Clin Cancer Res. 2010 Dec 1;16(23):5781-95.

Dietary Curcumin Attenuates Glioma Growth in a Syngeneic Mouse Model by Inhibition of the JAK1,2/STAT3 Signaling Pathway.

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Abstract

PURPOSE: Glioblastomas are the most common and most deadly primary brain tumors. Here, we evaluated the chemotherapeutic effect of the natural polyphenol curcumin on glioma cells in vitro and in vivo using an immunocompetent orthotopic mouse model.

EXPERIMENTAL DESIGN: Curcumin's effects on proliferation, cell cycle, migration, invasion, JAK/STAT3 signaling, STAT3 target gene expression, and STAT3C rescue experiments were determined in murine glioma cell lines in vitro. Therapeutic effects of curcumin in vivo were evaluated in tumor-bearing mice fed a Western-type diet fortified with curcumin (0.05%, w/w) and in control animals. Tumor growth patterns and survival were evaluated by immunohistochemistry, morphometric analyses, and Kaplan-Meier plots.

RESULTS: In vitro, curcumin inhibited JAK1,2/STAT3 tyrosine-phosphorylation in a dose-dependent fashion in murine glioma cell lines. Real-time RT-PCR revealed that curcumin downregulated transcription of the STAT3 target genes c-Myc, MMP-9, Snail, and Twist, and of the proliferation marker Ki67. Curcumin dose-dependently suppressed cell proliferation by inducing a G2/M phase arrest. In wound healing and Matrigel invasion assays, curcumin treatment resulted in a dose-dependent attenuation of the glioma cells' migratory and invasive behavior, which could be rescued by constitutively active STAT3C. In vivo, curcumin intake reduced the growth and midline crossing of intracranially implanted tumors and proliferation of tumor cells ensuing in significant long-term survival compared with control diet.

CONCLUSION: This preclinical study shows that curcumin is capable of suppressing malignant glioma growth in vitro and in vivo. Our data suggest that the pharmacologically safe agent curcumin holds promise for clinical application in glioma therapy. Clin Cancer Res; 16(23); 5781-95. ©2010 AACR.

PMID: 21138870 [PubMed - in process]