Garcinol inhibits cell growth in hepatocellular carcinoma Hep3B cells through induction of ROS-dependent apoptosis.

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Abstract

Garcinol, derived from Garcinia indica and other related species, has been found to modulate several cell signalling pathways involved in apoptosis and cancer development. Growth arrest and DNA damage-inducible gene 153 (GADD153) is a member of the CCAAT/enhancer-binding protein (C/EBP) family of transcription factors; it is expressed at low levels under normal conditions but strongly induced upon growth arrest, DNA damage, and endoplasmic reticulum (ER) stress. This study investigated the effect of garcinol on Hep3B cells, a human hepatocellular cancer cell line lacking functional p53, with the goal of elucidating the molecular mechanisms of p53-independent apoptosis in hepatocellular cancer. Overall, garcinol activated not only the death receptor and the mitochondrial apoptosis pathways but also the ER stress modulator GADD153. Garcinol treatment led to the accumulation of reactive oxygen species (ROS), increased GADD153 expression, and reduced mitochondrial membrane potential. An increase in the Bax/Bcl-2 ratio resulted in enhanced apoptosis. Caspase-8 and tBid (truncated Bid) expression also increased in a time-dependent manner. The enzymatic activities of caspase-3 and caspase-9 increased approximately 13-fold and 7.8-fold, respectively. In addition, the proteolytic cleavage of poly-(ADP-ribose)-polymerase (PARP) and DNA fragmentation factor-45 (DFF-45) increased in dose- and time-dependent manners. Our data suggest a promising therapeutic application of garcinol in p53-independent apoptosis in cancers.