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Curcumin inhibits the Sonic Hedgehog signaling pathway and triggers apoptosis in medulloblastoma cells.

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Medulloblastoma is an aggressive primary brain tumor that arises in the cerebellum of children and young adults. The Sonic Hedgehog (Shh) signaling pathway that plays important roles in the pathology of this aggressive disease is a promising therapeutic target. In the present report we have shown that curcumin has cytotoxic effects on medulloblastoma cells. Curcumin suppressed also cell proliferation and triggered cell-cycle arrest at G(2)/M phase. Moreover, curcumin inhibited the Shh-Gli1 signaling pathway by downregulating the Shh protein and its most important downstream targets GLI1 and PTCH1. Furthermore, curcumin reduced the levels of beta-catenin, the activate/phosphorylated form of Akt and NF-kappaB, which led to downregulating the three common key effectors, namely C-myc, N-myc, and Cyclin D1. Consequently, apoptosis was triggered by curcumin through the mitochondrial pathway via downregulation of Bcl-2, a downstream anti-apoptotic effector of the Shh signaling. Importantly, the resistant cells that exhibited no decrease in the levels of Shh and Bcl-2, were sensitized to curcumin by the addition of the Shh antagonist, cyclopamine. Furthermore, we have shown that curcumin enhances the killing efficiency of nontoxic doses of cisplatin and gamma-rays. In addition, we present clear evidence that piperine, an enhancer of curcumin bioavailability in humans, potentiates the apoptotic effect of curcumin against medulloblastoma cells. This effect was mediated through strong downregulation of Bcl-2. These results indicate that curcumin, a natural nontoxic compound, represents great promise as Shh-targeted therapy for medulloblastomas. (c) 2009 Wiley-Liss, Inc.

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