppression of the human hepatocellular carcinoma cell growth involves inhibition of IL-8 expression, elevated levels of TRAIL receptors, oxidative stress and apoptosis (Article)

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Abstract

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Hepatocellular carcinoma (HCC) is the fourth most common solid tumor worldwide. The chemokine interleukin-8 (IL-8) is overexpressed in HCC and is a potential target for therapy. Although the transcription factor NF-κB regulates IL-8 expression, and while thymoquinone (TQ; the most bioactive constituent of black seed oil) inhibits NF-κB activity, the precise mechanisms by which TQ regulates IL-8 and cancer cell growth remain to be clarified. Here, we report that TQ inhibited growth of HCC cells in a dose- and time-dependent manner, caused G2M cell cycle arrest, and stimulated apoptosis. Apoptosis was substantiated by activation of caspase-3 and -9, as well as cleavage of poly(ADP-ribose)polymerase. TQ treatments inhibited expression of NF-κB and suppressed IL-8 and its receptors. TQ treatments caused increased levels of reactive oxygen species (ROS) and mRNAs of oxidative stress-related genes, NQO1 and HO-1. Pretreatment of HepG2 cells with N-acetylcysteine, a scavenger of ROS, prevented TQ-induced cell death. TQ treatment stimulated mRNA expression of pro-apoptotic Bcl-xS and TRAIL death receptors, and inhibited expression of the anti-apoptotic gene Bcl-2. TQ enhanced TRAIL-induced death of HepG2 cells, in part by up-regulating TRAIL death receptors, inhibiting NF-κB and IL-8 and stimulating apoptosis. Altogether, these findings provide insights into the pleiotropic molecular mechanisms of TQ-dependent suppression of HCC cell growth and underscore potential of this compound as anti-HCC drug. © 2014 Springer Science+Business Media.

Author keywords

Apoptosis | HCC | IL-8 | NF-κB | Oxidative stress | Thymoquinone | TRAIL

Indexed keywords

EMTREE drug terms: acetylcysteine | bcl xs protein | caspase 3 | caspase 9 | heme oxygenase 1 | interleukin 8 | interleukin 8 receptor | messenger RNA | nicotinamide adenine dinucleotide adenosine diphosphate ribosyltransferase | oxidoreductase | quinone oxidoreductase 1 | reactive oxygen metabolite | thymoquinone | tumor necrosis factor related apoptosis inducing ligand receptor | tumor suppressor protein | unclassified drug

EMTREE medical terms: antineoplastic activity | apoptosis | article | carcinoma cell | cell death | cell growth | cell strain HepG2 | cell viability | controlled study | flow cytometry | G2 phase cell cycle checkpoint | gene expression | growth inhibition | human | human cell

MeSH: Apoptosis | bcl-X Protein | Benzoquinones | Carcinoma, Hepatocellular | Caspase 3 | Caspase 9 | Cell Line, Tumor | Cell Proliferation | G2 Phase Cell Cycle Checkpoints | Hep G2 Cells | Humans | Interleukin-8 | Liver Neoplasms | M Phase Cell Cycle Checkpoints | NF-kappa B | Oxidative Stress | Poly(ADP-ribose) Polymerases | Proto-Oncogene Proteins c-bcl-2 | Reactive Oxygen Species | Receptors, TNF-Related Apoptosis-Inducing Ligand

Chemicals and CAS Registry Numbers:

acetylcysteine, 616-91-1; caspase 3, 169592-56-7; caspase 9, 180189-96-2; interleukin 8, 114308-91-7; nicotinamide adenine dinucleotide adenosine diphosphate ribosyltransferase, 58319-92-9; oxidoreductase, 9035-73-8, 9035-82-9, 9037-80-3, 9055-15-6; thymoquinone, 490-91-5

Manufacturers:

Drug manufacturer:

Sigma Aldrich, United States

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	U.S. Department of Veterans Affairs	VA	See opportunities by VA
ARP-29-265	King Abdulaziz City for Science and Technology	KACST	

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